

Production, Quality Control and Clinical Applications of Radiosynovectomy agents

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FOREWORD

Therapeutic radiopharmaceuticals are a major role player in today's nuclear medicine, especially for the treatment of cancer. One of the interesting and long practiced fields of their application is 'radiation synovectomy,' or in short 'radiosynovectomy'. In the last decades, the production and quality control of radiopharmaceuticals for use in radiosynovectomy has gone from simple phosphorous-32 (^{32}P) colloids to recently developed matrixes labelled with short/medium range beta emitters. It is a well-established technique with growing applications worldwide. However, the lack of generic and peer-reviewed production, quality control and clinical application guidelines and recommendations, are a major concern for their application in human patients.

Based on both, IAEA's global efforts in supporting Member States in the application of nuclear techniques in radiopharmacy and health, and on several requests from Member States as well as professional societies in recent years, formulation of an IAEA technical publication on the subject became pertinent. Currently, there is a lack of international standardized regulations of RSV production and clinical use. This publication is meant to be utilized by all involved professionals in the field by specifying ideal quality control and quality assurance procedures in the production of several radiopharmaceuticals for performing radiosynovectomy, as well as standard operation procedures needed for achieving successful therapeutic effects in patients.

This publication is an outcome of continuous efforts of an international expert team who was in the field between 2016-2018; thus, the IAEA wishes to thank the experts for their valuable work and scientific contribution, especially Mr. A. Dash and Mr. J. Farahati. The IAEA technical officers responsible for this publication were Mr A. R. Jalilian of the Division of Physical and Chemical Sciences and Mr F. Giammarile of the Division of Physical and Chemical Sciences of the Division of Human Health of IAEA. Special thanks to Ms J.S. Vera Araujo from the Division of Physical and Chemical Sciences for her support in revising and editing.

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1. INTRODUCTION

1.1.BACKGROUND

Radiopharmaceuticals have an incremental positive impact in the health sector, especially in the diagnosis and treatment of diseases. Particularly in the treatment of joint inflammations, radiosynovectomy (RSV) has been used as an alternative minimally invasive treatment for joint complications. A common one is rheumatoid arthritis, which despite recent therapeutic advances it remains incurable. As adjunct to the conventional treatments of corticosteroids, arthroscopic synovectomy and arthrodesis, RSV has been used over 50 years for the treatment of refractory painful and disabling synovitis in patients with rheumatoid arthritis and other inflammatory synoviopathies, such as activated osteoarthritis and haemophilic. RSV is a local treatment with ionizing radiation involving the coupling of a proper unsealed beta-emitting radioisotope with a proper colloid applied intra-articular to irradiate the pathological superficial synovial membrane. A multidisciplinary approach involving rheumatologists, orthopaedists, and nuclear medicine physicians, as well as a good understanding of the pathophysiology of synoviopathy, are essential for selecting the most appropriate treatment for individualized joints in order to optimize the result of this intelligent minimally invasive local therapy. Hence, RSV production and application should be carefully handled and administrated, as there are several requirements to meet for delivering successful outcomes.

RSV response rates range from 60% to 80% depending on different joints, underlying disease and the stage of the disease. The best results are reported in haemophilic haemarthropathy with a response rate of approximately 90%. In guidelines for handling haemophilia, RSV is considered as the initial local preferred choice for the treatment of patients with refractory hemarthrosis in haemophilia [1–3]. Regarding other diseases, well-designed double-trials have assessed the effectiveness of RSV and concluded that this is an alternative local treatment option for pain relieve in patients with synovitis in rheumatoid arthritis or synovitis after other arthropathies that cause swollenness and inflammation [1]. RSV obtains comparable results as of surgical synovectomies, and it is known for being well tolerated, having low rates of adverse effects, costing less, permitting patients to be ambulatory, as well as being repeatable and simultaneously performed in multiple joints [1]. Therefore, the use of radiopharmaceuticals for RSV treatment is a well-established treatment with high positive outcomes across different diseases and applications.

RSV radiopharmaceuticals are not commonly available across the world because of production complications and difficult access to cost-effective strategies. For example, ^{169}Er for treating finger and toe joints is recommended and available only in Europe in patients with polyarthritis, however not available in many other parts of the world. Some countries in Latin America, Middle East, and Asia use alternative radionuclides such as ^{188}Re (obtained from a radioisotope generator), ^{177}Lu , ^{153}Sm , which are different from European recommendations with nice results, due to the availability and costs of clinical studies. Hence, this publication has the potential to avoid the neglect or misuse of these radiopharmaceuticals. This creates an opportunity for the IAEA to provide guidance on international standards for successful production and application of radiopharmaceuticals in RSV, and to provide a platform for scientific knowledge sharing for Member States and their potential improvement of health care delivery.

1.2. OBJECTIVES

Due to the diverse application and new candidates as RSV radiopharmaceuticals entering the clinical field worldwide, this publication will present recommendations and suggestions on quality control and quality assurance procedures for Member States laboratories in charge of radiopharmaceutical production with a new look at the latest developed agents in RSV. It also provides proposed standard operation procedures for RSV application in patients. This publication aims to create an international standard for new comers in the field that need guidance, and for current ones to have an established and comparable levels of international regulations for successful practices.

Only limited companies worldwide produce these agents, where both the long-distance transportation (that is affected by the short shelf life of radiopharmaceuticals due to their half-lives), commercial availability and high prices have influenced some Member States to produce their own products according to their local capacities and regulations. This has presented a challenge for several reasons, including a lack of international guidelines on production and quality control, and lack of resources and personnel to meet RSV standards. It is important to emphasize proper care and attention of its production and administration, or there could be some negative consequences, such as radioactive leaks, secondary infection, inflammation, among others.

1.3.SCOPE

The purpose of this publication is to provide a general overview on:

- Evaluating appropriate patients for radiosynovectomy;
- Understanding the pathophysiology of underlying diseases causing synovitis;
- RSV's mechanism of action and appropriate utilized radiopharmaceuticals;
- Appropriate facilities needed to perform RSV;
- Preparing technical prerequisites and utensils for RSV;
- Pre-therapeutic imaging;
- Evaluating the indications and contraindications;
- Optimal preparation of the patients with informed consents about the procedure and the adverse effects;
- Intra-articular administration of radiopharmaceuticals;
- Post-radiosynovectomy procedures and instructions for patients;
- Follow-up of patients to monitor the treatment's effect; and
- Radiation protection.

1.4.STRUCTURE

This publication aims to help radiopharmaceutical production centres and nuclear medicine units for accessing knowledge to understand the background and standard operation procedures of production, quality control and clinical applications. The structure of the publication is divided in eight chapters, where the first one explains background, objective, scope and structure of the paper. The second chapter explains the definition and history of radiosynovectomy for treating synovitis and other five diseases that affect joints. The third chapter describes the conditions for the selection of patients to administrate RSV, including

required actions, indications, contraindications, and adverse effects. The fourth chapter specifies characteristics of radionuclides used in RSV, and the fifth chapter indicates production of radiopharmaceuticals using mentioned radioisotopes. The sixth chapter explains four used methods for preparing particles for RSV, including precipitation, emulsion, sol-gel process and spray drying. The seventh chapter goes into more detail regarding regulatory and manufacturing issues, especially with required quality assurance, quality control and documentation procedures. Finally, the eight chapter illustrates the implementing processes for operating RSVs, including consent forms' examples, diagnostic, facilities, patients' preparations, utensils, post-RSV procedures, among others. Hence, this publication aims to include the most relevant aspects for the production procedures and clinical uses of RSV radiopharmaceuticals.

2. RSV IN THE TREATMENT OF SYNOVITIS

2.1.DEFINITION

The original name 'radio-synovi-orthesis' reflects exactly the nature of this treatment and means 'restoration' of the synovial membrane with radiation. Radiosynovectomy or radiosynoviorthesis (RSV) is a minimally invasive local treatment with ionizing radiation that involves the coupling of a proper unsealed beta emitting radioisotope with a proper colloid applied intra-articularly to irradiate the inflamed synovial membrane.

The striking diffusion and exciting perspective of RSV are primarily attributed due to the following reasons [1, 3]:

- A local, alternative and minimally aggressive treatment option;
- Generally performed on an ambulatory basis and it involves overnight hospital stay;
- Useful for all joints including small and peripheral ones;
- Favourable benefit–cost ratio;
- Precludes the need for postoperative physical therapy to prevent and relieve joint stiffness associated with surgical synovectomy;
- Lack of surgical/anaesthetic risk;
- Provision of an alternative treatment choice for inoperable patients;
- Minimal length and intensity of recuperation period;
- Need of low radiation dose for effective outcome;
- Possible treatment of multiple joints concurrently on an ambulatory, by performing the procedure on an ambulatory basis;
- Provide the scope of repeating the procedure after 6 months in case of failure;
- Generally, it is more reliable and quicker at inactivating the synovium than chemical synovectomy;
- Minimum side effects; and
- Satisfactory control of synovitis.

2.2.HISTORY

The first concepts to irradiate the synovitis were reported by Ishido in animals in 1924 [4]. Fellingner & Schmid published the first treatments with radiation synovectomy in knee joints of patients with rheumatoid arthritis [5]. Nonetheless, in 1963 the first clinical study was performed to treat synovitis of knee in patients with rheumatoid arthritis with colloidal ^{198}Au [1, 6].

Today, ^{90}Y , ^{186}Re and ^{169}Er are the most preferred beta emitters radioisotopes in Europe [7], and have been used over 50 years for local treatment of refractory synovitis of non-respondent individual joints after long term systemic pharmacotherapy and intraarticular steroid injections [1, 8–18].

RSV is commonly recognized as a beneficial option to surgical synovectomy in treating rheumatoid arthritis and other inflammatory synoviopathies like osteoarthritis and haemophilic arthropathy [1, 3]. Ideally, it should be employed before radiological signs of joint destruction occur. However, it is unusual to have a referred patient in the clinic having not previously been treated by a general physician, orthopaedics or rheumatologist, and most patients have already had symptoms for many months, despite prolonged conservative treatment, multiple applications of intra-articular corticosteroid, and in many cases after prosthesis surgery. In other words, unfortunately RSV is considered by specialists of musculoskeletal diseases as the last shot option. On the other hand, the increasing demand for this procedure is also as a result of aging the population worldwide especially in EU countries [18].

2.3.SYNOVIAL JOINTS

Before delving any discussion about RSV, a brief discussion on synovial joints is relevant since the foundation of synovitis reside on it.

The skeletal system contains the following 6 different types of synovial joints [19]:

- (1) Plane or inter-tarsal joints are the joints of the tarsal bones in the foot which offers limited gliding movements. The most important intertarsal joints are the subtalar, the talocalcaneonavicular, and the calcaneocuboid;
- (2) Hinge (Elbow) is a joint between 2 bones such that allows movement along one axis only and provides movements along one axis for flexion or extension;
- (3) Pivot (C1 to C2 vertebral joint) allows rotary movement around a single axis and some bending;
- (4) Ellipsoid/Condyloid (Radius to carpal joint – wrist) is where the articular surface of one bone has an ovoid convexity sitting within an ellipsoidal cavity of the other bone which permits two planes of movement, and allows flexion, extension, adduction, abduction, and circumduction;
- (5) Saddle (base of the thumb) joint is where one of the bones forming the joint is shaped like a saddle with the other bone resting on it like a rider on a horse, which allows movement in the sagittal and frontal planes; and
- (6) Ball-and-socket (Hip) joint is where the ball shaped surface of one rounded-bone fits into the cup-like depression of another bone to allow rotary motion in every direction within certain limits, and it is the most mobile of the synovial joints.

Schematic representation of different types synovial joints is shown in Figure 1.

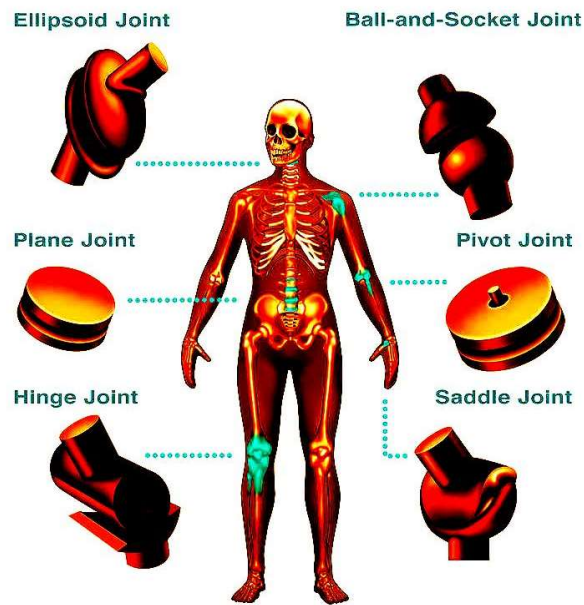


FIG. 1. Types of synovial joints¹

The internal structure of each of these joints, though vary in the number of ligaments, tendons, and other specialised attributes, are essentially the same. Each joint contains:

- An articular cartilage that allows smooth pain free movement of the bones with very little friction;
- A synovial membrane, which is a layer of connective tissue that lines the cavities of the joint and joint cavity, filled with synovial fluid to provide lubricant for the joint to move smoothly and pain free;
- Outside of their articulating surfaces, the bones are connected by ligaments made up of bundles of dense regular connective tissue that hold the 2 involved bones in the joint together, and help to restrict movement of that join;
- Although not part of the structure of a joint, muscle tendons are the next layer around joints and may have a bursa (pad for cushioning) at key points of friction in a joint, providing the joint with free movement. Bursa reduces friction by separating the adjacent structures and by preventing them from rubbing directly against each other;
- Some joints, such as the knee, also have a meniscus consisting of elastic collagen fibre tissue to offer a cushion within the joint. The meniscus is also responsible for shock absorption and joint lubrication and provides stability of the entire joint. It is normally found in joints that bear large loads, such as the knee.

A schematic representation of a synovial joint is shown below in Figure 2.

¹ Figure 1 available at <https://fineartamerica.com/featured/human-joint-replacements-illustration-gwen-shockey.html>

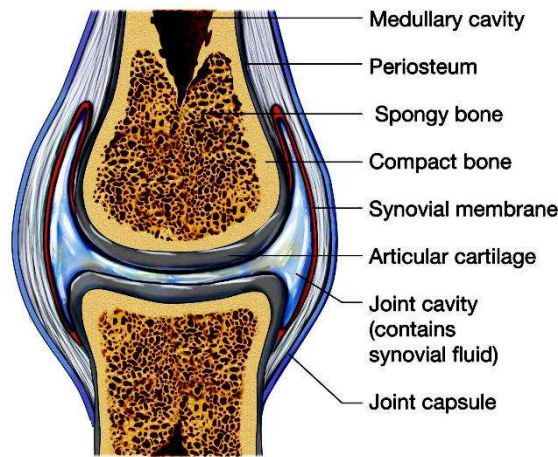


FIG. 2. Schematic of a synovial joint [19]

2.4.SYNOVITIS

The joint capsule consists of an outer fibrous membrane and an inner synovial membrane that produces synovial fluid, which lubricates the joint during movement and supply a vascular cartilage. The inner synovial membrane is essential for maintaining joint homeostasis [20]. The synovial membrane is a highly specialized, multifunctional structure consisting of intima, a thin (20 to 40 um) but highly cellular lining inner layer containing synovial fibroblasts and synovial macrophages [20, 21], and an outer subintima layer (5 mm), containing loose connective tissue with fibroblasts. It is a rich network of sympathetic and sensory nerves, where blood and lymphatic vasculature supply oxygen/nutrients and immune drainage [22].

Synovial fibroblasts provide the extracellular matrix that supports the structure of the synovium and secrete hyaluronic acid and lubricin into the synovial fluid [20, 21]. Synovial tissue macrophages are constitutively resident in healthy synovium. However, other immune cells such as lymphocytes, mast cells and dendritic cells are scarce in the normal synovium and localized mainly in perivascular areas of the subintima [23]. In patients with rheumatoid arthritis, the synovial membrane becomes hypertrophic due to synovial fibroblast proliferation, increased blood–lymphatic vasculature and an inflammatory influx of immune cells from the circulation resulting in the destruction of cartilage and bone, and pain and loss of joint function [24–26].

Histopathological analysis of synovium in patients with osteoarthritis (OA) reveals abundant inflammation in the majority of OA patients [27]. While traditionally considered primarily a disease of hyaline cartilage with associated bone involvement, caused by overload or overuse, the pathophysiology of OA development is now more complex. Mounting evidence suggests that synovitis and the resultant proinflammatory mediators are important in the pathogenesis of OA with effects on articular cartilage [28, 29]. Recently, synovitis is reported as a common feature of symptomatic and pre-radiographic OA criteria [30], indicating that chronic, early stage joint inflammation occurs well before significant radiographic changes.

In contrast, haemophilia is a bleeding disorder caused by a deficiency of clotting factor VIII [31]. Approximately 50% of patients suffer from severe haemophilia and bleeding, and

without suitable treatment, the condition can become into an irreversible haemarthropathy (HA) [32–36]. Bleeding in joint may result in iron-mediated synoviopathy and irreversible hemarthropathy. Experimental joint bleedings is reported to cause progressive degenerative joint damage [34, 36].

The prerequisite of RSV response is a homogenous distribution of radiopharmaceuticals in the joint cavity, phagocytosis, and holding of the radiopharmaceutical to gain the highest radiation dose to the synovialis by direct radiation or by a cross fire radiation effect [31]. Different colloid particle sizes have been suggested to be appropriate for RSV. Most studies in Europe, performed in patients with rheumatoid arthritis, have been done by using colloid size ranging between 2 and 10 μm based on the hypothesis that it needs to be small enough to be engulfed by phagocytes and large enough not to leakage rapidly from the joint [37]. In contrast, preferred particle sizes of colloids utilized to couple isotopes (in general ^{32}P) for RSV of haemophilia in USA by specialists, are approximately 10 times larger as compared to radiopharmaceuticals utilized in Europe.

2.5.RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic inflammatory autoimmune disease associated with multisystemic manifestations, characterized by persistent inflammatory synovitis of peripheral joints in symmetric distribution. It causes destruction of diarthrodial or synovial joints, increases levels of disability, reduces quality of life, and creates pain in patients [38–41]. In addition, RA patients display a variety of other clinical features, such as pain, morning stiffness, weakness, fatigue, fever, weight loss, and depression [20, 42, 43].

One of the most likely autoimmune diseases is rheumatoid arthritis [1]. Annual incidence of rheumatoid arthritis is estimated to be between 20 and 50 cases per 100 000 people in European countries [44]. Recent studies have suggested that more than 2 300 000 individuals are diagnosed with rheumatoid arthritis in Europe [45]. The prevalence of rheumatoid arthritis varies by population, with Europe yielding prevalence rates between 0.32% in France and 0.89% in the UK [46], and somewhat larger prevalence rates around 1% reported for the US [47]. Typically, females are affected approximately two to three times more often than males [47, 48]. Rheumatoid arthritis can occur at any age, but typically manifests between 40 and 70 years of age, with a peak of disease manifestation at 56 years of age in Germany [49].

Diagnosis is made by studying the patient's history and symptoms, and conducting joint exams, blood tests, and diagnostic imaging. However, gradual onset of clinical symptoms is common in rheumatoid arthritis, and often contributes to a delay in referral and diagnosis [50].

Local and systemic drug treatment, physiotherapy, and lifestyle changes are concerned as primary treatments. In case of persistent and refractory synovitis after non-invasive strategies, surgical, chemical, or radiation synovectomy may be an option.

There are three main groups of drugs used for the management of rheumatoid arthritis: painkillers including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying anti-rheumatic drugs (DMARDs) [51, 52]. Recent advances in rheumatoid arthritis therapies mainly target the mediators of inflammation (e.g., tumour necrosis factor (TNF), interleukin (IL-6R)), or block the adaptive immune response (e.g., T cell stimulation or B cell function). These treatments are expensive and must be taken continuously lifelong

with inadequate responses from 30% to 50% of cases [53, 54]. In addition, half of responders will relapse within months of treatment cessation [22, 53, 54].

From 1951, reduction of local pain by using chemical synovectomy with intraarticular injection of several chemicals, such as thiotepa and osmic acid, have shown small achievement rates [55–60]. In addition, massive haemorrhaging is reported after chemo-synovectomy with osmic acid in haemophilic patients with recurrent hemarthrosis [61]. In contrast, open and surgical synovectomy to remove inflamed synovial membrane is reported to be successful in 40% to 90% of treated patients, with a remission time between several months up to more than 10 years [62–68].

2.6. OSTEOARTHRITIS

Osteoarthritis (OA) is the most common form of arthritis and a leading cause of disability worldwide, largely due to pain, the primary symptom of the disease. The aetiology of pain in osteoarthritis is recognized to be multifactorial, with both intra-articular and extra-articular risk factors. Nonetheless, greater insights are needed into pain mechanisms in osteoarthritis to enable rational mechanism-based management of pain. Consequences of pain related to osteoarthritis contribute to a substantial socioeconomic burden.

People with OA typically experience joint pain, stiffness, and swelling in long term periods, resulting in progressive physical disability and pain. The aetiology of OA is multifactorial [69], with both systemic and local biomechanical factors identified [70]. In the hip and knee, OA often causes progressive joint damage with growing numbers requiring joint replacement surgery. Approximately 27 000 000 US adults and 8 500 000 UK adults are estimated to have clinical OA, based on symptoms and physical findings that accounts for 25% of visits to primary care physicians [71–73].

Symptomatic OA indicates the presence of both radiographic OA and symptoms (i.e., pain, aching, stiffness) in the same joint attributable to OA; as such, its prevalence is generally lower than that of radiographic OA. For example, the prevalence of radiographic knee OA is reported to be 19% and 28% among adults age ≥ 45 years in the Framingham study and Johnston County Osteoarthritis Project, respectively, while the prevalence of symptomatic knee OA was 7% in Framingham and 17% in the Johnston County Osteoarthritis Project [74, 75]. “The prevalence of symptomatic knee OA in two UK studies ranged from 11 to 19%, and estimates of 5 to 15%, were noted in surveys undertaken in other countries” [70, 76].

As a result of degenerative knee diseases approximately 25% of people over 45 years, experience pain and other symptoms that may be severe and negatively impact their quality of life [73, 77]. Total knee arthroplasty is the only definitive therapy available but is reserved for patients with severe diseases who fail conservative management. In the USA, arthroscopic knee surgery in people with degenerative knee disease is the most common ambulatory orthopaedic procedure, and it is the ninth most commonly performed ambulatory procedure overall [78, 79]. Such surgery results in transient increase in pain and the necessity for restriction in activities for a period of 2 to 12 weeks. Randomised clinical trials compared arthroscopic surgery with a conservative management strategy in patients with degenerative knee disease revealed no benefits of arthroscopy as compared to conservative management [80]. The review of 13 randomised clinical trials and 12 observational studies included in this analysis, identified high certainty evidence that knee arthroscopy results in a very small reduction in pain up to 3

months (mean difference =5.4 on a 100-point scale, 95% CI 2.0 to 8.8) and very small or no pain reduction up to 2 years (mean difference =3.1, 95% CI -0.2 to 6.4) when compared with conservative management [80]. With respect to function, the review identified with moderate certainty evidence that knee arthroscopy results in a very small improvement in the short term (mean difference=4.9 on a 100-point scale, 95% CI 1.5 to 8.4) and very small or no improved function up to 2 years (mean difference=3.2, 95% CI -0.5 to 6.8) [80]. Low quality evidence suggested a very low probability of serious complications after knee arthroscopy. Recently, an expert panel made a strong recommendation against the use of arthroscopy in nearly all patients with degenerative knee disease [81].

Modern diagnostic modalities have confirmed the role of synovitis as an active component of the OA process, associated with both pain and structural progression:

- Clinical hallmarks of painful synovitis in patients with osteoarthritis such as effusion and swelling of joint [29, 82, 83];
- Histologically observed synovial hypertrophy and hyperplasia [27, 84–88];
- Increased periarticular perfusion and blood pool detected by 3 phase bone scan and contrast enhanced hypertrophic synovial membrane visualized by MRI [31, 89–96];
- Production and release of pro-inflammatory cytokines; (TNF, IL-1Beta, IL-6, IL-8, IL-15, IL-17, IL-18, IL-21), and
- Response to anti-inflammatory therapy with intra-articular corticosteroids and RSV [1, 7, 97–103].

Thus, non-operative treatments directed at managing inflammation and future trials targeting the synovial tissue for treatment should consider these two factors as potential inclusion criteria [30].

2.7.HAEMOPHILIA

Haemophilia is the most common bleeding disorder. Haemophilia is an X chromosome linked disease caused by mutation of clotting factor genes resulting in a deficiency of clotting factors VIII (Haemophilia A) and IX (Haemophilia B)[104]. The most common complication and primary morbidity of haemophilia is the musculoskeletal bleeding, particularly in target joints [105]. Haemophilic patients, particularly those suffering from moderate to severe haemophilia have often a serious joint involvement. Such condition, called 'haemophilic arthropathy', is the result of a vicious circle that starts in the target joints as a response to the first episode of hemarthrosis, generally during childhood [106]. The presence of blood within the joint triggers the synovial tissue and induces a direct damage to the cartilage [107]. The result is a progressive and irreversible arthropathy, which early affects the bone, until the ultimate disabling and painful condition for the daily life activities of generally young subjects [108, 109]. Arthropathy mainly involves synovial joints, as elbows, ankles, and knees, and from a clinical point of view it may present differently according to the stage of the disease [110]. Inadequate replacement of factor VIII and IX, and lack of patient education of physician education regarding simple techniques (application of ice or ice packs, immobilisation of affected joints, use of slings), of physiotherapy, and of new therapy methods like radiation synovectomy, have contributed to the fact that more than 50% of these patients suffer from physical disability and crippling arthropathy [111].

Haemophilic arthropathy in one or more joints, mainly ankles, elbows and knees affect about 90% of people with haemophilia patients by 20 to 30 years of age. Recurrent bleedings into joints (hemarthroses) result in progressive proliferative and degenerative articular changes. To prevent these complications, regular factor replacement therapy with deficient protein from an early age is key to prevent synovitis and haemophilic arthropathy [112]. However, despite primary prophylaxis, some patients suffer from clinical bleeding due to an insufficient dosing regimen or non-adherence while others may experience subclinical joint bleeding. Although the pathogenesis of haemophilic arthropathy is not fully understood [113], it is generally assumed that primary prophylaxis prevents bleeding and haemophilic arthropathy [108, 114].

The diagnosis of haemophilic synovitis is usually made following examination of the knee with typical signs of joint swelling and warmth but with or without painful symptoms and reductions in motion of the knee [112]. Ultrasonography can be used to demonstrate hypertrophy of the synovium and the presence of fluid [115].

Chronic haemophilic synovitis and cartilage destruction are the main findings of haemophilic arthropathy, both phenomena due to severe or recurrent hemarthroses. Experimental studies have also demonstrated that after a major hemarthrosis the joint cavity is filled with a dense inflammatory infiltrate, and the tissues become brown-stained due to hemosiderin deposition following the breakdown of erythrocytes [116, 117]. Vascular hyperplasia takes place resulting in tenuous and friable vessels prone to bleed, creating a viscous cycle of bleeding-vascular hyperplasia-bleeding. The articular surface becomes rugose with pannus formation and the subchondral bone becomes dysmorphic. After about one month, cartilage and bone erosions are evident [112].

Loading of the affected joint with blood and blood break down products may play a role in the mechanism of cartilage degeneration in haemophilia, which was found in an experimental murine model that haemorrhage is induced by a controlled, and blunt trauma injury causes joint inflammation, synovitis and haemophilic arthropathy [118, 119]. Molecular changes induced by iron in the blood are reported to increase cell proliferation in the synovial membrane causing chronic inflammation of synovium.

The main therapeutic approach is to prevent articular damage which is achieved by controlling bleeding episodes, factor replacement and physiotherapy in the initial period. However, in cases with refractory chronic hemarthrosis, open surgical or arthroscopic options are used in addition to the non-surgical methods either by chemical or radioisotope agents [120]. Compared to surgical synovectomy, RSV is less invasive because it requires minimal factor replacement prior to the procedure and could be performed as an ambulatory procedure with a relatively lower cost [121–123]. The bleeding episodes and pain are significantly reduced following the radiosynovectomy, and improvement in range of motion is noted [124–128].

2.8. PIGMENTED VILLONODULAR SYNOVITIS

Pigmented villonodular synovitis is a rare benign joint disorder characterized by a slowly progressive proliferation of synovial tissue and deposit of intracellular hemosiderin [14, 129]. The peak age of affected patients is the second and fourth decade of life, and knee is the most frequently involved joint. Complete excision of the mass in the affected joint is the treatment of choice in the localized form. More common extensive diffuse cases are treated by total synovectomy; however, it is almost impossible to achieve complete remission. The main goal is to eradicate the synovial disease, while avoiding the need for joint replacement in this young patient population. RSV has been reported to be effective in reducing the rate of local recurrence without relevant joint destruction [130].

3. PATIENTS SELECTION FOR RSV

3.1. MECHANISM OF ACTION

“Radiosynoviorthesis (RSV) is a local selective treatment with intra-articular application of a proper unsealed β^- emitting radioisotope to irradiate a pathological synovial membrane that may be causing fibrosis and reducing joint effusion” [1, 31]. Nowadays, the radiopharmaceuticals used for this purpose in Europe are mainly [^{90}Y] Citrate (for the knee), [^{186}Re] Sulphide (for shoulder and ankles), [^{169}Er] Citrate (for interphalangeal joints), and [^{32}P] colloid (also for knee joints in many countries). The major indications are haemarthropathy in haemophilia, synovitis in rheumatoid arthritis, and exudative OA [131, 132].

After discovery of radioactivity by Henri Becquerel and Marie Curie, a number of radioisotopes, such as ^{131}I , ^{32}P , ^{90}Sr , and ^{90}Y have been used to treat various malignancies and pain management [133]. Since the first RSV performed by Fellingner using [^{198}Au] colloid, a large number of radioisotopes in different chemical forms have been utilized to find the ideal compound [5]. Today, RSV is developing rapidly as an alternative choice of treatment for synoviopathies with different underlying diseases. The low-invasiveness of this procedure and relatively low complications in comparison to conventional surgical synovectomy make RSV an attractive and realistic alternative in the management of patients with refractory joint inflammation.

The major physical characteristics for radionuclide therapy include the physical half-life, type of emissions, energy of the radiation, daughter product, method of production, and radionuclide purity [134–136]. The biochemical aspects of ideal radiopharmaceuticals include in-vivo stability, toxicity, target uptake, spatial and temporal distribution, retention, metabolism, clearance and excretion within the body [137, 138].

With a half-life ranging from 3 to 10 days, commercial available radiopharmaceuticals used for RSV (Table 1) can continuously irradiate the synovial membrane for several weeks [37]. High energy β^- emitters can cause ultimate damage to the absorbing cells of synovial membrane, resulting in ionization of the molecules inside the medium and generation of

secondary particles [1]. The generated free radicals result in biochemical effects evolving apoptosis and subsequent ablation by fibrosis and necrosis of inflamed synoviocytes in the synovial membrane [1, 139]. The Monte Carlo simulation has shown absorbed doses per unit activity of 0.01 to 2 Gy/MBq in the synovial membrane, resulting (depending on radionuclide and disease state) in an accumulated dose of up to 100 Gy [13, 17, 141]. This process inhibits the progression of synovitis and diminishes the serious exudative inflammation of the joint [141].

Autoradiography after intra-articular application reveal that colloid particles labelled with beta emitting isotopes are incorporated and rapidly phagocytized by macrophages located in the inflamed intima layer of synovial membrane [1, 142]. In synovial biopsies, colloidal particles are abundant in vacuolar cavities in the cytoplasm of the cells lining [143]. Utility of an appropriate radiopharmaceutical is essential to avoid a significant leakage of the isotope from the joint cavity. Thus, β emitting isotope for RSV should be coupled to a particle that is small enough to be phagocytised and large enough to avoid leakage from the joint before being phagocytized; the appropriate size range is usually considered to be from 2 to 10 microns phagocytised [144, 145]. Binding between radioisotopes and particles should be stable during the application of the RSV, which is determined by the physical and biological half-life of the radioisotope [1–3].

To achieve an optimal target/non-target ratio, the energy of the selected β^- radiation should be high enough to reach the whole depth of the inflamed synovial membrane without damaging the adjacent cartilage or the subchondral bone tissue, as well as the skin. Radiopharmaceuticals used in RSV have a very limited tissue penetration, depositing more than 90% of energy within maximal 11mm from the point of origin, thus affecting almost exclusively the joint cavity. Most of the radiation is absorbed by the synovium, synovial fluid, superficial layers of cartilage and articular capsule. Subchondral bone and other para-articular tissues receive negligible doses of radiation [146]. Appropriate energy for radiosynovectomy are provided by the commercially available radiocolloids (Table 1).

The mean and maximum penetration depths of β^- rays of ^{90}Y are 3.6 and 11 mm, respectively. The penetration depths of the β^- rays of ^{186}Re are 1.2 and 3.7 mm, and of ^{169}Er are only 0.3 and 1.0 mm. Because of these penetration rates, [^{90}Y] colloid is used for RSV of the knee, [^{186}Re] colloid for medium-sized joints such as shoulder, ankle, elbow, radio-carpal and hip joints, and [^{169}Er] colloid for finger and toe joints.

In the United States of America gold ^{198}Au , ^{32}P chromic phosphate, and ^{165}Dy ferric hydroxide macroaggregate are the most used radiopharmaceuticals [1]. Since these radiopharmaceuticals have disadvantages with respect to high lymphatic transport, they are no longer included in the guidelines of the European Association for Nuclear Medicine and the German Society of Nuclear Medicine [1, 61, 132, 148].

It is difficult to determine exactly the amount of activity of any radionuclide needed to achieve a therapeutic response. The absorbed dose is not only dependent on the type of radionuclide and the amount of activity used, but also on various other factors such as the type and size of the joint cavity, underlying pathophysiology of synovial membrane, synovial thickness, distribution of the colloids in the joint fluids, and the inflammatory activity of the joint. Approximately 100 Gy per 100 g of synovial tissue should be absorbed to have an optimal effect [1]. Standard available radiopharmaceuticals used in EU and USA are listed in Table 1.

RSV is usually performed as an outpatient procedure, no hospitality is needed, is minimal invasive as compared to surgical synovectomy. After 48 hours, moderate rehabilitation enables for daily activity.

TABLE 1: RADIONUCLIDES USED FOR JOINT PAIN TREATMENTS

(Radionuclides depicted in table 1 can be used for the treatment of joint pain arising from arthropathies, including RA, spondyloarthritis, other inflammatory joint diseases (lyme disease, behçet's disease), persistent synovial effusion, haemophilic arthritis, calcium pyrophosphate dihydrate arthritis, pigmented villonodular synovitis, and undifferentiated arthritis [1, 132, 148])

RADIONUCLIDE (particle)	VOI. (ml)	PARTICLES (μm)	HALF-LIFE (d)	β -MAX e (mev)	β -PARTICLE PENETRATION (mm)	GAMMA ENERGY (keV)	ACTIVITY (mBq)	JOINT
Yttrium-90 (Citrate)	<2	3-6	2.7	2.2	3.8-11	n.a	185-275	Knee
Re-186 (Colloid/Sulfide)	<1	5-10	3.7	1.07	1.2-3.7	140	110-185	Shoulder
Er-169 (Citrate)	<0.2	3-8	9.4	0.34	0.3-1.0	n.a	9-18,5	Proximal interphalangeal
P-32 (Chromic)	10	20	14	1.7	2.6-7.9	n.a	n.a	Knee
Dy-165 (FHMA)	n/a	3-10	0.09	1.3	1.4-5.6	95	n/a	Knee
Re-188 (Tin-colloid)	0.5	n.a.	0.7	2.12 / 1.96	11.0	155	370	Proximal Interphalangeal
Ho-166 (FHMA)	n/a	5-10	1.2	1.8	2.2-8.7	81	n/a	Knee
Sm-153 (particulate hydroxyapatite)	n/a	n/a	1.9	0.67 / 0.81	2.5	103	218-840	Knee
Au-198 (Colloid)	n/a	2.7	0.96	n/a	1.2-3.6	411	n/a	Knee
Lu-177 (particulate hydroxyapatite)	n/a	1.7	6.7	0.48	1.7	208	333 \pm 46	Elbow

Pd-109	-	-	0.56	1.03	0.42	n.a	-	No human report
Yb-175	-	-	4.2	0.47	n.a	396	-	No human report
Sn-177m	-	-	13.6	0.151	0.3	158.6	-	No human report

3.2.INDICATIONS

According to the guidelines for radiosynovectomy published by the German Society of Nuclear Medicine and European Association of Nuclear Medicine, the major indication for RSV are rheumatoid arthritis, spondylarthropathy (e.g. reactive or psoriatic arthritis), other inflammatory joint diseases, e.g. Lyme disease, Behcet's disease, persistent synovial effusion, haemophilic arthritis, calcium pyrophosphate dihydrate, arthritis pigmented villonodular synovitis, persistent effusion after joint prosthesis, and undifferentiated arthritis (where the arthritis is characterised by synovitis, synovial thickening or effusion) [149]. However, the common basic target among all the listed diseases making a patient eligible for RSV is synoviopathy, which is an inflammatory reaction of the synovial membrane. Indeed, RSV is not a systemic or specific treatment for any of the those specified and is not indicated as a first line of treatment. Thus, it can be concluded, that RSV is a local therapy option in patients with refractory synovial inflammation.

Irrespective of the underlying disease, the higher inflammation signs of synovitis and the lower the degeneration signs of arthrosis, the more successful RSV appears to be [150]. Thus, the best results of intra-articular radionuclide therapy can be achieved at an early stage of synoviopathy, when systemic anti-rheumatoid therapy appears to be insufficient.

Indications for RSV in patients with refractory synoviopathy [1]:

- (1) Haemarthropathy: haemophilia
- (2) Arthritis:
 - Rheumatoid arthritis;
 - Other accompanied inflammatory joint diseases, e.g. Lyme disease, Behcet's disease, psoriatic arthritis, ankylosing spondylitis;
- (3) Exudative synoviopathy:
 - Exudative osteoarthritis;
 - Postoperative effusion;
- (4) Villonodular synovitis

In addition, RSV is indicated in:

- (1) Relapsing synovitis after surgical synovitis;
- (2) Inoperable or multi-morbid patients with clinically relevant synovitis;
- (3) Patient's preference.

Indication should be performed with respect to age, affected joint, stage of disease to estimate ratio of target/nontarget (inflammation/degeneration) radiation, multi-morbidity, and lab status. Good understanding of the pathophysiology of the disease and interdisciplinary collaboration for decision-making is mandatory for individualized risk/benefit analysis and justification of treatment.

Ultrasound may be useful in case of RSV of shoulder joint because it provides information on abnormalities in and around the joint cavity such as presence and extension of effusion, rotator cuff rupture, bursitis subdeltoid, tenosynovitis, and enthesitis. The success rate for RSV of olecranon bursitis is reported between 50% and 80%, depending on the localization and the amount of inflammatory activity [151–153]. In patients with bursal disease, RSV should be attempted on the basis of an individual treatment trial. The β radiation is expected to affect the epithelium cells of the cysts, reducing effusion.

3.3. PATIENT'S PREFERENCE

Patient centeredness has become increasingly important in health care delivery and is justified on both humane [154, 155] and medical legal grounds [156]. Shared decision making is used when there is no clear 'right' or 'wrong' treatment, as it is in the case of equivocal or uncertain evidence of benefit [157]. Involved physician and patient are considered equal partners who go through the process of decision-making together, sharing information and preferences so that the patients are able to evaluate the trade-offs between the advantages and disadvantages of an alternative treatment [158, 159]. Thus, both jointly arrive at a consensus on treatment [160]. This is in contrast to other models, where decisions are made on behalf of only the clinician (paternalistic model) [161] or only the patient (autonomous model) [162]. Physicians involved in the treatment of patients with persistent synovitis, are committed to inform about alternative therapy options.

3.4. INDICATION FOR REPEATING RSV

In contrast to surgical 'synovectomy' with surgical removal of inflamed synovial membrane, 'radiosynoviorthese' aims to 'restore' the synovial membrane by irradiating the pathological superficial inflamed membrane. The protracted continuous irradiation of inflamed layers and restoration of the synovial-membrane after radiosynovectomy is reported to occur after a period of 6 to 8 weeks, and in some cases, it can be achieved up to 6 months after the treatment. To avoid any overtreatment, the results of RSV should be evaluated 3 to 6 months after the treatment. Fractionated RSV can be useful in cases with proliferating synovitis e.g. pigmented villonodular synovitis. However, a cumulative activity should not exceed 400 mCi for ^{90}Y .

Prompt response after RSV is less likely to be attributed to the radiation effect and is most likely resulted by co-injected corticosteroids and/or immobilisation of the joint, and usually for a short duration. In contrast, the following temporary increased sign of inflammation is due to radiation synovitis and does not indicate a non-response of RSV. Patients should be informed of RSV healing procedure to avoid over expectations after prompt healing, but short-term effect duration. Radiation induced synovitis needs generally no medication or local intervention and can be easily alleviated by a cooling pad.

In case of persistent radiation synovitis, treated joint should be checked for any complications. An emergency aspiration biopsy in case of severe acute synovitis with swelling of joint should

be preferably performed and documented by the responsible nuclear physician [131, 132, 163, 164].

3.5.CONTRAINDICATIONS

According to the Guidelines of Deutsche Gesellschaft Nuklearmedizin and the European Association of Nuclear Medicine, in several cases RSV is absolutely and/or relatively contraindicated; thus, any decision to perform RSV should be made with cautiousness. In case of suspicious bacterial infection in the joint and infection or skin diseases around the proposed injection site, RSV is absolutely contraindicated. Furthermore, in patients with highly advanced joint and bone destruction, and increased joint instability, radiation synovectomy is less likely to be successful. Also, lack of intra-articular retention may lead to lymphatic transport of the radiopharmaceutical, resulting in undesirable side effects.

In children and adolescents (patients younger than 20 years of age), benefits of the treatment are considered to be greater than a potential hazard resulting from RSV [1]. However, lack of calm attitude and non-compliance in children may result in leaking of the radiopharmaceutical from the joint after RSV. This may be the case in haemophilic patients and some patients with severe juvenile rheumatoid arthritis.

Indication for RSV in the presence of Baker's cyst is controversial. A Baker's cyst of the knee joint may be missed by clinical examination and would be ruptured due to radiation induced synovitis after RSV [165]. Thus, it is recommended to clarify the presence of Baker's cyst before performing RSV of the knee joint. The prevalence of a Baker cyst among 980 cases of knee joints treated with RSV –assessed by arthrosonography– has been reported to be 25% [166]. A prominent Baker's cyst should be aspirated by ultrasound guided puncture following instillation of corticosteroids prior to radiosynovectomy. There are reports on successful recovery from simultaneously presenting Baker's cysts after treatment of the knee joint [103]. However, direct puncture of popliteal cyst should be avoided in these cases. In general, there is no indication for RSV of Baker's cysts alone.

Absolute contraindications of RSV include [1]:

- Pregnancy
- Breast-feeding
- Ruptured Baker's cyst (knee)
- Local skin infection
- Massive hemarthrosis
- Joint infection
- Shoulder rotator cuff defect

Relative contraindications of RSV include [1]:

- Patients younger than 20 years of age;
- Evidence of significant cartilage loss;
- Joint instability with bone destruction;
- Bursal disease; and
- Post RSV joint immobility not warranted after RSV.

3.6. ADVERSE EFFECTS OF RSV

In case of properly joint puncture and impeccable intra-articular instillation of the radiopharmaceutical, side effects are rarely expected. Reactive radiation induced synovitis after RSV may cause transient increase of the swelling and pain within the first few days. These symptoms can be easily relieved by conventional measures and are reported to occur in up to 24% of patients treated with RSV [167]. However, other studies report on lower frequency of side effects, and some report no local adverse reactions. A needle tract burn, which is a radiation burn of the needle tract caused by back-flushing of the radioisotope is a rare adverse effect of RSV, sometimes resulting in a fistula [168].

Thrombosis and joint infection are two rare but serious adverse effects [169]. Extra-articular administration of radiopharmaceuticals leads to skin necrosis, especially by using ^{90}Y . It is considered as a serious side effect rarely occurring at an estimated rate of less than 1:1000 [170]. It can cause iatrogenic by extra-articular instillation or leakage of radiopharmaceutical during injection; it can be avoided by radiographic guided application of radiopharmaceutical.

Inappropriate application of higher activities or radioisotopes with higher energy (e.g. ^{90}Y for ankle joint) may also cause necrosis and is considered as a medical malpractice. The majority of post-therapeutic skin necrosis are, however, non-iatrogenic and caused by non-compliance of patients and premature mobilization of the treated joint. Quality of radiopharmaceuticals may also cause necrosis due to degradation and/or diffusion of the radiopharmaceutical from the joint. Post-RSV skin necrosis justifies special attention. Conservative treatment is highly recommended accompanied by patience. Surgical excision should be avoided since the radiogenic lesions reveal a delayed tendency of healing. Wait and watch is recommended until necrosis discards by itself; however, a secondary infection should be prevented using ointment.

The high incidence of radiation induced skin reactions in radiotherapy has generated interest in methods of preventing and effectively treating such reactions [171]. Nevertheless, no general accord has been achieved across radiotherapy centres about the treatment of radiation skin toxicities.

Causes of necrosis are:

(1) Directly related to the administration:

- Extra-articular instillation of radiopharmaceuticals;
- Leakage in injection channel by non-proper injection or by multiple insertion of needle by puncture;
- Higher activities than recommended; and
- Radioisotopes with higher energy for smaller joints (e.g. ^{90}Y instead of ^{186}Re for ankle-joint).

(2) Indirectly related to the administration:

- Non-compliance of patients and premature mobilization of the treated joint;
- Degradation of the radiopharmaceutical; and
- Extraarticular diffusion of the radiopharmaceutical.

Septic arthritis of knee is one of the known complications of intraarticular corticosteroid injection. The incidence of septic arthritis of knee after intraarticular corticosteroid injection ranges from one in 3 000 to one in 50 000, and may be higher in immune compromised patients [172]. In rheumatoid patients in long term immune-suppressive treatment, intraarticular injection raises from one in 2000 within 3 months [173]. Skin is the most common source of infection in rheumatoid patients, which accounts for 75% of infections.

The treatment of iatrogenic septic arthritis requires multiple joint washout and debridement, long term antibiotic therapy and prolonged inpatient hospital stay. A higher rate of infectious complications following intra-articular injection can be expected in immune compromised patients [174]. However, due to the extremely high local radiation dose of more than 100 Gy over the superficial layers of inflamed synovial membrane, a pyarthrosis is less likely to occur after RSV [175].

Lymph node swelling and pain can be the result of insufficient immobilisation and high extra-articular outflow of the beta emitter during the first 48 hours after RSV. For ^{186}Re an effective dose of 27 mSv was measured at an administered activity of 70 MBq. A total activity of 30 MBq ^{169}Er resulted in less than 1mSv effective dose [176].

Cytogenetic analyses after radiosynovectomy with ^{90}Y did not reveal any significant radiation doses for the peripheral lymphocytes in children having a high cancer risk [124]. The risk of malignancy remains theoretical but there has been no report on cancer induced by RSV. There are no indications on increased incidence of cancer after radiosynovectomy in the literature [169, 177]. Animal studies revealed no histological or genetical damage to cartilage [178]. The rate of chromosomal aberration before (0.25%) and after (0.41%) RSV with [^{90}Y] colloid was not different in a study published by Voth et al. and Vuorela et al. [167, 169], where it was observed no significant risk of cancer among 143 patients treated with [^{90}Y] colloid as compared to 1 085 patients in the control group.

In a German survey from 20 insurance companies, 28 cases with skin necrosis, 13 intra-articular infections and 12 thromboses were reported [179]. The frequency of thrombosis can be reduced by anticoagulation during the period of immobilization.

Late effects of normal application are still not fully determined. Experimental animal data shows some mild effects on morphologic changes of the cartilage, supported by in vitro cultured chondrocytes after exposure to ^{90}Y [180]. Changes of the cartilage after the ^{90}Y radiation could represent a factor predisposing the treated joint to a subsequent development of osteoarthritis. Long term clinical trials are needed to evaluate this issue.

In the lower limb joints, long time immobilization of joints may cause deep vein thrombosis [37]. Inflammatory joint and long-term corticosteroid treatment in patients with rheumatoid disease are risk factors for deep vein thrombosis. Thus, further anticoagulation therapy is strongly advised [181]. Post-RSV low molecular weight heparin for 3 to 5 days may be sufficient as prophylaxis. However, there are no guidelines for anticoagulation after RSV and any type duration of anticoagulation should be managed by the responsible nuclear medicine physician. It should be noted that in patients receiving oral anticoagulants, joint punctures do not increase the risk of bleeding and hemarthrosis [182]. RSV can be performed on an outpatient basis. The patient has to be informed about the RSV and the need for continuous treatment with DMARDs [37].

4. PRODUCTION OF RADIONUCLIDES REQUIRED FOR RSV

4.1. INTRODUCTION

Production of radionuclides is not only the first step in the preparation of therapeutic radiopharmaceuticals but also the cornerstone of the success as well as sustainable growth of radionuclide therapy [183]. The production of therapeutic radionuclides is carried out by the nuclear reactions either in a reactor or from charged particle bombardment in cyclotrons and accelerators. Depending on the production route, either no-carrier added (NCA) or carrier-added (CA) radionuclides are obtained. The reactor offers large volume for irradiation, simultaneous irradiation of several samples, economy of production and possibility to produce a wide variety of radioisotopes. The accelerator-produced isotopes relatively constitute a smaller percentage of total use. The accelerators are generally used to produce those isotopes which cannot be produced by reactor or which have unique properties.

4.2. TARGETRY

One of the important steps in the production of radionuclides is the preparation of reactor samples and/or accelerator targets, for irradiation. Targets used for neutron/charged particle activation constitute one of the most important steps in the production of a desired radionuclide. The selection of a target for reactor irradiation is based on number of considerations such as [111]:

- Cost effective availability of target material is essential to make the radionuclide more affordable;
- The target material should be sufficiently chemically pure;
- The chemical form of the targets should be such that it remains stable under irradiation conditions, resists any physical or chemical change during irradiation and enable easy post irradiation processing. Usually targets in metallic forms or oxides are preferred;
- Physical or chemical form of the target material should be such that it contains as much as possible of the target nuclide in unit volume;
- Possibility to handle the target material without any special precautions;
- Chemical form of the target material should be such that it contains those elements which will produce only negligibly small amounts of unwanted radionuclides, compared with the required nuclide during irradiation or generated radioactive impurities which can be easily removed from the product;
- Physical form of the target should be compatible for reactor/accelerator irradiation;
- The purity of the targets must be ensured to avoid the coproduction of unwanted radionuclides; and
- While the use of enriched target materials constitutes a positive step to augment the production yield as well as SA of radionuclide, the recycling of the enriched target is essential, wherever feasible, to make the radionuclide cost effective.

With a view to ensure safety of the reactor/accelerator, calculation of the reactivity effects, nuclear heating effects, radioactivity produced in the target is necessary [2]. These data are also helpful for the safe handling and transport of the irradiated materials [2]. For neutron irradiation, the most preferred targets are metals or inorganic salts usually oxide, carbonate,

nitrates, sulphates etc., but not halides. When the sample size for irradiation is large, one must pay attention to the self-shielding.

For accelerator production, considerable efforts are warranted while preparing the targets for charged particle irradiations. The chemical and mechanical design of the targets are crucial issues owing to the high rate of energy loss of charged particles in matter. In general, irradiation is performed in vacuum; thus, irradiation of liquids and gases targets are more involved but surmountable. The target materials used for accelerator production should possess favourable thermal properties such as high melting point or high boiling point and good heat transfer coefficients. It is necessary to provide a cooling system to dissipate the heat energy deposited in the target material during irradiation [184]. Additionally, the target used should have adequate corrosion and radiation resistance. Solids target in the form of thin foils or deposits on thin backing material of thickness ~ 0.1 - 5 mg/cm² is generally preferred, but depending on the rate of energy loss of the projectile passing through the target material [185]. Various methods have been developed for the preparation of accelerator targets including evaporation, vacuum deposition, electro spraying, electrodeposition and molecular plating [183].

4.2.1. ¹⁹⁸Au

The production route of ¹⁹⁸Au is primarily based on neutron irradiation of ¹⁹⁷Au targets by the ¹⁹⁷Au(n, γ)¹⁹⁸Au reaction [187]. This direct (n, γ) activation route offers the prospect of producing ¹⁹⁸Au of adequate SA owing to the very high thermal neutron capture cross section (26 500 barns). Use of gold foil or metallic gold bead target seemed to be sagacious due to their ability to remain stable under harsh irradiation conditions. The chemical processing of irradiation usually consists of dissolution of irradiated targets in aqua regia (3:1 HCl/HNO₃), followed by evaporation to near dryness and reconstitution with dilute HCl (normally 0.05M) to obtain H¹⁹⁸AuCl₄ in dilute HCl [187]. In order to reduce coproduction of ¹⁹⁹Au as a result of ¹⁹⁸Au(n, γ)¹⁹⁹Au reaction, short irradiation period is recommended. In light of the perceived need to remove trace radionuclide impurities, the prospect of extracting ¹⁹⁸AuCl₄⁻ into an organic solvent including chloroform, dichloromethane, or ethyl acetate as its tetrabutyl ammonium salt, TBA(AuCl₄) seemed to be an effective strategy [190, 191].

4.2.2. ¹⁶⁵Dy

¹⁶⁵Dy is produced by the nuclear reaction ¹⁶⁴Dy (n, γ) ¹⁶⁵Dy by irradiation of either Sm₂O₃ or Sm(NO₃)₃ targets in a nuclear reactor. Both natural or enriched ¹⁶⁴Dy are used. Thermal neutron radiative capture cross sections(σ_{th}) and epithermal neutron (σ_{epith}) values of ¹⁶⁴Dy(n, γ)¹⁶⁵Dy process are 2400 \pm 200 barn and 932 barn respectively [186, 187].

Naturally occurring dysprosium is composed of 7 stable isotopes, ¹⁵⁶Dy(0.056%), ¹⁵⁸Dy(0.095%), ¹⁶⁰Dy(2.329%), ¹⁶¹Dy(18.889%), ¹⁶²Dy(25.475%), ¹⁶³Dy(24.896%) and ¹⁶⁴Dy(28.260%), with ¹⁶⁴Dy being the most abundant. Neutron irradiation of natural dysprosium target as a result of (n, γ) nuclear reaction will produce radioactive isotopes such as ¹⁵⁷Dy(T_{1/2}=8.14 h), ¹⁵⁹Dy(T_{1/2}=144.4 d), ¹⁶⁵Dy(T_{1/2}=2.334 h), and ¹⁶⁶Dy(T_{1/2}=81.6 h). Owing to the low isotopic abundance of ¹⁵⁸Dy and relatively longer half-life of ¹⁵⁹Dy, production yield of ¹⁵⁹Dy is not significant. Additionally, both ¹⁵⁶Dy and ¹⁵⁹Dy decay by electron capture mode and will not pose any problem as far as radiation dose burden is concerned.

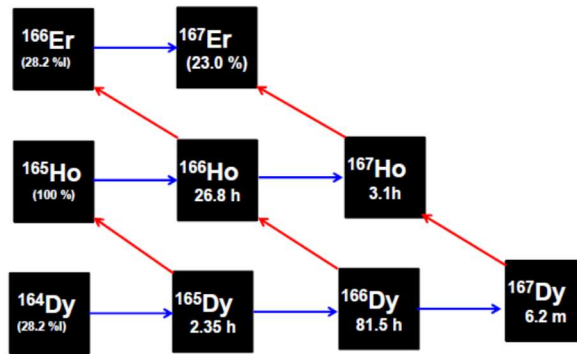


FIG. 3. Reactor production of ^{165}Dy [188]

Owing to the relatively high thermal ($\sigma_{\text{th}}=3600$ b) and epithermal ($\sigma_{\text{epith}}=22000$ b) neutron capture cross sections of $^{165}\text{Dy}(n,\gamma)^{166}\text{Dy}$ reaction, a significant amount of ^{166}Dy will be formed due to second neutron capture reaction [187]. Additionally, availability of efficient chemical separation methods to remove ^{166}Ho from macroscopic amounts of ^{166}Dy is desirable [187]. By judicious optimization of neutron irradiation parameters, it is possible to minimize concomitant production of ^{166}Dy .

4.2.3. ^{169}Er

The 9.4 d half-life of ^{169}Er is sufficiently long enough to offer easy transport to centers far off from a reactor site [3]. ^{169}Er could be produced by the nuclear reaction $^{168}\text{Er}(n,\gamma)^{169}\text{Er}$ by irradiation of ^{168}Er in a nuclear reactor. Isotopes of naturally occurring erbium consists of six stable isotopes: $^{162}\text{Er}(0.14\%)$, $^{164}\text{Er}(1.61\%)$, $^{166}\text{Er}(33.6\%)$, $^{167}\text{Er}(22.95\%)$, $^{168}\text{Er}(26.8\%)$ and $^{170}\text{Er}(14.9\%)$ [189]. Use of natural erbium target to produce ^{169}Er following direct (n, γ) activation results concomitant production of ^{165}Er and ^{171}Er . In this context, use of isotopically enriched ^{168}Er target is not only an interesting prospect, but also necessary to mitigate such disadvantages and thus pursued [187].

The low neutron capture cross section of ^{168}Er ($\sigma = 1.95$ barns) results in production of ^{169}Er of low SA which can be circumvented by target irradiation at higher possible flux [187]. Although the use of isotopically enriched ^{168}Er target is prolific to avail ^{169}Er of acceptable SA amenable for preparing RSV agents, concomitant production of ^{169}Yb ($t_{1/2} = 32$ d) due to the presence of ^{168}Yb impurity during the enrichment process of ^{168}Er , constitutes a roadblock and needs to be addressed suitably [187].

During the enrichment process of ^{168}Er , the level of ^{168}Yb in the target increases which on activation leads to concomitant production ^{169}Yb due to the very high thermal neutron capture cross-section (2300 b) of ^{168}Yb . ^{169}Yb with a half-life of 32.026 days decays by electron capture route (100%) followed by the emission of high abundance gamma photons [$E_{\gamma}= 177$ keV (22.5%), 197 keV (35.9%)] to stable ^{169}Tm . The gamma photons emitted by ^{169}Yb not only offer unnecessary dose to non-target organs, but also affects the dosimetric evaluation of the administered activity. Moreover, measurement of activity of ^{169}Er following gamma spectrometry is a problem as its lone low abundant gamma photon (110.5 keV) gets masked off by the same energy gamma peak emitted by ^{169}Er of much higher abundance (14%).

Therefore, complete removal of ^{169}Yb prior to radiolabelling does not only constitute a necessity but also a major determinant for its utilization in RSV. It has been developed and demonstrated a viable method for the reactor production of ^{169}Er with acceptable SA following electrochemical pathway. It is based on mercury-pool cathode to avail ^{169}Er in radionuclidically pure form amenable for radionuclide therapy [189].

4.2.4. ^{166}Ho

Production of ^{166}Ho can be carried out by a relatively easy route involving thermal neutron irradiation of ^{165}Ho using natural Ho_2O_3 (100% ^{165}Ho) target in research reactors. It precludes the use of enriched target and obviate the formation of radionuclide impurities by radiative capture during neutron activation. The high thermal neutron capture cross section of ^{165}Ho ($\sigma=66$ b) offers the scope for the production of ^{166}Ho of adequate quantity and sufficient SA [3] amenable for use in radiosynovectomy [190, 192, 193]. Dependency of neutron flux in the production of ^{166}Ho is shown in Figure 4.

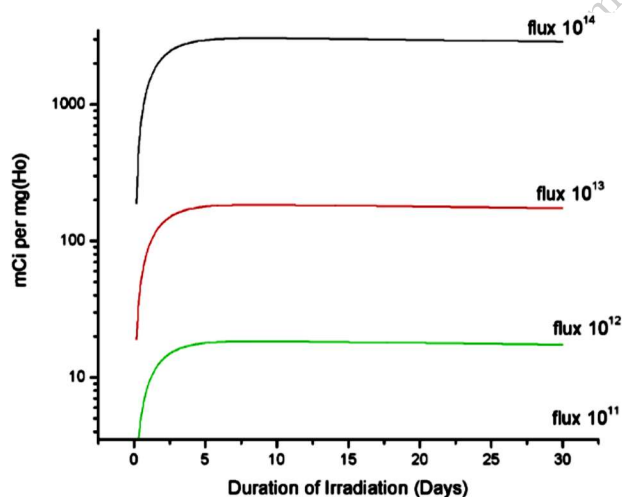


FIG. 4. Variation of production yield of ^{166}Ho at different neutron flux [188]

A method has been reported for the production of high SA ^{166}Ho exploiting hot atom reactions by neutron irradiation of organometallic compounds tris (cyclopentadienyl) holmium $(\text{C}_5\text{H}_5)_3\text{Ho}$. A chemical separation method was developed to separate the recoil ^{166}Ho from the irradiated compound [194].

Production of NCA ^{166}Ho can be carried out following an alternative path. In this mode, ^{166}Dy can be produced following $^{164}\text{Dy}(2n,\gamma)^{166}\text{Dy}$ reaction using isotopically enriched ^{164}Dy target which then decays by β^- emission to yield ^{166}Ho [187]. While this indirect production route offers the potential to provide ^{166}Ho of the highest possible, the requirement of an elaborate radiochemical separation as well as purification procedure for the effective separation of micro amounts of ^{166}Ho from macro amounts of the irradiated Dy target is challenging. Owing to the relatively high thermal ($\sigma_{\text{th}}=2731$ b) and epithermal ($\sigma_{\text{epith}}=932$ b) neutron capture cross sections of $^{164}\text{Dy}(n,\gamma)^{165}\text{Dy}$ reaction, a significant amount of ^{165}Dy ($T_{1/2}=2.33\text{h}$) will be formed. The relatively short half-life of ^{165}Dy is not an impediment owing to the high thermal ($\sigma_{\text{th}}=3600$ b) and epithermal ($\sigma_{\text{epith}}=22000$ b) neutron capture cross sections of $^{165}\text{Dy}(n,\gamma)^{166}\text{Dy}$ reaction

[187]. It was possible to produce close to the theoretical yield of 1.2 Ci of ^{166}Dy when 1 mg of enriched ^{164}Dy was irradiated over 155 hours at a thermal flux of 4×10^{14} neutrons $\text{cm}^{-2} \text{s}^{-1}$ and an epithermal flux of 1.6×10^{13} neutrons $\text{cm}^{-2} \text{s}^{-1}$ at the the University of Missouri Research Reactor (MURR[®]) [195].

The applicability of reversed phase ion-exchange chromatographic methods for the separation of carrier-free ^{166}Ho from milligram quantities of $^{164}\text{Dy}_2\text{O}_3$ irradiated targets has been reported using a metal-free HPLC system with Dowex AG 50WX12 or Aminex-A5 cation exchangers and α -hydroxy-isobutyric acid (α -HIBA) as the eluent (0.085 M, pH = 4.3 adjusted with NH_4OH). The Aminex-A5 column gave a separation factor of $\sim 10^3$ between Ho and Dy. Subsequent to the acidic destruction of the Ho-HIBA complex, Ho^{3+} was further purified on a small cation-exchange column from acidic chloride solutions [196]. Similar high performance liquid chromatography (HPLC) radiochemical separation method has also been reported of using Aminex A7 ion exchanger resin and α -HIBA as the mobile phase [197].

4.2.5. ^{177}Lu

Both the ‘direct’ and ‘indirect’ reactor production routes are used to produce high SA ^{177}Lu [198]. The direct production route is based on neutron activation of highly enriched ^{176}Lu targets following the $^{176}\text{Lu} (n,\gamma) ^{177}\text{Lu}$ reaction. The indirect production route consists of irradiation of enriched ^{176}Yb targets to produce ^{177}Yb followed by β^- decay to produce NCA ^{177}Lu ($^{176}\text{Yb}(n,\gamma)^{177}\text{Yb} \rightarrow ^{177}\text{Lu}$) [199, 200].

The radiochemical processing of neutron irradiated targets in the direct production route is facile as a target dissolution where gentle warming is needed to diluate mineral acid. On the other hand, target processing of indirect production route requires an elaborate radiochemical separation as well as purification procedure to separate ^{177}Lu from ytterbium [2]. The direct and indirect production route of ^{177}Lu is shown in Figure 5.

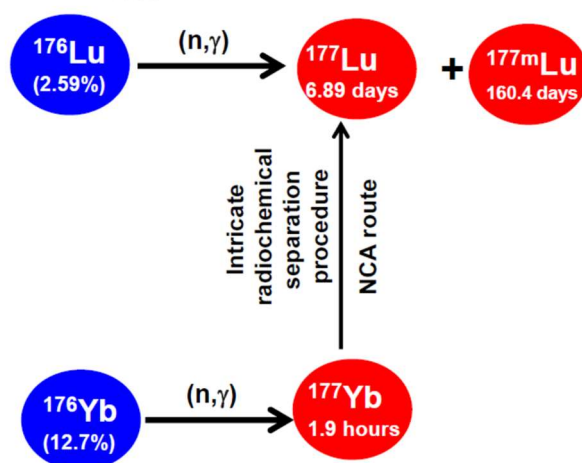


FIG. 5. Two different production route of ^{177}Lu ²

² Original figure available at DASH, A., PILLAI, M.R.A., KNAPP, F.F., Production of ^{177}Lu for Targeted Radionuclide Therapy: Available Options, Nuclear Medicine Molecular Imaging 49 2 (2015) 85.

Advantages of direct production route include simple irradiated target processing procedure, flexibility to tune the production scale without sacrificing efficiency and cost effective route to obtain ^{177}Lu of requisite purity. The necessity to use enriched ^{176}Lu targets due to the 2.6% abundance of natural ^{176}Lu in the unenriched targets, limits the concomitant production of $^{177\text{m}}\text{Lu}$. The presence of $^{177\text{m}}\text{Lu}$ raised concern on radiation protection and waste disposal problems by some countries [198]. Schematic diagram for the processing of neutron irradiated ^{176}Lu target to avail ^{177}Lu is depicted in Figure 6.

The surge of interest in the use of ^{177}Lu for a variety of therapeutic applications lead to the widespread use of (n, γ) method of ^{177}Lu production strategies [201–209].

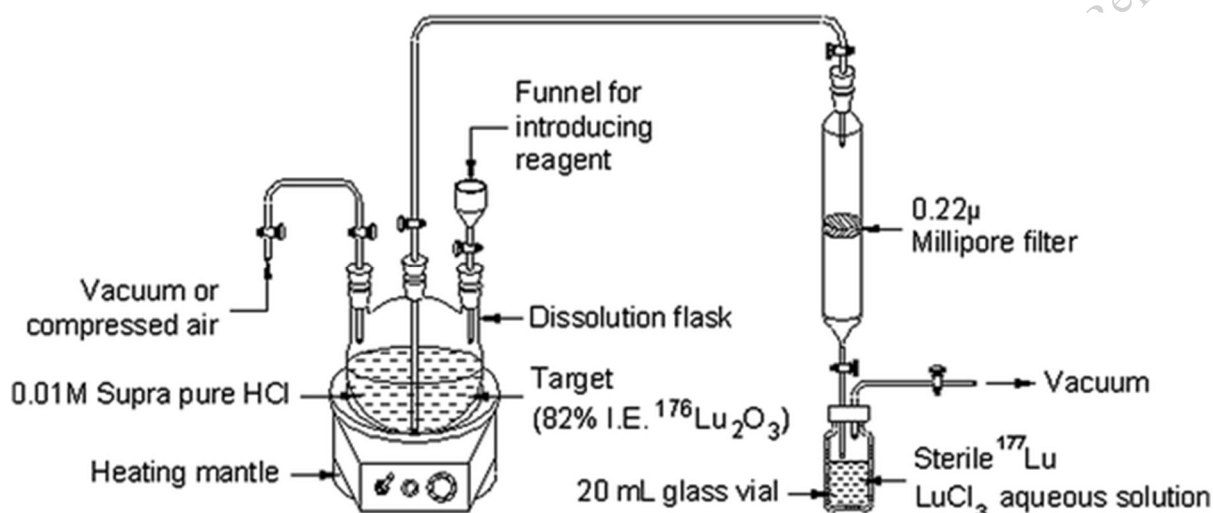


FIG. 6. Processing of neutron irradiated target for ^{177}Lu production³

The indirect production route provide that the prospect of availing ^{177}Lu highest SA free from long-lived radioactive impurities and neutron flux is not a determinant factor for SA [187]. The inherent limitations of indirect production route include: low production yields owing to the reduced ^{176}Yb reaction cross section ($\sigma_{\text{th}}=2.5$ b) barn) as compared to the ‘direct’ production route ($\sigma_{\text{th}}=2090$ b); it elaborates radiochemical separation and purification procedure; and it produces substantial amount of radioactive waste [187]. It is the most expensive method of producing ^{177}Lu of acceptable purity. The surge of interest to obtain NCA ^{177}Lu led to the development of myriad of radiochemical separation procedures by several groups [210–217]. Owing to their chemical similarity, separation of two neighboring elements in the lanthanide group is not only challenging, but also demanding [2, 187]. In light of the perceived need to separate microscopic amounts of ^{177}Lu from macroscopic amounts of ytterbium, every conceivable radiochemical separation strategy including ion-exchange chromatography, solvent extraction, supported liquid membrane extraction, extraction chromatography and electrochemical method have been exploited [196, 210–219].

³ Figure available at CHAKRABORTY, S., VIMALNATH, K.V., LOHAR, S.P., SHETTY, P., DASH, A., On the practical aspects of large-scale production of ^{177}Lu for peptide receptor radionuclide therapy using direct neutron activation of ^{176}Lu in a medium flux research reactor: The Indian experience, Journal of Radioanalytical and Nuclear Chemistry. **302** 1 (2014) 233.

4.2.6. ^{32}P

Production of ^{32}P in a reactor could be carried out following three routes, including $^{31}\text{P}(n,\gamma)^{32}\text{P}$, $^{32}\text{S}(n,p)^{32}\text{P}$ and $^{36}\text{Cl}(n,\alpha)^{32}\text{P}$. In practice, $^{35}\text{Cl}(n,\alpha)^{32}\text{P}$ production method is not practiced due to low production yield. The remaining two options are widely used for the large scale production of ^{32}P in a cost effective manner [221–229].

The neutron activation route of ^{32}P production following the $^{31}\text{P}(n,\gamma)^{32}\text{P}$ ($\sigma = 172$ mb) nuclear reaction is less demanding, uses low-cost natural elemental phosphorus (^{31}P) target material and involves simple irradiated target processing procedure [187]. A thorough optimization of irradiation parameters and careful consideration of the target is essential to obtain ^{32}P of required SA and yield [2, 198]. ^{32}P produced through this route is of low SA due to the low thermal neutron capture cross section. Owing to the small thermal neutron capture cross section of ^{32}P for $^{32}\text{P}(n,\gamma)^{33}\text{P}$, the concomitant ^{33}P production during target irradiation is insignificant. The indirect production route using $^{32}\text{S}(n,p)^{32}\text{P}$ nuclear reaction offers the scope of producing no carrier added ^{32}P . However, the low reaction cross-section (0.068b) and necessity to use fast neutron flux to produce appreciable active amounts, constitute the major road block for its widespread use. In order to produce few hundred MBq of ^{32}P following this route, several hundred grams of sulphur is needed to be irradiated. Even though the cross section values for the $^{32}\text{S}(n,p)^{32}\text{P}$ nuclear reaction are much lower than for the $^{31}\text{P}(n,\gamma)^{32}\text{P}$ route, this method of production holds significant promise owing to the ability to offer ^{32}P of higher possible specific activities [229]. Both, the wet chemical extraction and dry distillation methods of radiochemical processing procedures can be followed to separate and purify ^{32}P from neutron irradiated S [224, 230–232]. The apparatus used to perform distillation generally entails a vacuum system, gas-feeding apparatus and distillation assembly [226] and an appropriate optimal strategy to control pressure and temperature [224–232].

4.2.7. ^{186}Re

Both reactor and accelerator paths could produce ^{186}Re . In a research reactor, ^{186}Re is produced by direct neutron activation of metallic enriched ^{185}Re following the $^{185}\text{Re}(n,\gamma)^{186}\text{Re}$ nuclear reaction [2]. The radiochemical processing consists of dissolution of irradiated target in 5 to 6 M HNO_3 , evaporation of solution to incipient dryness and addition of water to the reaction mixture. In order to ensure complete elimination of HNO_3 thoroughly, the addition of water and evaporation process is recommended to repeat 4 to 5 times and finally ^{186}Re is taken-up in water. This is the simplest way to obtain ^{186}Re of required specific activities (SA) suitable for RSV, owing to the simplicity of dissolving target in dilute mineral acid on gentle warming and due to its extensive use [233, 234]. Due to the relatively large nuclear reaction cross section (106 barn), the yield of ^{186}Re is high and the SA is moderate. The SA as well as production yield of ^{186}Re is usually higher than the calculated one owing to the high epithermal neutron cross-section for ^{185}Re (1632 barn), which usually depends on the neutron energy spectrum of the reactor.

In a typical process reported by Deutsch et al [10], enriched (85.84%) ^{185}Re metal (1-2 mg) in a quartz vial was irradiated in a flux 10^{14} of neutrons $\text{cm}^{-2} \text{s}^{-1}$ at the University of Missouri's research reactor for 24 hours. The rhenium metal was then dissolved in concentrated nitric acid, the resulting solution was neutralized with ammonia and then diluted to obtain Re concentration of about 0.004M [235]. The radioactive concentration of the resulting solution

became 30mCi/mL. About 0.5mL of 0.1M tetrabutyl ammonium bromide (0.05 mmol) were added to aliquots (0.5-1.0mL) of this solution and passed through a Sep-Pak C₁₈ cartridge (Waters) that had been prepared by successive washings with three mL of 95% ethanol and three mL of 0.01M tetrabutyl ammonium bromide. The cartridge was washed with 20mL of water to remove aqueous soluble impurities added during the dissolution of irradiated target and ¹⁸⁶Re activity was eluted with a 99% yield with 2mL of absolute ethanol [236]. The SA of ¹⁸⁶Re is produced by using a reactor such as the Missouri University Research Reactor, MURR, with a thermal neutron flux 4.5×10^{14} n/cm² s, and it is about 3 Ci/mg Re.

With a view to produce higher SA ¹⁸⁶Re, the Szilard-Chalmers process using ReN(S₂CNET₂)₂ rhenium (V) nitride complex as target has also been tried [237]. The chemical and/or physical changes to Re that result from a neutron capture reaction are exploited advantageously. The ~6 MeV of excitation gamma energy emitted by the rhenium nucleus after thermal neutron capture nuclear reaction (i.e., recoil energy) ruptures the organometallic bonds. In this method, neutron irradiated rhenium compound was dissolved in dichloromethane solution and the recoiled ¹⁸⁶Re rhenium was isolated from the irradiated rhenium compound by stripping with an aqueous solution. Using this method, it was possible to avail ¹⁸⁶Re with a SA of 0.72 GBq/mg Re (19.5 mCi/mg Re). On a similar theme, investigators at the Missouri University Research Reactor (MURR) used a target consisting of thin-film and powdered ¹⁸⁵Re in the form of metal or oxide in which rhenium is present in a lower oxidation state [238]. Target irradiation was performed in the presence of an oxidizing medium sufficient to form ¹⁸⁶ReO₄⁻. Radiochemical processing of irradiated target consists of dissolution of target in a non-oxidizing solvent such as water or saline [237]. While the use of Szilard-Chalmers process is a step forward to obtain high SA ¹⁸⁶Re, time consuming radiochemical processing procedure, requirement of extensive handling and processing of irradiated materials, generation of unwanted by-products required to be separated from the perrhenate and the low production yields are the major road block that limits its wide scale use.

By taking into account the high SA production of ¹⁸⁶Re, accelerator routes had be explored succeeding ¹⁸⁶W(p,n)¹⁸⁶Re and ¹⁸⁶W(d,2n)¹⁸⁶Re reactions [239–242]. Among the two nuclear reactions, ¹⁸⁶W(p,n)¹⁸⁶Re route is not commonly followed due to the poor reaction cross section. In this context, the prospect of following ¹⁸⁶W(d,2n)¹⁸⁶Re reaction route is sagacious because of larger cross section [198, 239]. Post irradiation radiochemical processing is carried out by dissolving the target in a mixture of 30% H₂O₂ and 1 M NaOH followed by gentle heating. Recovery and recycle of expensive non-activated enriched ¹⁸⁶W target material constitutes a necessity for the cost effective production of ¹⁸⁸W [2, 198].

4.2.8. ¹⁸⁸Re

Radionuclidically pure ¹⁸⁸Re can be prepared by irradiating highly enriched ¹⁸⁷Re target in research reactors. The corresponding nuclear reaction cross section is 72 barns. While the (n,γ) method of production using enriched ¹⁸⁷Re target leads to carrier added (CA) ¹⁸⁸Re, the SA is adequate for: the preparation of radiopharmaceuticals useful for RSV; radiochemical processing of irradiated rhenium metal consisting of the target dissolution with concentrated nitric acid; and, neutralization of the resulting solution with ammonia followed by the treatment of the neutralized solution containing solubilized perrhenate with a soluble lipophilic counter ion, such as a solution of tetrabutyl ammonium bromide. The resulting solution is then passed through a Sep-Pak C₁₈ cartridge loaded with the lipophilic counter ion to retain both aqueous soluble impurities as well as ¹⁸⁸Re [243]. The aqueous soluble impurities from the Sep-Pak

C₁₈ cartridge is eluted with water and subsequently the perrhenate or pertechnetate compound can be eluted from the column with a less polar solvent such as ethanol [236]. While the (n,γ) method of production using enriched ¹⁸⁷Re target is prolific to avail ¹⁸⁸Re, the relatively short 16.9 h physical half-life of ¹⁸⁸Re emerged as a shortcoming for transport to sites away from the production site due to decay loss [198].

In view of this, use of ¹⁸⁸W/¹⁸⁸Re generator prolific to avail ¹⁸⁸Re may be viewed as a practical proposition. ¹⁸⁸W can only be produced by double neutron capture with low neutron absorption cross-sections [¹⁸⁶W(n,γ)¹⁸⁷W (σ=37.9±0.6 b); ¹⁸⁷W(n,γ)¹⁸⁸W (σ=64±10 b)], using enriched ¹⁸⁶W target. Since cross sections have relatively low values (~10⁻²⁴ cm²), the production yields are low even when very high flux research reactors are used [244]. Similarly, the neutron flux is very important as the production yield is a function of the square of the flux (φ). Increasing the flux by only one order will make two order higher amounts of ¹⁸⁸W activity. Hence, reactors having flux of >5x10¹⁴ n.cm⁻².sec⁻¹ are only suitable for the production of ¹⁸⁸W.

The natural abundance of ¹⁸⁶W is 28.6% and enriched targets are essential for the production of ¹⁸⁸W sufficient for generator use. By using enriched ¹⁸⁶W targets, the SA of ¹⁸⁸W is correspondingly augmented. Owing to the long half-life of ¹⁸⁸W, relatively long irradiation periods are required even for the production of ¹⁸⁸W of modest SA using high flux reactor [245]. A SA of up to 185 GBq (5 Ci)/g can be obtained by using enriched targets and following an irradiation cycle of about 20-24 days at 10¹⁵ n.cm⁻².sec⁻¹. The current status of reactor production and processing of ¹⁸⁸W is summarized in a chapter of a recent book published by the International Atomic Energy Agency [246]. As per this publication, for ¹⁸⁸W to have adequate SA suitable for the production of ¹⁸⁸W/¹⁸⁸Re generators, it can only be accomplished in a limited number of research reactors i.e. SM Reactor RIAR in Dmitrovgrad, Russian Federation; ORNL HFIR in USA and BR2 reactor in Belgium. Enriched ¹⁸⁶W in metal as well as oxide form is used for irradiation. At ORNL, 97% enriched ¹⁸⁶W as the oxide sealed in quartz tubes enclosed in aluminium capsules is irradiated for one or two cycles of 23-24 days each at a neutron flux of about 2.5×10¹⁵ n.cm⁻².s⁻¹ [247]. The production yields are substantially lower than the calculated values using reported cross sections for different reactions taking place during irradiation. The loss of ¹⁸⁸W due to neutron burn-up, ¹⁸⁸W(n, γ)¹⁸⁹W (σ= 12 barn), is one of the factors contributing to reduce production yields of ¹⁸⁸W [248]. The sodium tungstate solution required for subsequent treatment for generator loading is produced by dissolving tungsten oxide in sodium hydroxide solution with moderate heating [183].

Extensive efforts by investigators at the Oak Ridge National Laboratory (ORNL) in the mid-eighties have culminated in the emergence of a ¹⁸⁸W/¹⁸⁸Re generator system consisting of acidic alumina matrix analogous to the widely used of ⁹⁹Mo/^{99m}Tc generator [249–253]. Owing to the limited sorption capacity of alumina (maximum 50 mg W/g)[252], ¹⁸⁸Re availed from alumina based ¹⁸⁸W/¹⁸⁸Re generators is of low radioactivity concentration, if low SA ¹⁸⁸W is used. This in turn would require post-elution concentration of the ¹⁸⁸Re eluate [254–260]. The incredible prospects associated with the use of ¹⁸⁸Re availed form radionuclide generator have been directed to the development of automated systems for the concentration of ¹⁸⁸Re eluate [261, 262]. Over the years, different approaches such as gel generator, electrochemical generator, thermo-chromatographic generator, chromatographic generator with high capacity adsorbents and nanomaterial based adsorbents have been explored, which in turn has opened the prospect of using ¹⁸⁸Re for RSV.

4.2.9. ^{153}Sm

^{153}Sm is produced by the nuclear reaction $^{152}\text{Sm}(n,\gamma)^{153}\text{Sm}$ by irradiation of either Sm_2O_3 or $\text{Sm}(\text{NO}_3)_3$ targets in a nuclear reactor. Both natural samarium or enriched ^{152}Sm are used. Natural target will give long lived radionuclide impurities such as ^{145}Sm ($T_{1/2} = 345$ days), ^{151}Sm ($T_{1/2} = 90$ years) and ^{155}Eu ($T_{1/2} = 4.76$ years).

Chemical processing of neutron irradiated target is simple, concise and technically less challenging as it is possible to dissolve the target in dilute hydrochloric acid on gentle warming [198]. Due to the large thermal neutron capture cross-section of $^{152}\text{Sm}(n,\gamma)^{153}\text{Sm}$ reaction (206 barns), ^{153}Sm can be produced in large quantities and with a SA of 222 GBq/mg (6 Ci/mg) when irradiated at a flux of $1.2 \times 10^{14} \text{ N cm}^{-2} \text{ s}^{-1}$ for approximately 155 hours [111].

While the use of natural samarium as the target for the production of ^{153}Sm provide SA lower than enriched ^{152}Sm target, it is adequate for the preparation of radiopharmaceuticals for synovectomy [198]. Neutron irradiation of natural samarium target results concomitant production of long-lived radionuclide impurities such as ^{145}Sm ($T_{1/2} = 345$ days), ^{151}Sm ($T_{1/2} = 90$ years) and ^{155}Eu ($T_{1/2} = 4.76$ years) [187, 263]. ^{155}Eu could be separated from ^{145}Sm , ^{151}Sm and ^{153}Sm following ion-exchange chromatography technique [264]. The radionuclide impurity burden could be effectively reduced by optimization of irradiation parameters such as irradiation time and neutron flux. Its burden (^{145}Sm and ^{151}Sm) will not be too high to preclude its use for RSV [263].

4.2.10. $^{117\text{m}}\text{Sn}$

$^{117\text{m}}\text{Sn}$ was prepared at optimized conditions in research reactors to achieve the maximum SA (~20 Ci/g). However, later produced $^{117\text{m}}\text{Sn}$ with a SA of ~1,000 Ci/g were thereby allowed for the essential step of labelling targeting molecules used to treat a variety of life-threatening diseases.

4.2.11. ^{90}Y

^{90}Y can be directly produced by neutron activation of ^{89}Y in a nuclear reactor. As ^{89}Y is mononuclidic, there is no need for enriched isotopes for irradiation. The radionuclide purity of this directly (n,γ) activated product is generally very high. However, depending on the epithermal flux in the reactor, detectable levels of ^{89}Sr could be present owing to the (n,p) reaction. Due to the poor neutron absorption cross-section ($\sigma_{\text{th}}=0.001$ b) of $^{89}\text{Y}(n,\gamma)^{90}\text{Y}$ reaction, ^{90}Y availed following the (n,γ) production route is of low SA [265]. ^{90}Y of moderate SA can only be produced by irradiation of the target in high flux reactors.

Reactor production route of NCA ^{90}Y is possible by following the $^{90}\text{Zr}(n,p)^{90}\text{Y}$ reaction which requires 100% enriched ^{90}Zr target as well as fast neutron flux of $\sim 7.5 \times 10^{13} \text{ cm}^{-2} \text{ s}^{-1}$ [266]. While it is possible to produce NCA ^{90}Y pursuing this route, accessibility of expensive enriched ^{90}Zr on a sustainable basis makes it difficult: the need for fast neutron flux; challenges associated with target design; isolation of microscopic amount of ^{90}Y from macroscopic amount of ^{90}Zr ; and recovery of expensive ^{90}Zr target for recycling need to be addressed. Additionally, it is possible to produce limited quantities of NCA ^{90}Y following this route.

In this context, accessing large amounts of NCA ^{90}Y form from $^{90}\text{Sr}/^{90}\text{Y}$ generator seemed sagacious [2]. Being one of the major fission products of ^{235}U with fission yield of 5.93%, ^{90}Sr is abundantly available in high level waste (HLW) solutions and could be separated from other constituents of HLW by using suitable radiochemical separation methods [267–275]. ^{90}Sr used for making $^{90}\text{Sr}/^{90}\text{Y}$ generator for clinical applications should be of adequate purity and thus warranted intensive and stringent the quality control measures [2].

The separation of NCA ^{90}Y from ^{90}Sr for medical application is not a trivial process and poses formidable challenges due to the requirement of keeping the ^{90}Sr contamination in ^{90}Y within permissible levels to preclude ^{90}Sr localization in the skeleton. The maximum permissible body burden of ^{90}Sr was found to be 74 kBq (2 μCi) over patient lifetime [2]. With an aim to isolate ^{90}Y from ^{90}Sr , wide ranges of radiochemical separation strategies including precipitation, solvent extraction, ion-exchange chromatography, extraction-chromatography, electrophoresis, membrane-based separation, electrodeposition, among others, have been well described in the literature [276, 277]. Among the $^{90}\text{Sr}/^{90}\text{Y}$ generator technologies reported [277], the automated electrochemical $^{90}\text{Sr}/^{90}\text{Y}$ generator holds significant promise as it offers the scope of being adopted in centralized radiopharmacies set ups, which can provide ^{90}Y of acceptable quality and requisite quantity on a sustainable basis for a long period (>10 years) [2]. In order to preclude the radiotoxicity risk posed by ^{90}Sr and to ensure that it is well within the pharmacopeia established limits, availability of a reliable quality control (QC) technique for the reliable estimation of Bq levels of ^{90}Sr impurity in GBq quantities of ^{90}Y is essential. In this context, the scope of using EPC concept [278] based on the ability of the reagent 2-ethyl hexyl, 2-ethyl hexyl phosphonic acid to retain ^{90}Y selectively at the point of spotting seemed attractive [2].

5. RADIOPHARMACEUTICALS FOR RSV

5.1. PRINCIPLE

“Radiosynovectomy is defined as the restoration of the inflamed and damaged synovial membrane of the joints by an intra-articular injection of a beta emitting radionuclide in colloidal or particulate form into the synovial cavity” [3]. The radioactive compounds are phagocytized by the outermost cellular layer of the synovial membrane and deliver radiation dose to the synovium without excessive irradiation of surrounding tissue.

In the articular cavity of the joint, the radioactive colloid or particulate are recognised as foreign bodies by the subintima. As a result, they are phagocytosed by the type A synoviocytes and deliver selective radiation doses to the synovium without causing collateral damage to surrounding tissue [3]. This subsequently leads to fibrosis and sclerosis of synovial membrane, which results in apoptosis and ablation of the inflamed synovial membrane [279, 280].

This is followed by progressive fibrosis of the synovial stroma, the vessels and infrequently, mild diffuse damage to the joint bones [281]. Nevertheless, there is also a reduction in the filtration and re-absorption of the synovial fluid. After a few months the synovial membrane is

fibrosed without signs of mononuclear infiltration. In this way, further destruction of the joint cavity by immunological reactions is prevented and a long-term remission is achieved [282]. This process results in alleviation of the pain, improvement of mobility and preservation of joint function, where all contribute to significant improvement in quality of life.

While radiopharmaceuticals used for RSV in term of design perspective could be grouped into either colloids or larger aggregates, their selection is primarily governed by both the choice of carrier molecule as well as radionuclide. Radiopharmaceuticals used for RSV should have these standards [2, 3]:

- Radiopharmaceuticals used for RSV should contain a β^- emitting radionuclide of optimum tissue penetration range conjugated to the micro particle, owing to their ability to deliver localized cytotoxic ionizing radiation to ablate the inflamed synovial membrane;
- An important necessity is a suitable method to facilitate the preparation of radiolabelled agents for RSV to preclude the radiation exposure of the operating staff and minimize radioactive decay of radionuclides;
- It is essential to create metabolically resistant bonds between the radionuclide and carrier molecular, and the radiolabelled particle which possesses both 'in vitro' and 'in vivo' stability ;
- The radioactive particles should be minimally affected by changes in pH, temperature and other denaturing agents;
- Radiolabelled agents for RSV should be sufficiently small to be taken up by the type A synoviocytes that partly build up the surface layer of lining cells in the synovial membrane, but at the same time they should be large enough to preclude leakage beyond the joint prior to undergo phagocytosis. A particle size between 2-10 μ m is recommended;
- Minimal lymphatic leakage of the radioactive particle from the joints is desirable. Ideally, the rate of leakage of the nuclide vehicle from the treated region should be negligible in comparison with the rate of decay of the nuclide;
- Homogeneous distribution of the radiolabelled particles in the intra-articular space without initiating an inflammatory response; and
- Cost effective preparation of the radiopharmaceuticals is desirable.

Development of radiolabelled agents for RSV consists of the following major steps [2]:

- (1) In order to minimize radiogenic damage to the articular cartilage and the overlying skin, it is obligatory to choose a radionuclide of optimal beta energy appropriate for the size of the joints that will be treated;
- (2) Proper identification of the joints' size to be treated (large joints, intermediate-sized joints, and small joints) constitute the first step of RSV;
- (3) Identification of a particle for conjugation of the radionuclide;
- (4) Selection of a facile radiolabelling procedure associated with minimal manipulation, and capability of providing high labelling efficiency and high SA is a desirable proposition;
- (5) Quality control of radioactive particles; and
- (6) In vitro and in vivo stability evaluation of the radioactive particles.

5.1.1. Radionuclide selection

The success of RSV is primarily based on the selection of the suitable radionuclide which is governed by a number of factors described as follows [10, 283, 284]: beta particle emitting radionuclides, and Auger-electron emitting radionuclides well suited for RSV owing to their ability to deliver localized cytotoxic ionizing radiation [2]. Any accompanying radiation should not generate an unacceptable extraneous radiation dose to the patient [285]. The selections of β emitting radionuclides for RSV spawn mainly due its reasonable LET (high linear energy transfer) and its intermediate tissue penetration that ranges (typically several millimetres). It has the ability to deliver sculpted radiation doses to the synovium without collateral damage to the critical structures like cartilage, bone marrow and skin [3].

On the other hand, gamma rays with lower LET have the potential to deliver dose at lower levels over much greater distances, thus incapable of localizing the dose within a small region. Use of gamma emitting radionuclides will not only dilute its effect, but it is also prone to deliver doses adjacent to non-synovial tissues and will cause collateral damage to distant joint structures. While alpha particles can deliver lethal radiation dose as a consequence of their high LET without causing significant damage to the surrounding healthy tissue and possesses superior biological effectiveness than beta emitters, their short penetration depth necessitates intimate contact with the cells of the tissue to be treated for favourable therapeutic outcome [3].

The choice of emission type depends on the size of the synovial membrane of the joint to be treated. The penetration depth of the radiation emitted by the radionuclide should correspond to the thickness of the inflamed synovium in the treated joint to ablate the proliferating layer of the inflamed synovium, but it is important to avoid the cartilage, bone marrow and skin. While inadequate penetration will lead to an inferior therapeutic effect, excessive penetration depths may constitute radiation hazard to the cartilaginous surface. For smaller joints, radionuclide emitting shorter range beta particles should be used.

High-energy β^- emitters such as ^{90}Y and ^{188}Re are used for RSV of the knee. Medium-energy β^- emitters such as ^{186}Re , ^{153}Sm , and ^{177}Lu are used for RSV of medium-sized joints (such as the gleno-humeral joint, elbow, radio-carpal joint, hip, and tibio-tarsal joint). Low-energy β^- emitters (^{169}Er) and radionuclides that emit Auger and Coster-Kronig electrons ($^{117\text{m}}\text{Sn}$) are usually effective for smaller joints such as metacarpophalangeal, proximal interphalangeal and metatarsophalangeal [e.g. finger and toe joints][3]. Other joints for which ^{169}Er could be used are distal interphalangeal, tarsometatarsal, the proximal tibiofibular joint and the thumb base joint or first carpometacarpal [132, 286].

The beta emitting radionuclide should decay to stable nuclides with no relevance to the radioactive dose. In addition to the thickness of the synovium, the amount of the synovial fluid will also be obligatory to be considered while delivering radiation [1]. The radionuclide should have an optimal half-life which is long enough to ensure homogenous distribution within the synovium's surface to deliver the needed radiation dose, and concurrently short enough to prevent excessive irradiation within the joint. Preferably, the half-life of the radionuclide should be significantly less than the retention time of the radiolabelled particle in the articular cavity. Moreover, the half-life should be long enough to minimize decay loss during transportation and distribution from the site of manufacture to the users [3].

While high in vivo thermodynamic stability and kinetic inertness of the radionuclide and particle conjugate is a desirable proposition, in reality no conjugate is 100 percent kinetically stable due to the substantial variation in biological systems of different patients; as a consequence, radioactive leakage from the joint subsequent to administration cannot be avoided. Nevertheless, the stability of the complex to a larger extent depends on the half-life of the radionuclide being used and could be successfully exploited. After the radionuclide has decayed to an insignificant level, the stability of the complex is of little interest and utility [285]. The radionuclide should be available with high purity levels (radionuclide, radiochemical, and elemental purity). Trace metal contaminants are a concern while using metallic radionuclides, as they interfere with chelate radiolabelling.

While the therapeutic potential of the radionuclide governed by the particulate emission properties, the presence of low-energy (100-200 keV) gamma emission photons of low abundance enables: imaging low doses for evaluating distribution of the particles in the articular cavity; assessing extra-articular leakage from a joint; performing dosimetry; and for monitoring residual activity usage of an angler gamma ray camera or single photon computed tomography system [2].

The chemical characteristics of the radionuclide should pave the way for conjugating a variety of particulates of variable chemical characteristics [2]. Availability of large scale cost-effective production of radionuclides of acceptable SA and requisite purity contributes to the widespread adoption in RSV. Radionuclides that exhibit attractive characteristics, but which lack a cost-effective production route will find difficulty for wide scale utility in RSV.

5.2. CHARACTERISTICS OF RADIONUCLIDES USED IN RSV

The selection criteria of a radionuclide for its utility in RSV are primarily based on its nuclear decay characteristics, its production and chemistry. The important nuclear decay characteristics to consider include the radionuclide half-life, the type, energy, and branching ratio of particulate radiation; energies of gamma ray, percentage abundances, and depth penetration of the emitted radiation in biological tissues [3]. The half-life of the radionuclide should be long enough to permit homogenous distribution within the synovium and adequate radiation doses, while being short enough to preclude unnecessary radiation doses and substantial leakage from the joint cavity [3].

The use of radionuclides with some gamma emission would allow gamma camera imaging for dosimetry as well as leakage studies. Alternatively, they can be investigated using bremsstrahlung imaging. Unfortunately, scintigraphic resolution from bremsstrahlung may be poor, making quantitation for dosimetry difficult. The tissue penetration depth should commensurate with the thickness of the synovium in the treated joint [3]. The time of retention of the nuclide within the synovial capsule is an important criterion that dictates the success of RSV. This should ideally be longer than the decay time of the nuclide. Beta emitters offer a much wider choice of candidates with a selection of particle ranges and chemical properties.

5.3. PARTICLES FOR RADIONUCLIDES

Administration of unconjugated radionuclides into the synovial cavity is not recommended as it would rapidly diffuse out of the joint cavity due to its small molecular size. With the objective

to preclude the radiation dose to normal organs, attachment of the radionuclides to non-diffusible micro particles is a desirable proposition [2, 3].

5.3.1. Particle selection

The particle required for RSV should meet the following requirements:

- (1) Biologically inert and the particle chosen should be non-toxic, physiologically inert, and should not invoke inflammatory or toxic response;
- (2) Non-immunogenic should not provoke an immune response (absence of body recognition could cause rejection);
- (3) The density of the particle should be similar to the blood in order to achieve a very slow, if any, sedimentation during therapy;
- (4) The particle selected should have good uptake by the synovial lining macrophages of the joints;
- (5) The particles should be free-flowing and should not exhibit aggregation or adherence. They should also be minimally affected by changes in pH, temperature and other denaturing agents or environmental conditions;
- (6) Favourable chemical characteristics to permit radiolabelling with a variety of radionuclides to form a thermodynamical stable and kinetically inert conjugate;
- (7) Chemically stable, resists 'in vivo' degradation and should be able to maintain size range in normal physiological conditions and during the process of therapy;
- (8) Once administered, particles should be sufficiently strong to maintain its size and properties until it is taken up by the macrophages of the joints. They should be removable from the joint by the normal biological degradation mechanisms in the joint by itself, and should be cleared from the body in standard ways in a rapid manner with little or no toxicological effects;
- (9) Biocompatibility of the particle is one of the main prerequisites for their use in RSV. It should not elicit any undesirable local or systemic effects in the synovial tissue of the host. Accumulation of non-biocompatible material in synovial cavity may likely cause inflammation;
- (10) Resistance to radiological degradation;
- (11) Commercial availability, capacity to manufacture particles in large quantities, or availability of quick, easy, and reproducible preparation method; and
- (12) Could be easily sterilized.

5.3.2. Particle size

Particle size plays an important role in RSV. The size of the radionuclide and particle conjugate is sufficient to remain intact in the synovial joint to be phagocyted by the superficial cells of the synovium administration. In order to prepare radioactive particle possessing excellent synovectomy properties, the size and properties of the particle need to be defined and controlled before it is conjugated to the radionuclide of interest [285]. Inappropriate particle size will lead to extra-articular leakage of radionuclides to regional lymph nodes and non-target organs outside the injected joint such as liver and spleen [13].

- (1) Particle size must be small enough to be phagocyted by the superficial cells of the synovium, but not so small as to facilitate a fast-biological clearance by diffusion from the joint;

- (2) While a small diameter particle allows homogeneous distribution on the synovium to be irradiated, it seems to be associated with a high frequency of extra-articular spread. On the other hand, a large particle although resists leakage, results in heterogeneous distribution which in turn may give rise to a variable irradiation of the synovial membrane;
- (3) There appears to be enticing interest to consider the use of micro-particulates having a substantially uniform size distribution with a view to offer homogeneous radiation dose distribution around the synovium for reliable therapeutic outcome;
- (4) Micro-particulates are of a size such that they will maintain their characteristics during radiolabelling as it involves several manipulations such as aliquoting, mixing, vortexing, centrifuging, and ultra-sonication. Furthermore, they should be able to form physiologically acceptable, injectable or infusible suspensions or dispersions when added to physiologically acceptable liquid carriers such as isotonic saline or phosphate buffer solution for in vivo injection and/or infusion (should not sediment or aggregate);
- (5) Micro-particulates are of a size able to remain stable in liquid carriers for heat treatment at a temperature of at least 100° C for the purposes of sterilisation. This is particularly significant as they will not be easily sterilised by filtration;
- (6) The particulates may have any shape or mixture of shapes including spheres, plates, needles, rods etc; and
- (7) The most appropriate particle size that avoid leakage out of the joint cavity by lymphatic drainage is between 2 and 10 μm [1].

5.3.3. Common particles used in RSV

Common particles used in RSV along with abbreviations are depicted in Table 2.

TABLE 2. COMMON PARTICLES USED IN RSV

ABBREVIATION	FULL NAME
FHMA	Ferric Hydroxide Macro Aggregate
HA	Hydroxy Apatite Macro Aggregate
GMS	Glass Microspheres
COL	Colloid
OXP	Oxalate Particles
SIL	Silicate
CIT	Citrate
PMS	Polymeric Microspheres
HSA	Human Serum Albumin Microspheres
PLA	Poly Lactic Acid Microspheres
HMA	Hydroxide Macro Aggregate

5.4. KEY PARTICLES USED IN RSV

5.4.1. Glass

Glass has several advantages including excellent stability, resistant to radiation damage, highly insoluble, non-toxic, ability to produce different composition, and minimal leaching [287, 288]. However, high density, irregular particle shape, and non-biodegradability are the major disadvantages that limit its applicability. The high density of glass makes it difficult to keep the particles in suspension in the liquids used to inject them into the body. Non-biodegradability can lead to immunologic reactions.

The glass mixture containing the nonradioactive precursor is melted in a platinum crucible at formation temperature of glass, annealed, crushed and sieved [187, 289]. Sol-gel method and the flame spheroidisation process are the other two methods by which glass may be prepared. Strategies to prepare glass microspheres from biodegradable glass material have been studied elaborately [287, 289–292].

5.4.2. Chitosan

Chitosan (poly- β -(1-4)-2-amino-2-deoxy-D-glucose) is an amino-polysaccharide that is a cationic polymer produced by the N-deacetylation of chitin. Chitin (poly- β -(1-4)-N-acetyl D-glucosamine) constitutes one of the most abundant natural biopolymers, second only to cellulose. It is mostly found in the exoskeletons of crustaceans, in the cartilage of molluscs, in the cuticles of insects, and in the cell walls of micro-organisms. It has recently been recognized as a biosorbent owing to the existence of amino and hydroxyl groups in its molecules that paves the adsorption interactions between chitosan and radionuclide [293, 294]. The interesting characteristics of chitosan such as biocompatibility, non-toxicity, low allergenicity and biodegradability, allow it to be used in various applications [295]. The Chitosan can be easily obtained by alkaline hydrolysis of chitin, because of being abundant next to cellulose in nature, and chitosan is particularly contained much in shells of shrimp, lobster, crab and oyster. Chemical structure of Chitosan is shown in Figure 7.

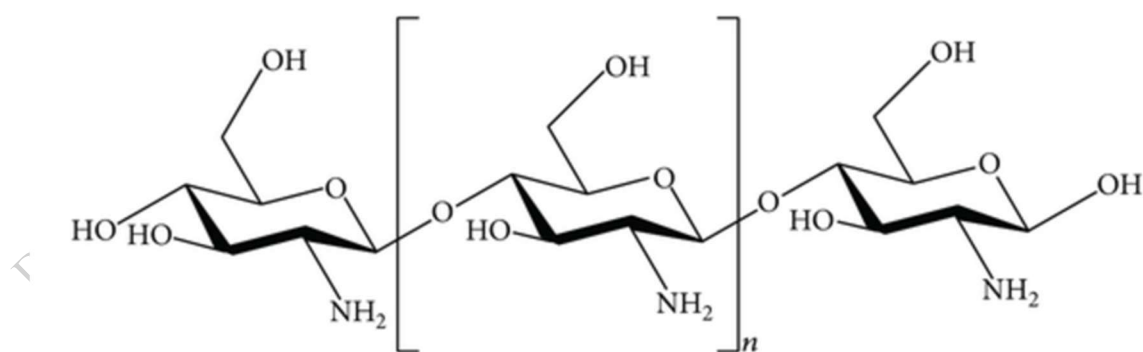


FIG. 7. Chemical structure of Chitosan [296]

Chitosan microspheres can be produced via spray drying [295,296] emulsification [299], internal gelation [300], electrospinning and freeze-drying processes. Several studies dealing with Chitosan as a particle in RSV have been reported [301–305].

5.4.3. Silicate

Silica possess remarkable attributes, including availability of facile, controllable, and scalable synthesis protocols, inexpensive costs, biocompatibility, negligible toxicity, exhibit ‘in vitro’ and ‘in vivo’ stability, and flexibility for surface modification to radiolabel radionuclide of interest [306]. It is possible to precisely control silica particle size, porosity, crystallinity, and shape. Furthermore, it is possible to modify the surface of silica particles to allow precise control of surface chemistry to bind a wide variety of radioisotopes without additional selective chelation molecules. The ability to combine these properties makes silica particles a desirable platform for radiosynovectomy.

5.4.4. Citrate

Citric acid, historically known as an intermediate in the Krebs cycle, is a multifunctional, nontoxic, readily available, and inexpensive chemical used as citrate in the preparation of RSV agents. Due to the antimicrobial nature of citric acid, citrate-based RSV agents could possess intrinsic antimicrobial properties.

5.4.5. Poly lactic acid

Poly lactic acid (PLA) is an aliphatic polyester, having extraordinary preferences over several polymers. The use of PLA and its derivatives have attracted attention due to its mechanical and biological unique properties such as, biocompatibility, biodegradability and non-toxicity. The nontoxic and non-carcinogenic effects on the human body make PLA and its degradation products like H₂O and CO₂ acceptable candidate for RSV. Since the 1970's, PLA have been approved by the US food and drug administration for food and pharmaceutical applications. PLA is usually synthesized using a range of processes including polycondensation, polymerization and azeotropic dehydration condensation reaction [307–310].

‘In vitro’ degradation analysis over a 52 week period of holmium-loaded PLLA microspheres (before and after neutron or gamma irradiation) was investigated by Zielhuis et al [309]. Preparation of PLA microspheres by an emulsion-solvent evaporation method based on solution induced phase separation, has been well described by Hong et al [311]. Other method of synthesis includes polycondensation [312, 313]. The prospect associated with the use of PLA led to a number of studies in RSV [314–317].

5.4.6. Hydroxyapatite

Hydroxyapatite (HA) has been receiving a great deal of attention in their applications as a particle in RSV. The inimitable physicochemical characteristics of HA include biocompatibility, bioresorbability, non-allergenic, non-toxic, non-immunogenic, porous with superior mechanical properties, and chemical similarity to the carbonated apatite in human bones and teeth. It is the natural mineral constituent of human bone matrix and has the ability to get converted into Ca²⁺ and PO₄³⁻ ions by natural metabolic process which could be

eliminated over a period of 6 weeks. The particles have sites on the surface that permit absorption or covalent binding of the radionuclide or radionuclide complex [285].

HA is a stoichiometric apatite phase with a Ca/P molar ratio of 1.67 and is considered as the most stable calcium phosphate salt at normal temperatures and pH between 4 and 12. Thermodynamically, HA is the most stable calcium phosphate compound under physiological conditions such as temperature, pH and composition of the body fluids. A myriad of techniques to synthesize HA had been reported in the literature with each method having advantages and disadvantages.

5.4.6.1. Precipitation

Precipitation is the most common and widely researched method of synthesis of HA [318–324]. It is also called ‘wet precipitation’, ‘chemical precipitation’ or ‘aqueous precipitation’. Precipitation typically involves slow addition of di-ammonium hydrogen orthophosphate into a solution of calcium nitrate by keeping pH ~10 with steady drop-wise addition of ammonium hydroxide under continuous stirring to ensure a constant pH. The resulting precipitate is washed to remove nitrates and the ammonium hydroxide [318, 319].

In this method, continuous stirring is essential to ensure the slow incorporation of calcium into the apatite structure to reach stoichiometric Ca/P ratio. The reaction temperature offers to change the size of the HA particles, with higher temperature generally resulting in more whisker-like particles, although NH₄OH consumption goes up. Other factors such as reaction rate (length of time for additions) of the HA provide the scope to improve stoichiometric quality.

5.4.6.2. Advantages

- (1) Simplicity;
- (2) Low operating costs;
- (3) Relatively inexpensive raw materials;
- (4) Production batch can be easily scalable;
- (5) Low reaction temperatures;
- (6) Water is the only by product; and
- (7) This method leads to obtaining a hydroxyapatite characterized by high precise superficial area and small particle size distribution.

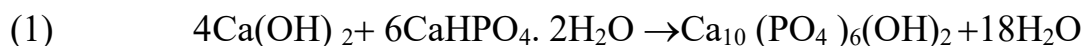
5.4.6.3. Disadvantages

- (1) This process depends on several influences such as reactants involved in synthesis, concentration and preliminary pH of solutions, reaction temperature, etc;
- (2) Difficulty to obtain stoichiometric HA;
- (3) Need of high pH to prevent formation of Ca-deficient HA; and
- (4) Need of high sintering temperature to form crystalline HA;

5.4.7. Hydro- and Solvo-thermal

Hydro- and solvo-thermal process of synthesis involves the use of a solvent (with precursor soluble ions) in a sealed vessel under moderate to high pressure (typically between 1 atm and

10 000 atm) and temperature (typically between 100 °C and 1 000 °C) that facilitates the interaction of precursors during synthesis. In this process, calcium and phosphate solutions are reacted in a sealed vessel kept at very high pressures and temperatures to produce HA particles [325–337]. A variety of starting calcium and phosphate salts have been respectively reported, including: calcium hydroxide; calcium nitrate; calcium carbonate and calcium chloride; calcium hydrogen phosphate and dipotassium; and diammonium hydrogen phosphates. A typical hydrothermal reaction is shown in the following equation:



5.4.7.1. Advantages [338]

- (1) HA can be produced in one step;
- (2) It is energy efficient as synthesis can be performed at low temperatures;
- (3) It is an environmentally friendly process because of closed system conditions and ability to recycle unused components;
- (4) High purity products can be synthesized;
- (5) Yields approaching 100%; and
- (6) Relatively low-cost reagents and short time reaction.

5.4.7.2. Disadvantages

- (1) Batch sizes are limited to the size of the reaction vessel; and
- (2) High pressures required for processing.

5.4.8. Solid state reactions

The main difference between wet chemistry and similar products of solid phase synthesis is that much smaller grains (crystallites) usually has lower temperature and shorter duration of phase formation than in the former. In this method, precursors are first milled and then calcined at a very high temperature (e.g. 1000 °C) which leads to formation of a highly crystallized structure [339–341]. While the procedure relies on the solid diffusion of ions amongst precursors, it requires relatively high temperature processing (>1250°C) to initiate the reaction. Even though the technique is comparatively simple, it is associated with a number of processes.

5.4.8.1. Advantages

- (1) Simple procedure;
- (2) Low cost;
- (3) Appropriate for mass producing HA powder; and
- (4) Preferred option for commercial production.

5.4.8.2. Disadvantages [342]

- (1) Heterogeneity in phase composition owing to the small diffusion of ions during the reaction;
- (2) Large size of particles;
- (3) No control on particle morphology; and

(4) Unattractive, both scientifically and technologically.

5.4.9. Sol-gel process

The first stage of this method is to form a 'sol': a dispersion of solid particles, a liquid. Precursor materials such as metal alkoxides (e.g. tetraethoxysilane to introduce silicon) and metal salts (e.g. calcium nitrate to add calcium; ammonium phosphate to add phosphorus) are mechanically mixed in a solvent at a pH that prevents precipitation. Hydrolysis and polycondensation reactions occur to link these monomer units and form M-O-M bonds within the sol causing the viscosity to increase; this process is termed gelation. The next step is the removal of the liquid via a drying process [344–348].

5.4.9.1. Advantages

- (1) Low temperature formation;
- (2) Increased control over formation of particular phases and phase purity;
- (3) Improving chemical homogeneity of the resulting powder; and
- (4) A stoichiometric structure with a large surface area and a small cluster size HA is attainable.

5.4.9.2. Disadvantages

- (1) High cost of some of the starting materials, especially alkoxide based precursors. The energy saving gained from the low temperatures used is offset by the high cost of the reactants;
- (2) Generation of secondary phase (usually calcium oxide, CaO); and
- (3) Sol-gel techniques have very limited scalability due to the sensitivity of the process.

5.2. PREPARATION OF RADIOACTIVE PARTICLES

Radiolabelled particles can be prepared either during or after their preparation. Important factors include ease and efficiency of preparation as well as stability of isotope-particle conjugate without 'in vitro' or 'in vivo' release of the radioisotope.

5.4.10. Radiolabelling during the particle preparation

In this method, an inorganic compound of a radioisotope is precipitated to form relatively homogeneous particles. The method essentially consists of first transforming a radioactive substance into a precipitate and subsequent conversion of precipitate into particles. Colloids are frequently used to be radiolabelled during preparation. They usually consist of the defined inorganic compounds of a radioisotope which have precipitated into relatively homogeneous particles. While a myriad of factors contribute to the successful optimization of preparation conditions, temperature and pH of the reaction mixture are the key parameters that determine the range/size of particles.

5.5.2. Radiolabelled particle after their preparation

5.5.2.1. Neutron activation of pre-made particles

In this case, particles containing the non-radioactive precursor are synthesised and activated in a nuclear reactor to induce radioactivity shortly before use [3]. During neutron-activation, the non-radioactive precursor captured neutron became radioactive.

Advantages

- (1) Preclude the handling of radioactivity for radiolabelling;
- (2) Activity content can be controlled by irradiation time as well as neutron flux;
- (3) Simple post irradiation processing.

Disadvantages

- (1) Availability of a reactor;
- (2) Activation of isotopes is practically possible only with high activation cross sections;
- (3) Success of the technique reside on the radiation stability of the particle;
- (4) Susceptible to radiolytic degradation: leakage of radionuclide.

By far the most stable matrix for this method of radioactive particle preparation through neutron activation is glass [349].

5.5.2.2. Reaction of radionuclide with particles

In this case, non-radioactive particles are radiolabelled shortly before use. Compared to radiolabelling during particle preparation, methods of radiolabelling already prepared particles are conceptually more straightforward [349]. The advantage of this process is that radiochemical stability problems during irradiation could be minimized, and logistical problems inherent to the use of radiolabelled particle can be avoided.

In this method, it is essential to consider whether the radionuclide can be incorporated into the particle, which can be assessed from a knowledge of the chemical characteristics of the two partners. It is also crucial to ascertain the amount of each component to be added. An unduly high or low concentration of any component may likely affect the integrity of the radiolabelled particles.

Various techniques used for radiolabelling are:

(1) Isotope Exchange Reactions

In this technique, one or more of the atoms in a particle of interest is substituted for a radioactive atom of the same element. As the radiolabelled and the nonlabelled particles are chemically identical, they are expected to possess the same chemical properties. For isotope exchange labelling, it is crucial that the radionuclide should be no-carrier-added to ensure optimal labelling yields.

(2) Introduction of a Foreign Label

In this type of radiolabelling, a radionuclide is incorporated into a particle of interest by adsorption processes, by the formation of covalent bonds or by chelation. While the tagging radionuclide is foreign to the particle, it is distributed throughout the entire volume, or gets attached only on certain structural components of the particles, including the surface, the outer or inner wall [3].

(3) Covalent attachment or Chelation (complex formation) of the radionuclide

Techniques resulting in covalent attachment of the radionuclide use chemical linker molecules and a number of wet-chemistry steps to facilitate the attachment [349]. With a view to create stable covalent binding sites on the surface of the particle for the attachment of radionuclide, myriad of functional groups such as -OH, -NH₂, -SH and -COOH are conjugated to the particles either covalently or may simply adsorb very strongly to the surface of the particle. Each process requires a tailored functionalization protocol making use of chemical linker molecules and associated wet chemistry.

Ligands that can be used for chelation are preferably polydentate, i.e., containing more than two coordinating atoms per ligand molecule. A coordinating atom is defined as one that has a free pair of electrons which can be bonded to the radionuclide. This atom is preferably separated by two or more atoms from any other coordinating atom. The coordinating atoms are chosen from nitrogen, oxygen, sulphur, phosphorus or carbon with nitrogen and/or oxygen and/or sulphur being the preferred coordinating atoms. Examples of chelates include all phosphonate carboxylate and amine carboxylate ligands, MAG3 (mercapto acetyl glycyl glycine), and all polycarboxylic acid-amine ligands especially DTPA (diethylenetriaminepentaacetic acid) For example, EDTA (ethylenediamine- tetraacetic acid), DADS (N,N'-bis (mercaptoacetamido) ethylenediamine and CO₂-DADS N,N'-bis (mercaptoacetamido)-2,3-diaminopropanoic acid) and their derivatives. Also, mono- and poly-phosphonates, BATs (N,N'-bis(2-mercaptoethyl)ethylene-diamine) and thiosemicarbazones, PnAO, and other amine-oxime ligands, macrocyclic and open chain tetra-, penta-, hexa-, hepta- and octa coordinating nitrogen containing compounds with or without other coordinating atoms or unsaturation [285].

(4) Adsorption

It is a valuable way to incorporate the radionuclide from the solution to the solid particles. While both physical and chemical adsorptions are capable of retaining the radionuclide of interest on the particle, chemisorption follows due to the chemical reaction between the surface and the radionuclide leading to the formation of chemical bonds at the particle surface. The physical adsorption interaction between the particle surface and radionuclide is primarily due to weak molecular forces which embrace permanent dipole, induced dipole, and quadruple attraction. Chemisorption, on the other hand, involves the rearrangement of the electrons of the interacting radionuclide, with consequential formation and rupture of chemical bonds. Enthalpy changes in physical adsorption are small, typically in the range -10 to -40 kJ mol⁻¹, whereas that of chemisorption are typically in the range of 80 kJ mol⁻¹ to 400 kJ mol⁻¹ [350]. Factors affecting the extent of chemisorption are chemical characteristics of the radionuclide

and particle, radionuclide concentration in the solution, adsorption temperature, pH of the reaction media and specific surface area, pore volume and pore structure of the particle.

5.5. KEY RADIONUCLIDES EVALUATED FOR SYNOVECTOMY

5.5.1. ^{198}Au

^{198}Au ($E_{\beta\text{max}} = 0.96 \text{ MeV}$, $E_{\gamma} = 412 \text{ keV}$ (95.6 %), $T_{1/2} = 2.7\text{d}$) with a half-life of 2.7 days decays to ^{198}Hg with the emission of beta and gamma radiation. About 99 % of the beta emission has an energy of 0-0.96 MeV, where the maximum range in soft tissue being 3 to 8 mm., but most of the energy is absorbed in the first 1 mm. About 95% of the gamma emission is at 0 -412 MeV. The decay characteristic of ^{198}Au is shown in Figure 8.

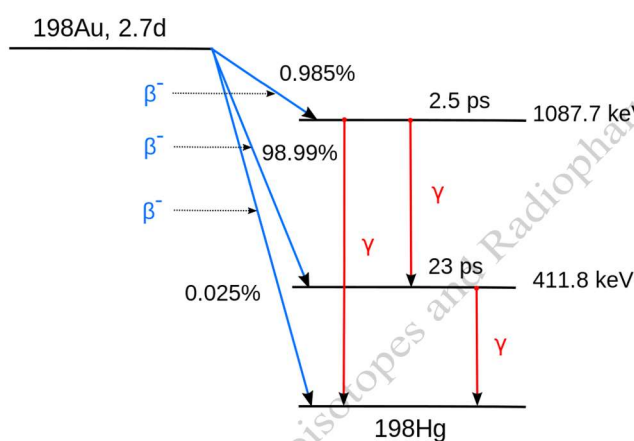


FIG. 8. Decay characteristic of ^{198}Au [351]

Use of ^{198}Au in RSV is associated with the following advantages and limitations.

5.5.1.1. Advantages

- (1) 0.96 MeV, energy of beta emissions is suitable for the treatment of inflamed joints;
- (2) The mean range of beta energy lies between 3 to 8 mm and is amenable for using in radiation synovectomy of large joints;
- (3) Facial reactor production technology. High SA ^{198}Au can be produced by the reactor irradiation of metallic gold target. Radiochemical processing of irradiated target is facile as simple target dissolution would suffice; and
- (4) The 2.7 day half-life of ^{198}Au is adequate to perform radiolabelling, and for completing quality control and patient administration [198].

5.5.1.2. Disadvantages

- (1) ^{198}Au has a β particle of maximum range in tissue of only 4 mm., and the synovium in these chronic knee effusions can attain a thickness of greater than 1 cm., but not a complete synovial ablation is produced;

- (2) The leakage (related to particle size) when combined with its relatively long half-life of approximately 2.7 days of each results in significant integrated radiation doses to other organs, such as the lymph nodes, liver and kidneys;
- (3) ^{198}Au possesses a significant gamma ray component (411 keV gamma emission) which creates an unnecessary radiation hazard while undertaking preparation of synovial agents and this gives an unwanted radiation dose to the proximal lymph nodes; and
- (4) The high costs have also impeded its routine application.

The first papers concerning the use of ^{198}Au in RSV were reported in 1963 where patients with chronic effusions of the knee were treated by using 370 MBq of ^{198}Au colloids [6]. Subsequently, few more studies on the use of ^{198}Au have been reported in the literature [352–362].

5.5.2. ^{165}Dy

^{165}Dy emerged as the first RSV agent which motivated clinicians to treat refractory synovitis as a substitute to surgical intervention [3]. ^{165}Dy has a 139mm half-life, a 1.3 MeV maximum beta energy, and little accompanying gamma emission. This radionuclide has a 3.6 abundance of gamma emission at 108 keV that can be used by the gamma camera to detect a possible leak. It has a tissue penetration range of 5.7 mm. Nuclear decay characteristic of ^{165}Dy is depicted in Figure 9.

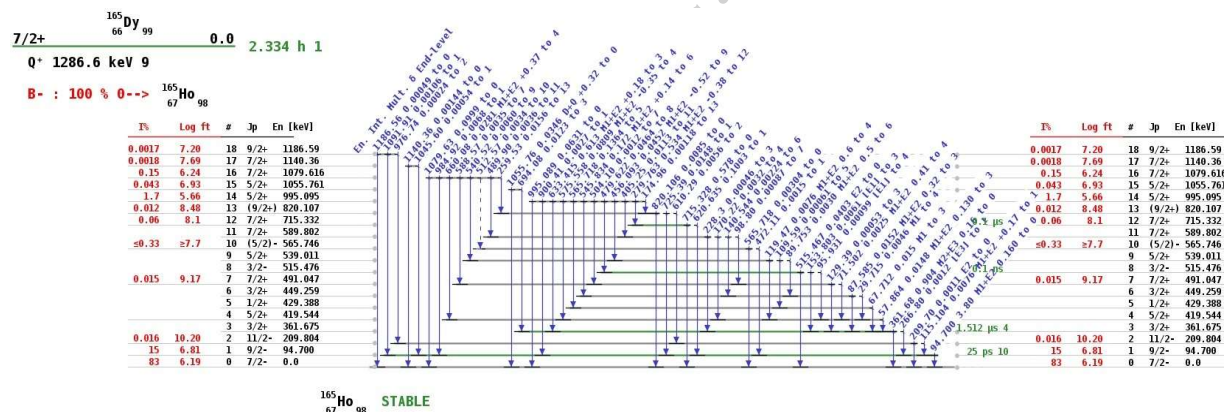


FIG. 9. Nuclear decay characteristic of ^{165}Dy ⁴

^{165}Dy possesses the following advantages and disadvantages:

5.5.2.1. Advantages [198]

- (1) A 1.3 MeV energy of beta emissions is suitable for therapy;
- (2) An extremely short half-life of 2.3 hours reduces the effects of potential leakage;
- (3) Facial reactor production technology: high SA ^{165}Dy can be produced by the irradiation of dysprosium oxide with neutrons in a nuclear reactor for 1 day. Post irradiation

⁴ Figure 9 available at the IAEA database <https://www-nds.iaea.org/relnsd/vcharthtml/VChartHTML.html>

processing of targets is simple and rapid and essentially consists of dissolution of neutron irradiated targets in dilute mineral acid followed by gentle warming;

- (4) ^{165}Dy has a gamma emission of 3.6% abundance at 108 keV, permitting gamma camera imaging for dosimetry as well as leakage studies;
- (5) Minimal radiation dose during radiopharmaceutical preparation and patient administration owing to the emission of the moderate energy beta β^- particles, as well as low energy gamma photons. This facilitates handling relatively high ^{165}Dy activity;
- (6) The chemical characteristics of Dy^{+3} are favourable to perform radiolabelling with a broad range of particles; and
- (7) The mean penetration range of β^- particles emitted by ^{165}Dy in soft is $< 10 \mu\text{m}$, making this radionuclide ideal for delivering energy to small volumes with less damage to surrounding normal bone and tissue.

5.5.2.2. Disadvantages

- (1) Owing to the short half-life of ^{165}Dy , it necessitates a nuclear reactor close to the hospital for regular production; and
- (2) To be injected within a few hours.

[^{165}Dy] ferric hydroxide macroaggregate appeared to be the first RSV agent which motivated clinicians for its increasing use because it is the treatment of refractory synovitis as an alternative to surgical intervention [363–376]. Although ^{165}Dy has several attractive attributes, the radionuclide has not met with widespread acceptance because the extremely short half-life requires that the medical centre be located within a short distance from a high-flux nuclear reactor. Despite ground-breaking clinical outcomes and proven therapeutic effectiveness, the US food and drug administration has not approved the use of this radionuclide in RSV on the basis of the dosimetric implications of 'potential capsule' leakage which would result in significant integrated radiation doses to other organs, such as the lymph nodes, liver and kidneys [3].

5.5.3. ^{169}Er

^{169}Er ($T_{1/2} = 9.4 \text{ d}$, $E_{\beta(\text{max})} = 342 \text{ keV (45\%)} \text{ and } 351 \text{ keV (55\%)}$, $E_{\gamma} = 110.5 \text{ KeV (0.0014\%)}$) decays under emission of beta particles to stable ^{169}Tm with a physical half-life of 9.5 days. The maximum range in soft tissue is 1mm, whereas the mean range lies between 0.2 and 0.3mm. The fraction of gamma rays is negligible; therefore, a distribution post-therapeutic scintigraphy is not possible. Nuclear decay characteristic of ^{169}Er is shown in Figure 10.

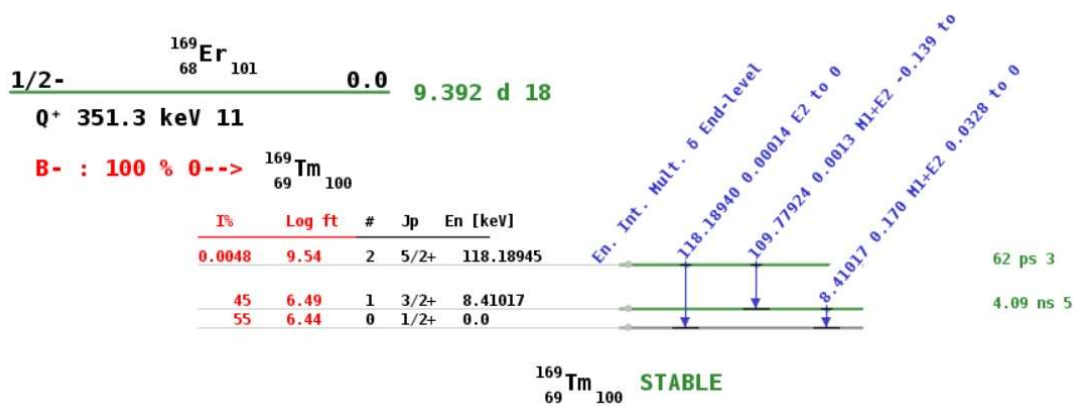


FIG. 10. Nuclear decay characteristics of ^{169}Er ⁵

^{169}Er offers the following advantages and disadvantages when used in RSV.

5.5.3.1. Advantages

- (1) 342 keV energy of beta emissions is suitable to treat painful inflamed small joints;
- (2) The maximum range in soft tissue is 1mm, whereas the mean range lies between 0.2 and 0.3mm is amenable for use in RSV of digital joints;
- (3) Facial reactor production technology. High SA ^{169}Er can be produced by the reactor irradiation of Er_2O_3 target. Radiochemical processing of irradiated targets is facile as a simple target dissolution in dilute mineral acid on gentle warming suffices;
- (4) 9.4 days half-life of ^{169}Er is conducive to perform radiolabelling, and quality control and patient administration without significant radioactivity decay;
- (5) The relatively long 9.4 days physical half-life of ^{169}Er is long enough to minimize decay loss during transportation and distribution from the site of manufacture to the users; and
- (6) The chemical characteristics of Dy^{+3} is conducive to permit radiolabelling with a broad range of particles.

5.5.3.2. Disadvantage

- The fraction of gamma rays is negligible; therefore, a distribution post-therapeutic scintigraphy is not possible.

^{169}Er is the most preferred option for RSV of digital joints [11, 132, 377–384]. A review concerning the use of ^{169}Er for the RSV for small joints has been published [286]. There is considerable variation in the administered activity as well as the injected volume according to the size of the joint to be treated [132].

- 10–20 MBq for proximal or distal interphalangeal joints;
- 20–40 MBq for metacarpophalangeal or metatarsophalangeal joints; and
- 20–80 MBq for trapeziometacarpal joints.

⁵ Figure 10 available at the IAEA database: <https://www-nds.iaea.org/relnsd/vcharthtml/VChartHTML.html>

It is possible to treat as many joints using the same formulation at the same session, but the total activity of injected ^{169}Er should not exceed 750 MBq at a single session.

5.5.4. ^{166}Ho

^{166}Ho is predominantly a beta emitter ($E_{\text{max}} = 1.85 \text{ MeV}$) with $E_{\beta 1} = 651.9 \text{ keV}$ (47.7% abundance) and $E_{\beta 2} = 694.6 \text{ keV}$ (51.0% abundance) with a half-life of 26.808 h. It has a therapeutic radius of $\sim 2.1 \text{ mm}$. The soft tissue penetration range (average) is 3.2 mm, depositing 0.2 keV/mm. The total equilibrium dose constants D_{np} and D_{p} for non-penetrating and penetrating radiations of ^{166}Ho are $0.398 \text{ g Gy MBq}^{-1}\text{h}^{-1}$ and $0.017 \text{ g Gy MBq}^{-1}\text{h}^{-1}$, respectively. A reasonably short half-life (27 h) decreases the risks associated with eventual leakage of the radioisotope, and strong beta radiation energy ($\beta_{\text{max}} 1.8 \text{ MeV}$) ensures efficient radiation of the synovium. ^{166}Ho deposits ninety percent of its energy within an area 2.1 mm in diameter, while the remainder is deposited within an area measuring 2.1–8.7 mm [193]. Nuclear decay characteristic of ^{166}Ho is shown in Figure 12.

5.5.4.1. Advantages

- (1) A reasonably short half-life of $\sim 27 \text{ h}$ decreases the risks associated with eventual leakage of the radioisotope;
- (2) It decays by emission of 1.855 MeV (51%) and 1.776 MeV (48%) maximum energy beta particle which has an adequate penetration range for synovial ablation, while avoiding damage to adjacent cartilage or bone;
- (3) ^{166}Ho has an average soft tissue penetration of approximately 3.3 mm and a maximum soft tissue penetration of approximately 9 mm;
- (4) ^{166}Ho also emits gamma photons (0.081 MeV with less than 1% in abundance) that can be imaged with a gamma camera for quantitative dosimetric studies, but are of low enough photon yield (5.4%) to result in limited absorbed radiation dose to surrounding tissue; and
- (5) Cost effective availability: ^{166}Ho is produced in a simple way by the nuclear reaction $^{165}\text{Ho}(n,\gamma)^{166}\text{Ho}$ in a nuclear reactor. ^{165}Ho has a natural abundance of 100% and neutron capture cross-section of 64 barns. It can be produced from ^{165}Ho , a naturally abundant element, and is less expensive.

5.5.4.2. Disadvantages

- (1) Physical half-life is 26.8 h and offers a logistic difficulty for the transportation and distribution of radioactive particles from the site of manufacture to the user [187];
- (2) The prospect associated with the use of RSV led to a considerable amount of innovative work [178, 316, 398–404].

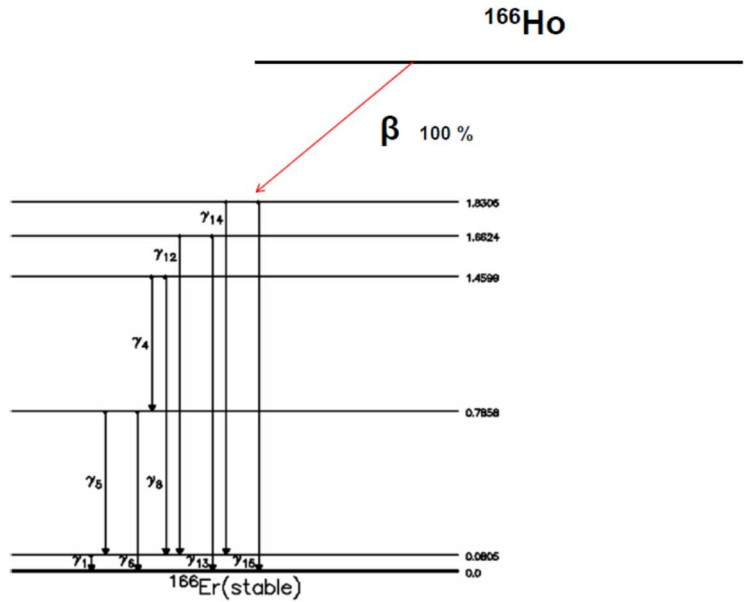


FIG. 11. Nuclear decay characteristic of ^{166}Ho (courtesy of Mr. Dash)

Utility of ^{166}Ho in RSV has been associated with the following advantages and limitations.

5.6.5. ^{177}Lu

^{177}Lu decays to stable ^{177}Hf with a half-life of 6.65 days. ^{177}Lu decays to excited (9.7% $E_{\beta(\text{max})} = 0.384$ MeV and 12% $E_{\beta(\text{max})} = 0.176$ MeV) and ground states (76% $E_{\beta(\text{max})} = 0.497$ MeV) of ^{177}Hf , by the emission of beta particles. ^{177}Lu decays to an excited state of ^{177}Hf , which energy level lies at 0.24967 MeV and 0.32132 MeV respectively above the ground state. It subsequently de-excites to the ground state accompanied by the emission of low-energy gamma photons ($E_{\gamma} = 113$ keV (6.6%), 208 keV (11%)) [198]. A simplified decay scheme for ^{177}Lu is shown in Figure 16.

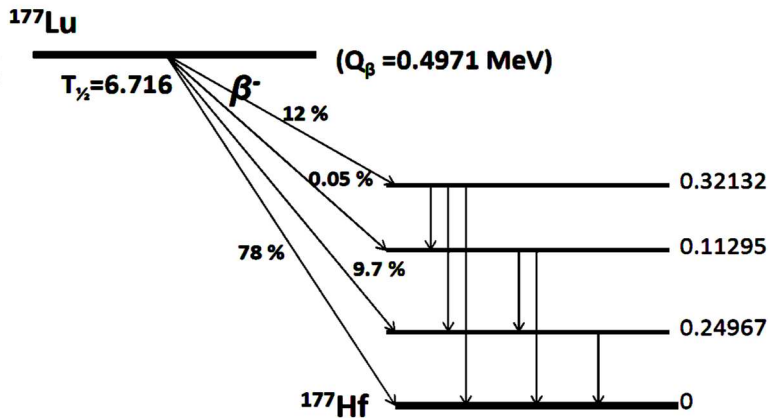


FIG. 12. Simplified decay scheme of ^{177}Lu [198]

Use of ^{177}Lu in RSV is associated with the following advantages and disadvantages [198].

5.6.5.1. Advantages

- (1) The beta particles emitted by ^{177}Lu have a mean range of 670 μm ; thus, it is considered suitable for synovectomy of median articulations;
- (2) The low-energy gamma photons ($E_{\gamma}=113\text{ keV}$ (6.6%), 208 keV (11%)) emitted by ^{177}Lu offers a good quality scintigraphic imaging for the evaluation of homogeneity of joint distribution, analysis of leakage to other organs, and dosimetry;
- (3) Lutetium exhibits an oxidation state of only +3, hence preventing any redox complications of its solution chemistry. Chemistry of ^{177}Lu is amenable for conjugating with a wide range of particles by following standard radiolabelling procedures; and
- (4) ^{177}Lu can be produced in many nuclear reactors throughout the world following $^{176}\text{Lu}(n,\gamma)^{177}\text{Lu}$ using enriched ^{176}Lu target. This reactor method of production provides ^{177}Lu very high activity and high SA.

5.6.5.2. Disadvantages

- (1) Requirement of enriched ^{176}Lu target to produce ^{177}Lu of acceptable SA and requisite quality makes it cost ineffective compare to ^{166}Ho [198]; and
- (2) The 6.65 days half-life of ^{177}Lu offers a logistic disadvantage for transportation and distribution of radioactive particles from the site of the manufacturer to the user.

Increasing use of ^{177}Lu in RSV has been impressive and the last 2 decades have witnessed extensive activity towards the development of a number of ^{177}Lu based RSV agents [384, 399, 438–442].

5.6.6. ^{32}P

^{32}P [$T_{1/2}=14.3$ days] decays to ^{32}S by beta emission [$E_{\beta\text{Max.}} = 1.7\text{ MeV}$] with a half-life of 14.3 days. It has mean and maximum tissue penetration depth of 2.2 mm and 7.9 mm respectively. The radioactive decay characteristics makes it suitable for RSV of the knee, where applied activity for knee joints should be 37–54 MBq [132]. Nuclear decay characteristic of ^{32}P is shown in Figure 11.

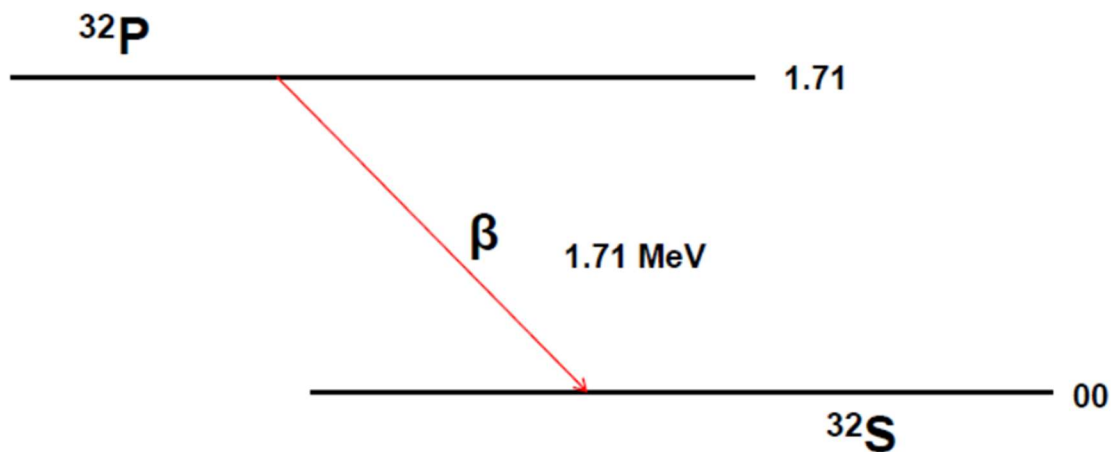


FIG. 13. Nuclear decay characteristic of ^{32}P

A vast number of studies that use ^{32}P for RSV of knee are available in the literature [385–396]. ^{32}P has the following advantages and disadvantages when used in RSV.

5.6.6.1. Advantages

- (1) The 1.7 MeV energy of beta emissions is suitable for the treatment of inflamed large joints such as the knee;
- (2) The maximum range in soft tissue is 7.9 mm, whereas the mean range is 2.2–0.3 mm, and thus, it is amenable to use in RSV of knee joints;
- (3) Most commonly available radionuclide with no carrier added form at a reasonable cost; thus, it ensures a cost-effective treatment option;
- (4) The 14.3-day half-life would allow a more gradual deposition of energy and preclude immediate inflammatory reactions;
- (5) The 14.3-day physical half-life is long enough to minimize decay loss during transportation and distribution from the site of manufacture to the user; and
- (6) The chemical characteristics of ^{32}P permit radiolabelling with a broad range of particles.

5.6.6.2. Disadvantages

- (1) It has no imageable gamma photon which makes very difficult to obtain quantitative dosimetric information on patients treated with agents based on ^{32}P ;
- (2) Any leakage of activity will give an unacceptable, extraneous bone dose; and
- (3) High energy beta radiation ($\beta_{\text{max}} = 1.7 \text{ MeV}$) induces injuries of both articular cartilage and the growth plate [397].

5.6.7. ^{186}Re

^{186}Re has a half-life of 90 hours (3.68 days) and decays with a beta particle emission of a maximum energy of 1.08 MeV with a mean tissue penetration depth of 0.92 mm. and a 135 keV (9%) gamma which permits imaging [187]. The 135 keV (9%) is ideal for gamma camera imaging and the very small fraction (0.05%) of higher energy gamma photons (>600 keV) result in minimal radiation exposure. It is ideal for treating medium sized joints: the hip, shoulder, elbow, wrist, ankle and subtalar joint. ^{186}Re labelled particles are commercially available in Europe, for example, for this clinical application. Nuclear decay characteristic of ^{186}Re is depicted in Figure 14.

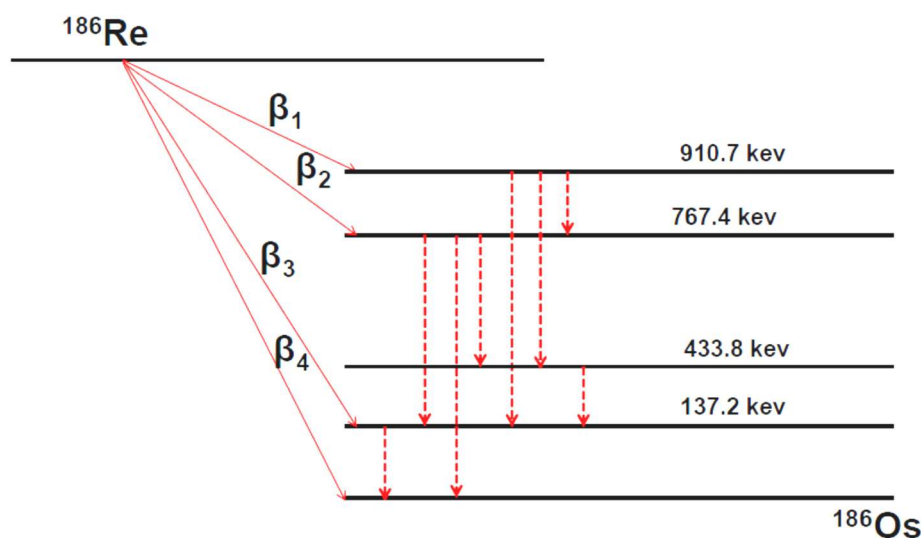


FIG. 14. Nuclear decay characteristic of ^{186}Re (courtesy of Mr. Dash)

While performing RSV with ^{186}Re sulphide colloid, the recommended activity range is as follows: for the hip, 74–185 MBq; shoulder, 74–185 MBq; elbow, 74–111 MBq; wrist, 37–74 MBq; ankle, 74 MBq; subtalar joint, 37 to 74 MBq [3]. In the situation where several joints are to be treated simultaneously in a single session, the total administered activity should be kept below 70 MBq [1].

5.6.7.1. Advantages

The possibility of using ^{186}Re for the preparation of bone seeking radiopharmaceuticals is enticing owing to the following:

- (1) The physical half-life of ^{186}Re is 3.8 days. It is long enough for radiopharmaceuticals preparation, quality control, shipment and distribution of the radiopharmaceutical to the end users distant from the production facility;
- (2) Its beta emission exhibits a mean energy of 349 keV and an average range in soft tissue of 1.1 mm (maximum range, 4.5 mm) [133]. Due to its short penetration distance, radiation reaches only structures in the immediate vicinity of the joint cavity [411];
- (3) It has a 9% abundant gamma emission (135 keV), which allows external imaging with a standard gamma camera and permits evaluation of dosimetry; and

- (4) One important advantage of using ^{186}Re is that it can be produced in many nuclear reactors throughout the world following $^{185}\text{Re}(n,\gamma)^{186}\text{Re}$ method by using enriched ^{185}Re target [184]. The SA of ^{186}Re vital for RSV could be attained owing to the high thermal and epithermal cross-sections for neutron capture of ^{185}Re (106 and 1632 barns, resp.).

5.6.7.2. Limitations

- (1) Requirement of enriched ^{185}Re target for the production of ^{186}Re makes it cost ineffective compare to ^{166}Ho ; and
- (2) Chemistry of ^{186}Re for radiolabelling is complicated compared to trivalent lanthanides.

The prospect of developing particles radiolabel ^{186}Re for usage in RSV has attracted considerable attention and led to a considerable amount of fascinating research and innovative strategies in the literature [179, 412–421].

5.6.8. ^{188}Re

^{188}Re has a half-life of 16.9 hours and decays to ^{188}Os with emission of β^- particle of maximum energy of 2.11 MeV, followed by a 155-keV gamma emission (15%) with an average tissue penetration depth of 3.5 mm. Its low-level gamma ray emission (155 keV) makes scintigraphic monitoring as well as dosimetry evaluation possible. The radionuclide ^{188}Re , has a beta ray emission of sufficient energy (2.11 MeV) to penetrate 5 to 10 mm of thickened synovial membrane. Its half-life (16.9 hr) is adequate in terms of obtaining an appropriate therapeutic effect, for handling the agent, or avoiding hazardous residual effects. Nuclear decay characteristic of ^{188}Re is shown in Figure 15.

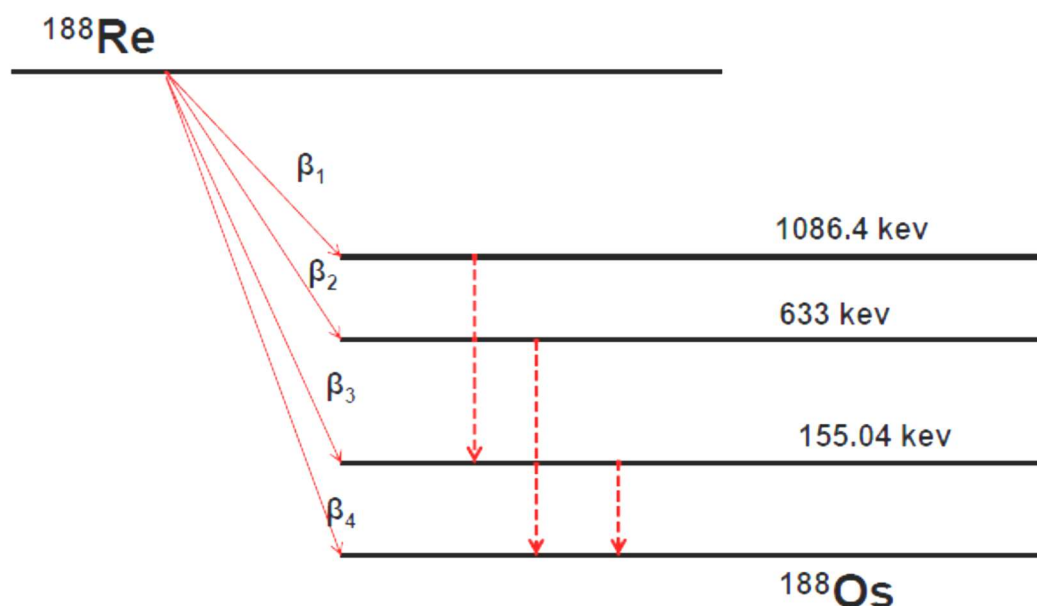


FIG. 15. Nuclear decay characteristic of ^{188}Re (courtesy of Mr. Dash)

Use of ^{188}Re in RSV is associated with the following advantages and disadvantages.

5.6.8.1. Advantages

- (1) ^{188}Re is a more attractive candidate than ^{186}Re since it can be obtained on demand in NCA form in a highly reproducible manner from a $^{188}\text{W}/^{188}\text{Re}$ generator from a hospital base or a central radiopharmacy. The long 69.7-day half-life of the ^{188}W generator parent ensures operational shelf-life of a generator for few months. It is possible to use one generator for 6 to 12 months (depending on the generator rated activity);
- (2) The highly energetic β^- radiations emitted by ^{188}Re ($E_{\beta(\text{max})} = 2.1 \text{ MeV}$) are able to penetrate 5 to 10 mm of thickened synovial membrane; thus, suitable for treating large joints like knees.
- (3) ^{188}Re decay is accompanied by a 155 keV predominant energy gamma emission, which could be detected by gamma cameras, for imaging, leakage, and dosimetry calculation;
- (4) The 16.7 hour half-life of ^{188}Re is optimum for preparing the radiolabelled particles either in a hospital radiopharmacy or centralized radiopharmacies, performing quality control and administration;
- (5) The versatile chemistry of rhenium emerging from eight possible oxidation states, provide the scope for attachment to a variety of bone targeting molecules with specific characteristics. Such a possibility provides great versatility for development of a range of ^{188}Re labelled bone seeking radiopharmaceuticals;
- (6) ^{188}Re is a non-bone seeking and non-residualizing radioisotope that does not linger in the body and lymph node due to extra-articular leakage, making ^{188}Re particularly attractive for RSV; and
- (7) ^{188}Re has the advantage of a tissue penetration equivalent to that of ^{90}Y but a shorter half-life, which is important for the radiation reduction dose due to leakage of radionuclides to non-target organs outside the injected joint.

5.6.8.2. Disadvantages

- Cost effective availability of the $^{188}\text{W}/^{188}\text{Re}$ emerged generator is the main road block which obstructs its wide scale utility in clinical practice.

The vast activity in the use of ^{188}Re in RSV is a reflection of its key clinical importance [280, 422–437].

5.6.9. ^{153}Sm

^{153}Sm decays with a physical half-life of 46.27 hours (1.93 days) by beta emissions of 0.810 MeV (20%), 0.710 MeV (49%), and 0.640 MeV (30%) maximum energies that has a penetration in average range of 0.8 mm and maximum of 3.1 mm in soft tissues. It is produced by neutron capture of natural or isotopically enriched ^{152}Sm with thermal and resonance neutron cross sections of 210 and 3 020 barns, respectively. Nuclear decay characteristic of ^{153}Sm is depicted in Figure 13.

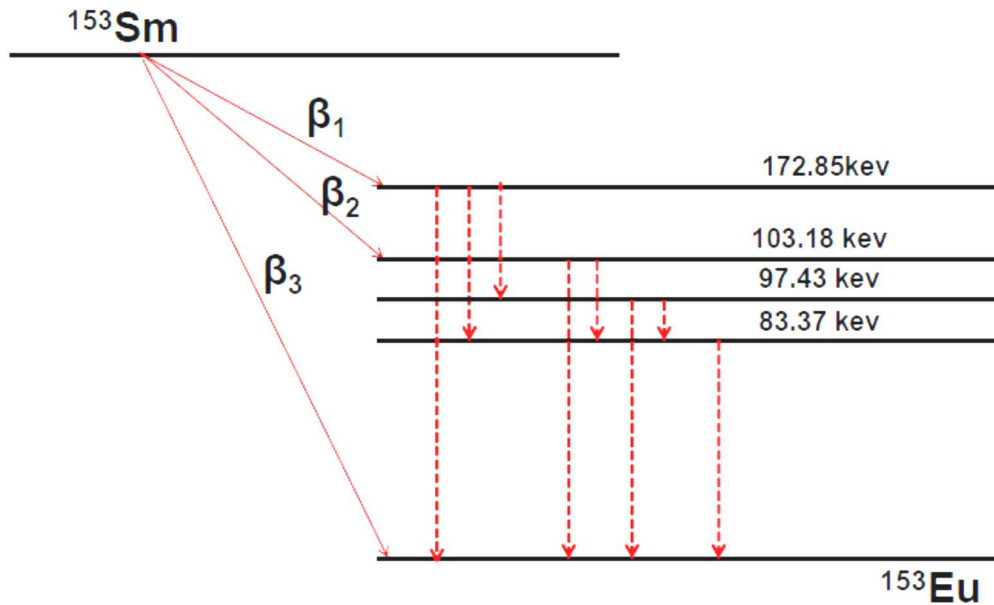


FIG. 16. Nuclear decay characteristic of ^{153}Sm (courtesy of Mr. Dash)

The main advantages of ^{153}Sm are its optimal half-life, relatively high thermal neutron activation cross-section (210 barns) and diagnostic gamma energy of 103 keV, which can be easily distinguished via energy windowing. Hence, images with high spatial resolution and minimal noises can be obtained following each procedure. Although its beta energy is about 2.8 times lower than ^{90}Y , this can always be compensated by administering higher activity of ^{153}Sm to deliver complementary therapeutic dose to the tumour, which can be easily achieved due to its high cross-section value. A number of studies using ^{153}Sm in RSV have been reported in the literature [303, 405–410]. ^{153}Sm has the following advantages and disadvantages when used in RSV.

5.6.9.1. Advantages

- (1) A reasonably half-life of ~ 46.27 h is an advantageous attribute as it decreases the risks associated with eventual leakage of the radioisotope;
- (2) The medium energy beta particles have an average range of 0.8 mm and maximum of 3.1 mm in soft tissues. This tissue penetration depth is satisfactory for synovial membrane ablation without causing substantial damage to nearby extra-articular tissue, including cartilage or bone. The beta energy emitted by ^{153}Sm is suitable for synoviorthesis of medium-sized joints such as hip, shoulder, elbow, wrist, ankle and subtalar joint, and at the same time it offers the possibility to improve the radionecrosis effect using higher radioactivity levels [1];
- (3) The medium energy beta emission offers the protection to the extra-articular tissue and adjacencies from radiation dose;
- (4) The beta decay is accompanied by 28% emission of 103.2 keV gamma rays which can be easily distinguished via energy windowing. Hence, images with high spatial resolution and minimal noises can be obtained following each procedure which can be used for the analysis of leakage to other organs;

- (5) Chemistry of ^{153}Sm offers an enormous scope of conjugating with a wide range of particles following standard radiolabelling procedures by a post-labelling approach; and
- (6) Cost effective production of ^{153}Sm required SA and quantities can be carried out from neutron capture of natural or isotopically enriched ^{153}Sm as Sm_2O_3 in a nuclear reactor following $^{152}\text{Sm}(n,\gamma)^{153}\text{Sm}$ path, due to the relatively high thermal neutron capture cross-section (206 barns). It can be produced in many nuclear reactors throughout the world and can offer a certain degree of independence to import of isotopes for performing RSV.

5.6.9.2. Disadvantages

- (1) The physical half-life is 46.27 hours and creates a logistic disadvantage for shipment to nuclear medicine centres far away from the reactors; and
- (2) Requirement of enriched ^{152}Sm target for the production of ^{153}Sm makes its cost ineffective compare to ^{166}Ho .

5.6.10. ^{117m}Sn

Initially low SA ^{117m}Sn was employed in Phase 1 and 2 clinical trials in the US and Canada for bone pain palliation. This radioisotope emits both conversion electrons (CE) for therapy and gamma energy for imaging. The energy emitted is lower than that of traditional radiation therapy with the CE depositing their energy in an absolute 1/3 mm range in a discreet, predictable fashion with ideal two-week half-life suitable for delivering an extended low dose rate treatment.

5.6.11. ^{90}Y

^{90}Y has a half-life of 64.1 hours and decays to the stable ^{90}Zr daughter product by emission of high energy β^- radiation ($E_{\beta_{\text{max}}}=2.28 \text{ MeV}$ & $E_{\beta_{\text{mean}}}=0.935 \text{ MeV}$). The beta radiation deposits ~80% of the energy in the first 4 to 5 mm, that makes it a nearly ideal radionuclide for intra-articular RSV of large joints (knees). ^{90}Y is an appropriate radionuclide for the knee joint and those with substantially thickened synovia. With a half-life of 2.7 days, the ionisation is persistent enough to shrink this tissue by reducing the production of synovial fluid. A simplified decay scheme for ^{90}Y is shown in Figure 17.

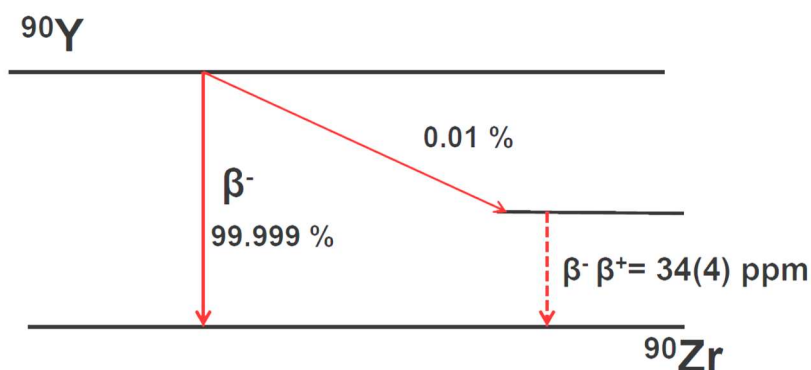


FIG. 17. Simplified decay scheme of ^{90}Y (courtesy of Mr. Dash)

The striking diffusion and the exciting perspective of ^{90}Y in RSV are primarily attributed due to the following reasons:

- (1) A half-life of 64.1 hours is convenient to radiolabel, and performing quality control and administration;
- (2) Being a pure beta emitter of the high energy β^- radiation ($E_{\beta\text{max}}=2.28$ MeV), ^{90}Y has the ability to penetrate deeply into the tissue which makes it an appropriate radionuclide for the knee joint and those with substantially thickened synovia;
- (3) Ensure availability of ^{90}Y on-demand in NCA form in a highly reproducible manner from a $^{90}\text{Sr}/^{90}\text{Y}$ generator from a hospital based or a central radiopharmacy. Owing to the 28.8 year half-life of ^{90}Sr , it is possible to obtain ^{90}Y for long-term usage. Widespread availability of ^{90}Y at a reasonable cost makes it an economical choice for RSV; and
- (4) Yttrium almost exclusively exists in tricationic state and is amenable for the conjugating with a wide range of particles following standard radiolabelling procedures.

5.6.11.1. *Limitations*

- (1) Because of the lack of gamma photons from ^{90}Y , conventional scintigraphic imaging and assessment of the post-therapy distribution of its radioactivity are challenging;
- (2) Handling ^{90}Y safely does require operators with the knowledge and skill to use appropriate radiation protection techniques to minimise the risk of a potentially harmful dose to the skin as it poses a high risk of the skin of the operators and patients; and
- (3) Any leakage that may occur from the joint when combined with the 2.7 days half-life is likely to result in significant integrated radiation doses to other organs, such as the lymph nodes, liver and kidneys.

By far, ^{90}Y is the radioisotope used most extensively in hypertrophic and exudative knee synovitis in patients with rheumatic diseases: rheumatoid arthritis, osteoarthritis and peripheral spondyloarthropathies (psoriatic arthritis and ankylosing spondylitis) [1, 17, 59, 101, 165, 167, 441, 443–475].

The homogeneous $^{117\text{m}}\text{Sn}$ colloid is manufactured to a consistent size range (full width 2 to 20 μm ; mean 5 to 6 μm). The particle size is large enough to allow the $^{117\text{m}}\text{Sn}$ colloid to remain >99% within the injected joint, and yet is small enough to be readily engulfed by the inflammatory synovial macrophages. Preclinical studies on animal models have been completed. A commercial $^{117\text{m}}\text{Sn}$ colloid formulation was well characterized with a validated shelf-life of 2 weeks and is finalizing a trial of dogs with naturally occurring elbow arthritis [476].

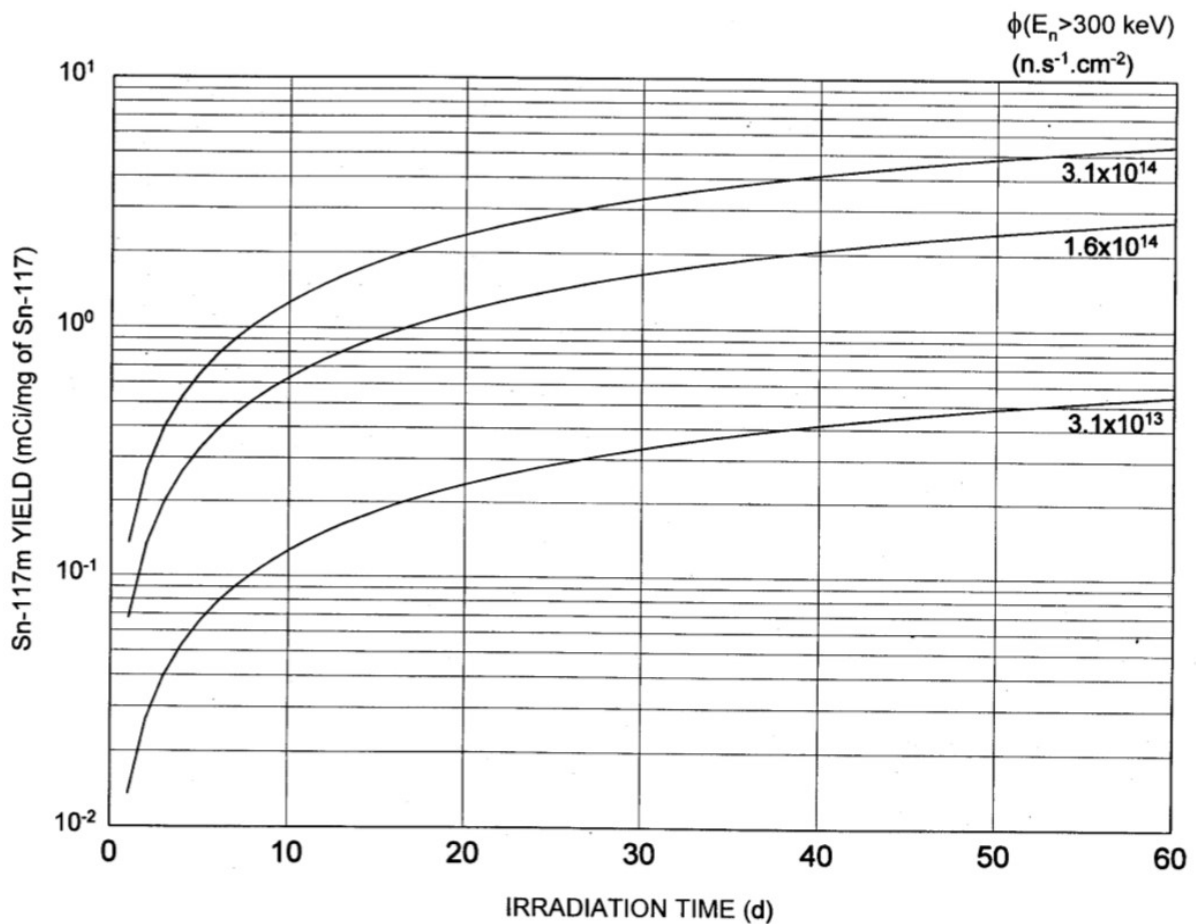


FIG. 18. Production yields of tin117m by the inelastic pathway [190]

6. METHOD USED FOR THE PREPARATION OF PARTICLES FOR RSV

6.1. INTRODUCTION

Particle is the term defined as particulate dispersions or solid particles with diameters in the micrometre range (typically from $1 \mu\text{m}$ to $1000 \mu\text{m}$). It is composed of a homogeneous mixture of a defined chemical composition and can be manufactured from a large variety of starting materials, both natural and synthetic, and by many different preparation techniques. Depending upon the method of preparation and starting materials, a wide variety of particles or microspheres in terms of size, size distribution, composition, surface chemistry, topography and morphology can be obtained. While microspheres are completely spherical and homogeneous in size, particles less homogeneous in size and shape are generally termed microspheres as well. Depending on the preparation method and material used, microspheres show a typical size distribution which often deviates from the mono-sized ideal [185].

Preparation of particles by a simple, low cost and in high yield has been a great challenge since the very early development of RSV. Numerous methods have been developed for preparing particles. The properties of particles depend largely on their preparation methods. Each procedure has specific benefits and drawbacks. The selection of an appropriate method for the preparation of particles depends on the size of required particles and physicochemical characteristics. In this chapter, the method used for the preparation of particles include:

- Precipitation;
- Emulsion;
- Evaporation or extraction of solvent;
- Sol-gel;
- Spray-Drying; and
- Electro spraying processes.

The techniques, principle, advantages and disadvantages of each preparation method are also the point of discussion.

6.2.PRECIPITATION

Precipitation involves mixing two aqueous solutions of soluble salts to form an insoluble precipitate that gets separated. In precipitation method, the precursors used are mostly inorganic salts (nitrate, chloride, sulphate, etc.) that are dissolved in water or any other suitable medium to form a homogeneous solution. The solution is then subjected to pH adjustment and precipitated by the addition of precipitating reagents, usually hydroxides, carbonates, oxalates or citrates etc. to the solution. Precipitation and their aggregation are influenced by the concentration of salt, temperature, the actual pH and the rate of pH change. In actual practice, the precipitate is heated to the required temperature in appropriate atmosphere to undergo condensation. Precipitation reactions involve the simultaneous occurrence of nucleation, growth, coarsening, and/or agglomeration processes.

Nucleation is the formation within a super-saturated solution of the smallest particles of a precipitate (nuclei) capable of spontaneous growth. If the precipitation is carried out in such a manner as to produce numerous nuclei, precipitation will be rapid, individual crystals will be small, filtration and washing difficult, and purity low. On the other hand, if precipitation is carried out so that only a few nuclei are formed, precipitation will be slower, crystals larger, filtration easier, and purity higher. Hence, control of nucleation processes is of considerable significance in precipitation. Once the crystal nuclei are formed, crystal growth proceeds through diffusion of the ions to the surface of the growing crystal and deposition of those ions on the surface. This crystal growth continues until super-saturation of the precipitating material is eliminated and equilibrium solubility is attained.

The reactions tend to exhibit the following characteristics:

- The products of precipitation reactions are generally sparingly soluble species formed under conditions of high super saturation;
- Such conditions dictate that nucleation will be a key step of the precipitation process and that a large number of small particles will be formed;

- Secondary processes, such as the Ostwald ripening and aggregation, will dramatically affect the size, morphology, and properties of the products; and
- The super-saturation conditions necessary to induce precipitation are usually the result of a chemical reaction.

A schematic diagram of precipitation process is illustrated in Figure 19.

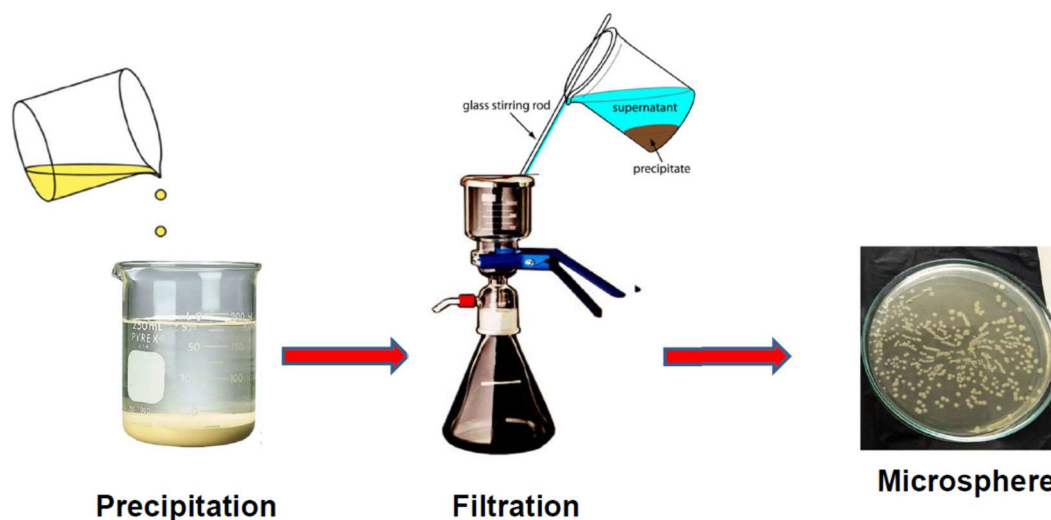


FIG. 19. Schematic illustration of the precipitation process

Precipitations are generally carried out from dilute solutions adding the precipitant slowly with some form of agitation to a hot solution. Normally, the precipitant is then allowed to age before it is removed by filtration and washed. Due to the seemed necessity to avail particles of desired sizes, these precipitates are subsequently calcined at appropriate temperatures, cooled and sieved to obtain the final product. Each precipitation reaction requires its own precursor and precipitating reagent and at the same time each precipitation process requires to control the concentration of the solution, pH, temperature and stirring speed of the mixture in order to obtain the final product with required properties.

Few commonly used steps that dictate the success of precipitation are:

- Taking appropriate stoichiometric amounts of starting materials;
- Making appropriate amount of solution of optimum pH;
- Maintaining optimum pH of the precipitation solution; and
- Performing filtration to remove water, undesired ions and impurities.

A precipitation process should satisfy the following three main requirements:

- (1) Quantitative precipitation is a desirable proposition;
- (2) The precipitate formed should be amenable for filtration and should not creep; and
- (3) The precipitate should be obtained from known purity.

Factors affecting precipitation are:

Rate of precipitation: A slow rate of precipitation is a desirable proposition as it favours the growth of larger crystals. Solubility of the larger crystals is less than that of smaller crystals due to exposure of less surface area to the solution. Gradual addition of dilute solution of the precipitant, with stirring, to a medium is desirable.

Concentration of Ions and Solubility of Solids: The rate of precipitation not only depends on the concentration of ions in solution, but also on the solubility of the solids formed during the equilibrium process. While a solution containing an optimal concentration of ions sufficient to form a precipitate will slow down the process, it is advantageous owing to the ability to form larger crystals of lower solubility.

Temperature: While precipitation at elevated temperatures is a desirable proposition to slow down the nucleation and crystal growth due to the increased thermal motion of the particles in solution, increase in solubility of the precipitate at elevated temperature is an impediment that reduces the precipitate yield. Therefore, an optimum temperature is chosen to balance these opposing factors.

Digestion: Digestion is a process which involves heating the solid and mother liquor for a certain period of time. Growth of larger nuclei or crystallites can be encouraged by digestion. During digestion, the small crystals dissolve and larger crystals grow (Ostwald ripening). Digestion also reduces impurities (occluded ions) effectively as the process reduces the surface area for adsorption of foreign ions owing to the recrystallization of the small crystals and growth of larger crystals. During the process of digestion, impurities are replaced by the common ions that properly fit the crystal lattice.

Solvent: The polarity of the solvent affects the solubility of an ionic solid (precipitate) in the solvent. Addition of other miscible solvent in the solution is avoided as it would alter the polarity. The polarity of water is reduced by the addition of alcohols, thereby reducing the solubility of precipitates.

Common-ion concentration: Addition of the reagent exploiting the common ion effect for the complete precipitation of a particular ion of a sparingly soluble salt having a low value of solubility product is a practice routine. However, in some cases, excess presence of common ions increases the solubility of the precipitate by decreasing the activity of the ions in solution, as they become more concentrated in solution and deviate from ideal behaviour.

Stirring: Stirring the solution during precipitation is desirable as it increases the motion of particles in solution and decreases the localized build-up of concentration of ions. Both of these properties not only slow nucleation and crystal growth, but also promote formation of larger and purer crystals. Stirring also promotes recrystallization because the smaller crystals, with their net larger surface area, are more soluble under these conditions.

Complex-Ion Formation: In order to hold back impurities from precipitating by producing a more soluble form of a solid, formation of complex ions seemed to be an effective approach if pursued diligently.

pH Effect: Altering the pH of aqueous solutions will alter the concentration of ions in the precipitation equilibrium by the common-ion effect if the hydrogen ion (H^+) or hydroxide ion (OH^-) is common to the equilibrium.

Precipitation from homogeneous solution: Addition of a precipitating agent to a solution of ions causes a localized excess of the reagent (higher concentrations) to form in the mixture. While the excess reagent is conducive to rapid formation of a large number of small crystals, it produces a precipitate of imperfect crystals that contains excessive impurities. The precipitate formed under these conditions is sometimes voluminous and difficult to filter. Localized excesses can also cause precipitation of more soluble solids than the expected precipitate.

Re-precipitation: This approach increases the purity of precipitates. During the initial precipitation, precipitate formed contains only a small number of foreign ions as a result of adsorption. Upon dissolution of the precipitate, the foreign ions are released into solution, producing a concentration of impurities much lower than that in the original precipitating solution [477]. On re-precipitation, a small fraction of impurities is carried down with the precipitate, but the relative amount is much less than the original because their concentration in solution is less. While elimination of foreign ions due to adsorption is not ruled out, their concentration can be reduced to an appreciable extent.

The precipitation method offers the following advantages:

- (1) Precipitation is a very simple and rapid method for the synthesis of small sized particles, homogeneously and evenly distributed having single phasic nature;
- (2) It requires very low heating treatment, sometimes no need to calcinate the product, only infrared or microwave drying is sufficient;
- (3) It is possible to avail uniform particle size;
- (4) Offer the scope for controlling the particle size and composition;
- (5) It is preferable when large quantities of particles are required;
- (6) It offers a variety of precursor selections to choose as starting materials from simple salts to complicated organic-inorganic materials;
- (7) Various possibilities to modify the particle surface state and overall homogeneity; and
- (8) Cost effective and easy to set-up and scale up.

Despite the above benefits, this method provided has its share of challenges:

- (1) Precipitation method has the difficulty of controlling the process in terms of reaction kinetics and the solid phase nucleation and growth processes. Therefore, solids obtained by chemical precipitation have a wide particle size distribution plus uncontrolled particle morphology, along with agglomeration;
- (2) Precipitation method is very much pH sensitive which should be carefully controlled to achieve better products;
- (3) Precipitation method is highly susceptible to the reaction conditions, and because of incomplete precipitation of the metal ions, control over the stoichiometry of the precursors is rather difficult to achieve; and
- (4) Precipitation method does not work well in cases where:
 - (i) The two reactants have different solubilities in water;
 - (ii) The reactants do not precipitate at the same rate; or
 - (iii) Super-saturated solutions commonly occur.

6.3. EMULSION: EVAPORATION OR EXTRACTION OF SOLVENT

The emulsion technique is used for the preparation of microsphere of natural polymers, i.e. proteins and carbohydrates. The process essentially consists of emulsification of polymers in oil-in-water (o/w) in which the organic phase composed of a volatile solvent dissolved the polymer and emulsified in an aqueous phase. In the light of perceived need to prevent the organic droplets from coalescing after their formation, inclusion of a surfactant in the aqueous phase deemed worthy of consideration. During the second step polymer solvent is evaporated, inducing precipitation. The particles are collected by ultracentrifugation and they are washed with distilled water to remove impurities. A flow sheet of emulsion technique is depicted in Figure 20.

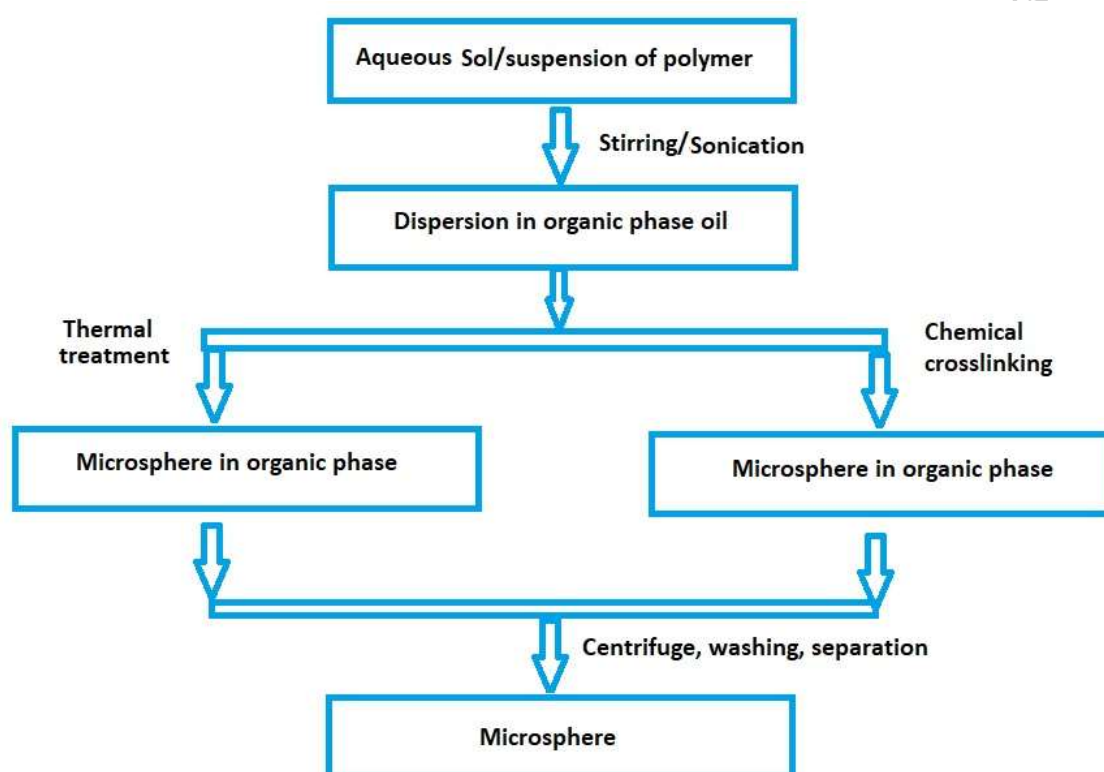


FIG. 20. A flow sheet of emulsion technique (courtesy of Mr. Dash and Mr. Jalilian)

The polymer solvent solution is emulsified (with appropriate experimental conditions) by using a propeller or magnetic bar for mixing the organic and aqueous phases to yield an o/w emulsion. The next step consists of cross linking the dispersed globule either by means of heat or by using the chemical cross linkers. Glutaraldehyde, formaldehyde, acid chloride etc are the common chemical cross-linking agents used. Heat denaturation is not recommended for thermolabile substances. The nature of the surfactants used to stabilize the emulsion phases can greatly influence the size, size distribution, surface morphology, and in vivo stability of the final particulate product [478, 479]. Particle preparation by emulsion technique is depicted in Figure 21.

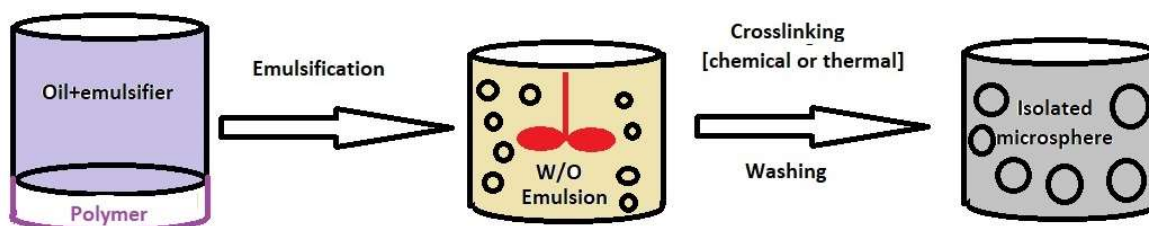


FIG. 21. Microparticle preparation by emulsion technique (courtesy of Mr. Dash and Mr. Jalilian)

The preparation method consists basically of four major steps [480]:

- (1) Dissolution of polymer in organic solvent containing the matrix forming material;
- (2) Emulsification of this organic phase called dispersed phase (DP) in an aqueous phase immiscible with the first one called continuous phase (CP);
- (3) Extraction of the solvent from the dispersed phase by the continuous phase and evaporation of solvent; and
- (4) Harvest and dry of the microspheres.

Operating conditions such as ratio of DP to CP, agitation, pressure and temperature have a great influence on the solvent evaporation and consequently on the structure of the particles.

The emulsion processes offer the following advantages:

- Easy to control the particle size;
- Gives potential for rapid polymerisation to yield high molecular weight polymer with low polydispersity;
- Viscosity of polymer emulsion is much lower than that of straight polymer in melt phase. Easier to process but also allows production of polymers that are extremely sticky as 100% polymer;
- Final product can easily be removed from reactor due to lower viscosity (and can be washed out with water); and
- Continuous phase (water) acts as a heat sink and allows temperature to be much better controlled, avoiding dangerous overheating.

Some disadvantages associated with this technique are:

- Emulsions are thermodynamically unstable and have short shelf-life;
- Polymer can easily become contaminated with traces of the emulsifier; and
- Improper selection of the emulsifying agent leads to phase inversion and sometimes it may also lead to cracking.

6.4.SOL-GEL PROCESS

Sol-gel is a wet chemistry processing route to prepare micro particles or microspheres that encompasses preparation of a sol, gelation of the sol to avail gel, and the removal of the liquid existing in fine interconnected channels within the gel. It basically involves the transformation of liquid precursors to a sol and finally to a network structure called a 'gel' which contains both liquid phase and solid phase. The morphologies of these two phases range from discrete particles to continue polymer networks and offer the scope for controlling the chemical composition of the product [481].

Sol: A sol is a dispersion of the solid particles ($\sim 0.1-1 \mu\text{m}$) in a liquid where only the Brownian motions suspend the particles [474]. A sol is a state in which solid particles are neither dissolved, nor agglomerated or sedimented. Generally, the sol particles may interact by van der Waals forces or hydrogen bonds. The stability of sols may be maintained by using dispersing agents' sols are commonly used in preparing sol-gel [482].

Gel: A gel is a state where both liquid and solid are dispersed in each other, which presents a solid network containing liquid components [483]. A gel is a solid, jelly-like material that can be defined as a substantially dilute cross-linked system, which exhibits no flow in the steady-state. While gels are mostly liquid by weigh, they behave like solids owing to the presence of three-dimensional cross-linked net-work within the liquid. The interactions between gel particles are of short-range and the gel process is irreversible [484, 485]. The solid network within the fluid of a gel contributes its structure (hardness) and primarily responsible for its adhesive characteristics [481].

The preparation method consists of the following steps:

- (1) Dispersion of the desired colloidal particles in a liquid to form a sol following hydrolysis and partial condensation of alkoxides;
- (2) Formation of the gel via polycondensation to form metal–oxo–metal or metal–hydroxy–metal bonds;
- (3) Syneresis or 'aging' where condensation continues within the gel network, often shrinking it and resulting in expulsion of solvent;
- (4) Drying the gel either to form a dense 'xerogel' via collapse of the porous network or an aerogel, for example through supercritical drying; and
- (5) Removal of surface M–OH groups through calcination at high temperature up to 800°C (if required).

A schematic diagram of various steps involved in the sol gel process for micro-particles/micro-spheres preparation by are shown in Figure 22.

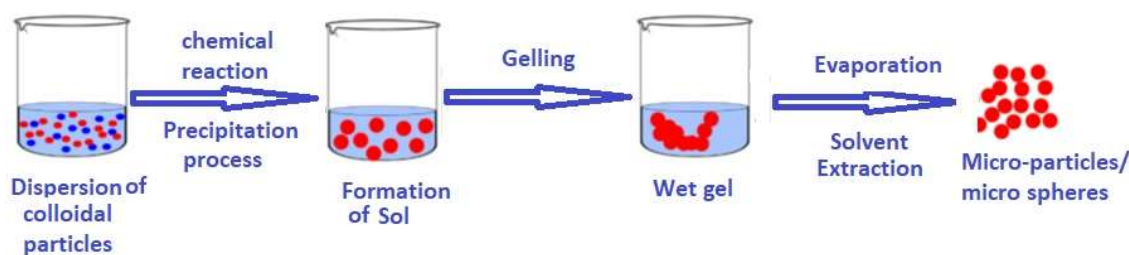


FIG. 22. Micro particles/micro spheres preparation by sol-gel (courtesy of Mr. Dash and Mr. Jalilian)

A sol-gel synthesis basically involves two major steps: the first step essentially consists of creation of a colloidal solution from the hydrolysis and polymerization reactions of the precursors; and the second step is the conversion of this solution into a gel usually by hydrolysis, by adding a gelling agent or by hydrothermal treatment. In the second step, the sol is chemically transformed into a gel [486]. Experimental factors that affect either or both of these reactions impact the properties of the gel and, in turn, the properties of the material at the subsequent processing steps. These factors include chemical nature of precursor, type of solvent, water content, acid or base content, precursor concentration, and temperature.

The physico-chemical process involved during the sol-gel process consists of:

- (1) **Mixing:** The alkoxide precursor is hydrolyzed by mixing it with water. In sol gel process, controlling the pH of starting solution is very important to avoid the precipitation as well as to form the homogenous gel, which can be achieved by the addition of base or acidic solutions [487];
- (2) **Gelation:** The condensation reaction can build up larger networks by processing polymerization to form a three-dimensional network, which leads to form the gel. The gelation time will depend up on the temperature, solvent, pH condition and also removal of the solvent;
- (3) **Aging:** After gelation, the wet gel can be either aged in its mother liquor, or in another solvent, or washed. The time between the formation of a gel and its drying is known as aging. During the aging, the polycondensation takes place and results in the expulsion of liquid from the pores. This increases the thickness of particle necks and decreases the porosity. Thus, with aging, the strength of the gel increases;
- (4) **Drying:** Liquid existing in the interconnected pore network is removed during the drying process. Thus, there is a decrease in the volume of the gel, which is equal to the volume of the liquid lost by evaporation. Here after drying, the pores of the gel are substantially emptied;
- (5) **Stabilization:** The removal of the unwanted elements likes H and R respectively from M-OH and M-OR bonds to obtain the chemically stabile required compound; and
- (6) **Densification:** Densification is the last treatment process of the gel. By heating the porous gel at high temperatures, the pores can be eliminated and densified where poly crystalline can be obtained. The densification temperature depends on the dimension of the pore network, the conductivity of pores, surface area, among others.

Sol-gel process possess the following advantages:

- There is no need to reach the melting temperature, since the network structure could be achieved at relatively low temperatures;
- Sol-gel process provide a variety of precursors to select as starting materials. It provides the scope for preparing microspheres of extended composition range, including inorganic as well as organic compositions;
- It is possible to control the structure of microspheres, including porosity and particle size;
- Sol-gel process produces homogeneous particles (due to mixing at the molecular level), having small and uniform size distribution;
- Sol-gel process yields predefined stoichiometric compound of monodispersive nature.
- Smaller particle size and offers the possibility to control the morphology;
- Sol-gel is very easy to handle and set-up, precluding the need for special or expensive equipment; and
- It is cost effective.

Besides those advantages, sol-gel process also has its own disadvantages:

- Requirement of expensive raw materials (in the case of metal alkoxides) compared to mineral based metal ion sources;
- Shrinkage of a wet gel upon drying may leads to fracture due to the generation of large capillary stresses. As a result, it is difficult to obtain large monolithic particles;
- Particles would contain high carbon content when organic reagents are used in preparative steps and this may inhibit densification during sintering;
- As the process is multistep, close monitoring of each step is warranted; and
- Difficulties encountered during the preferential precipitation of a particular oxide during sol formation, due to the different reactivity of the alkoxide precursors.

6.5.SPRAY DRYING

Spray drying is a technique in which a fluid is transformed from a fluid state into dried particulate form by spraying the feed into a hot drying medium by atomization in a hot drying gas stream that is generally air [488]. The process seemed sagacious as it involves both particle formation and drying. Based on the action of drying, transformation of liquid from a fluid state into dried particulate is divided into two main categories i.e. spray drying and spray congealing. In spray drying the action is primarily that of evaporation, whereas in spray congealing the action consists of a phase change from a liquid to a solid. While the two processes are similar, energy flow is different. In the case of spray drying, energy is applied to the droplet to cause evaporation of the medium resulting in both energy and mass transfer through the droplet. On the other hand, energy is only removed from the droplet, forcing the melted to solidify in spray congealing [489].

There are four fundamental steps involved in spray drying [490, 491]:

- (1) Atomization of a liquid feedstock into a spray of fine droplets. The atomization stage is designed to create the optimum conditions for evaporation and to lead a dried product having the desired characteristics. Selection of an atomizer is primarily based on the droplet sizes to be produced in order to meet the particle size required [492];

- (2) Spray-air contact, mixing and droplet/particle flow. When the feed is atomized and sprayed through the drying chamber, the droplets come into contact with the heated drying medium resulting in solvent evaporation;
- (3) The third stage consists of combination of drying and particle formation. As soon as contact between spray droplets and the drying air is established, evaporation of the solvent takes place immediately. In this process, diffusion of solvent from within the droplet is maintained at saturated surface conditions to result in a constant drying rate. When the solvent content in the droplet becomes too low to sustain a saturated surface, a dry layer began to form at the droplet surface; and
- (4) Particle separation from the drying air and collection of the dry product from the gas stream.

Figure 23 depicts a schematic diagram of the typical spray-drying process.

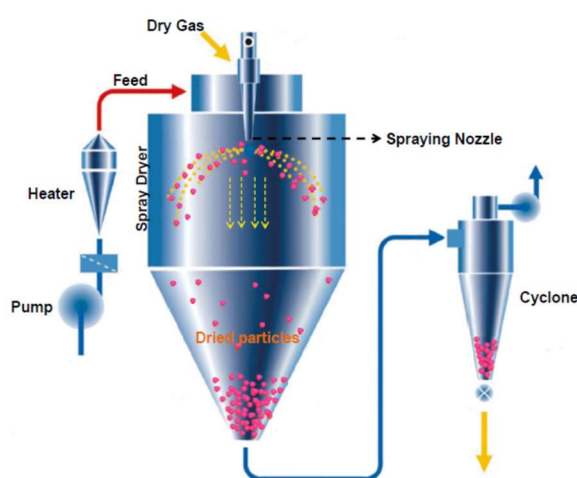


FIG. 23. A schematic diagram of the typical spray-drying process (Courtesy of Mr. Dash)

At the beginning, the fluid is fed into the drying chamber using a suitable pumping device through an atomizer or nozzle [493]. The small droplets generated (micrometre scale) are brought into contact with hot gas (usually air, at a vacuum) in a spray dry chamber, resulting in a fast solvent evaporation in the droplets leading to the formation of dry particles [494]. The way in which the spray makes contact with the air in the dryer influences the behaviour of the droplet during the drying phase and has a direct bearing on the properties of the dried product. Different products have differing evaporation and particle-forming characteristics. Some expand and others contract, fracture or disintegrate.

Following completion of drying, the product particles are separated from the drying air following primary and final separation strategies. Primary separation is realized by allowing the particles to fall at the bottom of the chamber in which a small fraction of the particles remain entrained with the air and could be recovered in separation equipment. Cyclone is used for the final separation stage to deposit particles in a glass collector situated in the bottom of the device.

The fluid used in spray-drying process includes solutions, suspensions, emulsions, slurries, pastes or melts [495, 496]. The operation configurations in spray-drying may be either open-loop or closed-loop. Air is used in open-loop configuration as drying gas and is not re-

circulated. On the other hand, an inert gas (e.g., nitrogen) is used as a drying gas in closed-loop configuration and is re-cycled in the drying chamber throughout the entire process. The open-loop configuration is widely used as it is more cost-effective and stable.

Operating parameters that can fine-tune to obtain product of desirable characteristics are:

- (i) Process parameters;
- (ii) Properties of the liquid feed;
- (iii) Equipment design.

The spray-drying process has the following advantages:

- The process is rapid, continuous, reproducible, single-step, and scalable;
- Product reproducibility: as long as the drying conditions remain constant, the dried product characteristic remains constant;
- Possibility to obtain uniform and controllable particle size;
- It is suitable for heat-sensitive and non-drying heat-sensitive materials without major detrimental effects, owing to the atomization of the liquid into small droplets with high surface area-to-volume ratio that results in very fast solvent evaporation;
- Solid products obtained after the process have the advantage of higher chemical and physical stability compared to liquid formulations;
- Commercial availability of a wide variety of sprays to meet the conditions;
- Provide the scope for precise control over particle size, bulk density, degree of crystallinity, organic volatile impurities and residual solvents; and
- Ability to produce nearly spherical uniform particles in sizes.

Regardless of the numerous advantages displayed by spray-drying process, it has the following limitations:

- Product yield strongly depends on the work scale while yields are high in larger scale setups. The yield being in the 20% to 70% range in the laboratory scale;
- Spray drying has dryer convection, and the thermal efficiency is relatively low, generally between 30% to 40%; and
- Expensive and bulky equipment.

5. Electro-spraying

In a typical electro hydrodynamic process, a liquid precursor is fed to a nozzle with an aim to form a droplet at the nozzle. Upon the exposure of the droplet to a strong electric field, a charge is induced on the surface of the droplet. Under the influence of the electrostatic field, the droplet at the tip of nozzle forms a conical shape spraying mode. From the tip of this cone, a charged jet of liquid precursor is driven to the collector, which carries a charge opposite to the droplet or is grounded.

Processing parameters (e.g. working distance, voltage) techniques can be effectively tuned to produce micro and nano scale fibres and particles composed of polymers, ceramics or composites [497, 498]. There are two main techniques in the electro hydrodynamic atomization processing: electro spraying and electro spinning. Electro spraying describes a technique where

particles are created while the term electro spinning is used in situations where fibres are created. Electro-spraying is a method of producing particles by using a high voltage electric field to break up a solution.

Electro-spraying is a physical process used for the formation of particles from a variety of materials in which a viscous liquid is subjected to an electrical shear stress by maintaining the nozzle at a high electric potential. This process precludes the use of additional mechanical energy other than that from the electric field. In this process a liquid precursor is passed through a capillary which is held at high potential. The effect of the high electric field as the solution emerges from the capillary nozzle in the form of a fine jet is to disperse into highly charged droplets [499]. The droplets produced by electro spraying are usually close to one-half of the Rayleigh limit, and can be smaller than 1 μm . The size distribution of the droplets is usually narrow, with low standard deviation. During that transition, the droplets reduce in size by evaporation of the solvent or by ‘Coulomb explosion’ (droplet subdivision resulting from the high charge density). Eventually, fully desolvated ions as a consequence from complete evaporation of the solvent or by field desorption from the charged droplets is formed. It is possible to produce small, nearly monodisperse particles using a colloidal suspension or a solution of a material through this route [500]. The size of the droplets can be effectively controlled mainly by fine tuning the liquid flow rate, and the droplet charge by regulating the voltage applied to the nozzle. It is important to emphasize that the charged aerosol is self-dispersing, which prevents the droplets from coagulation. The standard electro spraying configuration is shown in Figure 24.

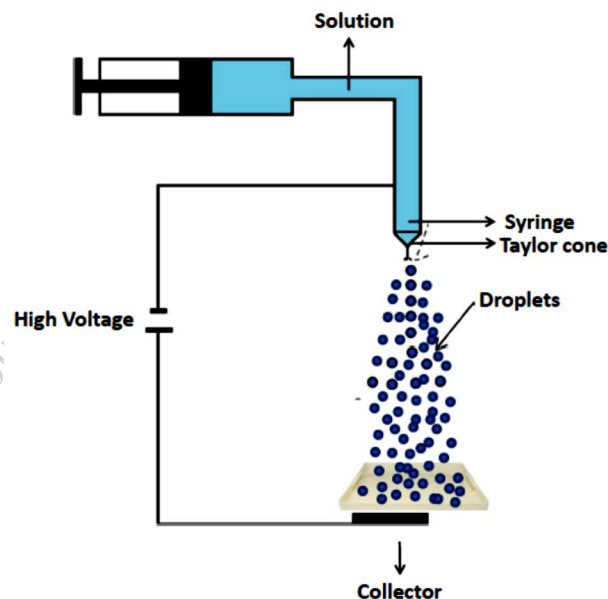


FIG. 24. Standard electro-spraying configuration (Courtesy of Mr. Dash)

It basically consists of four major components:

- (a) A pumping system (often a syringe pump);
- (b) A metal nozzle;
- (c) A high voltage power supply; and
- (d) A grounded substrate as collector.

The solution delivered to the tip of the electro-spray capillary experiences the electric field owing to the preservation of the tip at high potential. For a sufficiently high applied potential, the free charges at the surface of the liquid leaving the nozzle cause an electrical stress that leads to the formation of what is commonly called the Taylor cone-jet mode (the meniscus at the tip of the nozzle forms a conical shape) [501]. At the apex of the cone where the free charges are highly concentrated, the liquid accelerates away from the nozzle via a ‘budding’ process when the surface tension is exceeded by the applied electrostatic force and a jet with high charge density is obtained. The diameter of the droplets formed is influenced by a number of parameters, including the applied potential, the solution flow rate and solvent properties [502]. At this point of time, the fate of the jet is determined by the competition between the electrostatic repulsion and the surface tension stress on the liquid-gas interface holding the droplet together. The charged liquid jet, at some point, will break up into droplets. Fission (Coulomb explosion) will occur at the point (the Rayleigh limit) at which the magnitude of electrostatic repulsion is sufficient to overcome the surface tension holding the droplet together. During their flight to the collector, the solvent evaporation makes the primary droplets to shrink which leads to the increase in charge concentration, so the primary droplets finally will break up into smaller offspring. Various mechanisms operating in the electro spraying process of making particles/microsphere are shown in Figure 25.

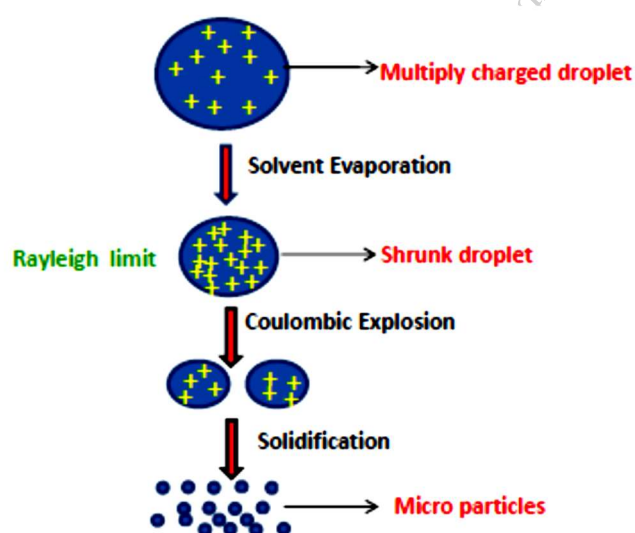


FIG. 25. Mechanism of electro-spraying process of making particles/microsphere (Courtesy of Mr. Dash)

There are numerous advantages of electro-spraying for particle generation:

- Ease of particle synthesis due to single-step processing: the electro-spray process lends itself well to efficient high through put particle formation as it is an easy and continuous process;
- Generate particles of uniform size and shape: as charged droplets are self-dispersing in the space, possibilities of droplet agglomeration and coagulation could be avoided;
- It offers the scope to operate at atmospheric conditions, and the rate of particle production is easy to tune by adjusting voltage and flow rate.

- Because the flow rates and compositions of the sprayed liquids are controlled independently, and both are independent of the composition of the collection liquid, the process is very flexible;
- Long-term stability of the emulsion is assured owing to the presence of residual charge on the particles;
- Possibility to fabricate smaller particles (of μm range) by tuning the solution and process parameters; and
- Narrow particle-size distribution, with low standard deviation.

Like any other process, the electro spraying process also has the following limitations:

- An equipment used for electro-spraying is inexpensive;
- Low-throughput of electro-spraying process;
- Difficulties encountered while controlling the mode of spraying;
- Electro spray is very sensitive to liquid, physical properties and the electric field in the vicinity of the emitter tip; and
- Highly conductive solutions, such as salt solutions, may be too conductive to hold a charge to reach the target droplet size.

7. REGULATORY AND MANUFACTURING ISSUES

7.1. THE RADIOPHARMACEUTICAL MANUFACTURING ELEMENTS

In Europe and US, radiopharmaceuticals are considered as a special group of medicines and are regulated by a number of directives, regulations and rules. One of the directives is that the manufacturing of radiopharmaceuticals for RSV should be undertaken in accordance with the principles of Good Manufacturing Practice (GMP). In Europe, GMP rules have legal character as they are issued by the European Medicines Agency (EMA) and the DG Enterprise & Industry of the European Commission. The level of precaution required depends in particular upon the radionuclide handled such as types of radiation, the energy of radiation and the half-lives.

The Radiopharmacy Committee of the European Association of Nuclear Medicine, has prepared a guidance document on 'Good Radiopharmaceutical Practice for small scale production of radiopharmaceuticals (cGRPP)', with an aim to provide a more sustainable alternative to the classic GMP that apply to the pharmaceutical industry, while maintaining the same quality, safety and efficacy standards. cGRPP should provide a general framework for the preparation of radiopharmaceuticals on a 'small scale' basis, which cover all practical aspects.

Preparation of radiopharmaceuticals for RSV should be carried out with strict adherence to radiation protection guidelines prescribed by the regulatory authority of the country. While undertaking the preparation of radiopharmaceuticals for synovectomy, care must be taken to the prevention of cross contamination, to the retention of radionuclide contaminants, and to waste disposal. Radiopharmaceuticals should be carried out under aseptic working conditions to avail sterile products.

As the radiolabelled particles for RSV is meant for parenteral administration, they should be sterile. The frequency of testing depends on the practice followed by the institution. Usually, the samples for sterility testing are stored with an aim to decay the radioactivity content sufficiently and then sent for sterility testing by an external, validated laboratory. Internal sterility testing is only recommended subjected to the availability of dedicated rooms and equipment. While awaiting the result of the sterility of the product that is not practicable before release for clinical use because of short half-life of the radionuclide, the test should constitute a part of QC. The production process of radiolabelled particles should be validated by using appropriate test runs at regular intervals as per pharmacopoeias.

The aseptic work area should be suitable for the preparation of radiolabelled particles. The light perceived needs to limit the presence of microorganisms and particulate matter, and the air quality in the aseptic processing area needs to be adequately controlled at regular intervals [503]. Critical activities in the preparation and testing of radiolabelled particles or the sterile surface of the container/closure system to the environment should be conducted within an aseptic workstation with a rating of Grade A [503], including the following:

- The aseptic workstation where radiolabelled particles preparation is carried out require to be sanitised at appropriate intervals;
- Microbiological monitoring of the workstation needs to be carried out during aseptic activities;
- Care should be taken in such a way that during that time no additional personnel enters the room;
- Items within the aseptic workstation should be kept to a minimum; and
- Working personnel should wear designated lab coats and sterile arm protection and sterile gloves when conducting an aseptic manipulation within the aseptic workstation, and that the work should be done in a well-planned and expedient way.

The basic concepts of QA, GMP, and QC are inter-related. In this chapter, we aim to portray their relationships and their importance pertaining to the production and control of products [504]. The basic requirements of GMP are as follows [505]:

- (a) Procedure for the preparation of radiolabelled particles for RSV should be clearly defined, systematically reviewed and shown to be capable of producing required quality and complying with their specifications consistently. Procedures are written in a clear and unambiguous language;
- (b) All critical parameters of preparation process are required to be validated;
- (c) All necessary facilities to ensure GMP include: suitable equipment and services; correct materials, containers and labels; approved procedures and instructions; adequate premises and space; and qualified and trained personnel.
- (d) Availability of trained personnel to perform and ensure product reproducibility correctly.
- (e) It is essential to record the defined procedures and instructions taken and the quantity and quality of the product obtained. Any significant deviations from the SOP must be fully recorded and investigated;
- (f) Complete history of a batch must be recorded and retained in a comprehensible and accessible form. Complaints about the quality of the supplied products are examined, the causes of quality deficiencies investigated, and appropriate measures taken to prevent reoccurrence; and

(g) Availability of a system to recall any batch of product, from sale or supply.

7.1.1. Personnel

- (1) Preparation should be carried out under the responsibility of personnel having competence in radiation protection and radiopharmaceutical specific aspects of the quality management system;
- (2) All personnel involved in the preparation of radiolabelled particles should receive appropriate training specific to radiolabelling procedures and products analysis; and
- (3) Personnel must be adequately trained in GMP regulations and the QA function.

7.1.2. Premises and equipment

- (1) Radioactive products should be handled in controlled designated areas. Preparation of radiolabelled particles should be carried out either in a lead shielded fume hood or in a special hot cell facility;
- (2) The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination;
- (3) Access to the radioactive area should be restricted to authorised personnel;
- (4) Working should be monitored regularly with respect to radioactive contamination, particulate and microbiological quality and should adhere established performance qualification;
- (5) Regular preventive maintenance, calibration and qualification programmes should be in place to ensure that facilities and equipment used in the preparation of radiolabelled particles are appropriate and qualified. Their records and logs should be maintained;
- (6) Appropriate controls should be in place not only to prevent radioactive contamination within the facility, but also to detect any radioactive contamination;
- (7) Appropriate measures should be taken to protect the areas where preparation of radiolabelled particles is carried out from particulate and microbial contamination; and
- (8) Hot-cells meant for radiolabelled particles preparation should meet a high degree of air cleanliness, with filtered feed air, when closed and operates under aseptic conditions.

7.1.3. Documentation

In light of perceived need to achieve GMP compliance, it is essential to have a full documentation system providing traceability that include [198]:

- Records of each lot of ingredients and excipients received with an identification code number;
- Records of each lot of radioisotope received with an identification code number;
- Records of product preparation: batch numbers, activity and volume added, results of quality control and release;
- Specifications of ingredients, excipients and radioisotopes;
- Laboratory cleaning and maintenance, in addition to the date, time and signature of the persons involved in these activities;
- Equipment calibration and maintenance, as well as the date, time and signature of the persons involved in these activities;
- Operating procedure;

- Batch processing records;
- Training of personnel;
- Transport of radioactive materials;
- Radioactive contamination monitoring and radioactive waste disposal, in addition to the date, time and signature of the persons involved in these activities;
- Product defects and events of non-conformity to SOP; and
- Microbiological monitoring.

A system of documentation must be in place to allow traceability of each preparation step [504]:

- (1) All documents related to the radiolabelled particles preparation should be made, reviewed, approved and followed as per the written procedures;
- (2) Specifications of the starting materials including radionuclides as well as the finished radiolabelled particles should not only be established, but also documented;
- (3) Specifications, any other critical items and those likely to impact on the quality should also be in place;
- (4) Acceptance criteria of radiolabelled particles including criteria for their release as well as shelf life for clinical use should be established and specified;
- (5) Procedures used for the preparation and sterilisation of radioactive particles including batch number, date, time and signature of the persons involved in these activities should be recorded; and
- (6) These records should be preserved for a duration of least 3 years unless and otherwise another time frame is specified in national requirements.

7.1.4. Training

- (1) All production and QC personnel should receive appropriate training in the principles of GMP, radiation protection and preparation of radiolabelled particles; and
- (2) Continuing training should be given by qualified individuals, and its practical effectiveness should be periodically assessed and recorded.

7.1.5. Quality Assurance

QA covers all activities which can individually or collectively influence the quality of radiolabelled particles for RSV. The system of QA should ensure that:

- (1) They are prepared considering the requirements of GMP;
- (2) Preparation and control operations are clearly specified and GMPs applied;
- (3) All staff responsible for ensuring the quality are clearly specified;
- (4) Necessary arrangements should be made to ensure availability of sufficient starting material and active pharmaceutical ingredients of requisite quality to undertake preparation of radiolabelled particles;
- (5) Preparation of radiolabelled particles should be carried out according to the defined procedures;
- (6) Radiolabelled particles should not be used for therapy unless an authorized person has certified that each batch has been produced and controlled in accordance with the

requirements of the regulatory authority of the country relevant to the production, control and release of radiopharmaceuticals for therapy;

- (7) Necessary arrangement should be in place to ensure that the radiolabelled particles are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life; and
- (8) A quality audit system is essential to regularly appraise the effectiveness and applicability of the quality assurance system.

The principles of qualification and validation should be applied to radiolabelled particles preparation and a risk management approach should be in place to determine the extent of qualification/validation, focusing on a combination of Good Manufacturing Practice and Radiation Protection.

7.1.6. Quality Control

QC of radiolabelled particles concerned with specifications, testing, documentation and release procedures ensure that the necessary and relevant tests are actually carried out for their safe clinical use. This is an important part of the overall quality control procedures performed in the nuclear medicine department. The basic requirements of QC mandated by GMPs are as follow:

- Adequate radiological facilities, skilled manpower and approved procedures are available for testing of starting materials, intermediate materials, and finished radiolabelled particles;
- A system to verify the quality of starting materials should be in place;
- Testing of starting materials, active pharmaceutical ingredients, intermediate materials, and finished radiolabelled particles should be carried out by trained personnel following approved validated QC methods;
- Records should be made to demonstrate that all the required testings are actually carried out and meet required specifications. Any deviations must be recorded and investigated;
- Batch processing records encompassing production conditions and analytical testing performed should be assessed by a designated person before sending it to the clinical department;
- It is necessary to ensure availability of a written procedure pertaining to the assessment of quality of the radiolabelled particles;
- Radiolabelled particles complying with the qualitative and quantitative acceptance criteria required for RSV should be enclosed in a proper glass container and correctly labelled;
- Radiolabelled particles that fail to meet acceptance criteria should be rejected;
- Product assessment including a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures should be in place;
- Batch of product released for clinical use should be certified by an authorized person ensuring that satisfactory test results have been received and assessed in accordance with the regulatory requirements of the country; and
- Samples of each batch of radiolabelled particles should be retained for at least six months unless otherwise justified through risk management practices.

7.1.7. Responsibilities

The responsible person for the preparation of radiopharmaceuticals should bear the following responsibilities [503]:

- To establish procedures for the examination and evaluation of incoming materials required for the preparation of RSV agents and ensure that each lot of incoming material comply with specifications;
- To review the preparation batch records and laboratory control records and conformance of established specifications before authorizing the final release or rejection of a batch;
- To approve preparation methods including related SOP and product specifications;
- To ensure the personnel involved in the preparation of radiolabelled particles are suitably trained and qualified;
- To scrutinize errors and ensure that corrective action is taken to preclude their reappearance; and
- To ensure that the radiolabelled particles have requisite strength, quality and purity amenable for RSV procedure.

The person responsible for QA should have the following responsibilities:

- To manage the overall QA system;
- To verify that the documentation is correctly written and followed; and
- To conduct periodic audits in order to ensure that established procedures and practices are in compliance with stipulated norms.

The person responsible for production should have the following responsibilities:

- (1) To write the SOP related to radiolabelled particles preparation, and to ensure that they are implemented;
- (2) To approve the radiolabelled particles preparation;
- (3) To evaluate, sign and store the production records;
- (4) To ensure that the radiolabelled particles are produced and stored according to the appropriate documentation in order to obtain the required quality; and
- (5) To verify that premises and hot cells are correctly maintained according to prescribed maintenance programme.

The person responsible for QC should have the following responsibilities [503]:

- (1) To write the SOP related to QC operations and verify that they are religiously followed;
- (2) To define specifications, test methods and other QC procedures are applicable;
- (3) To approve or reject starting materials based on their quality;
- (4) To evaluate, sign and store QC reports, records of starting materials and finished products;
- (5) To evaluate the batch records; and
- (6) To verify that premises and QC equipment are correctly maintained according to prescribed maintenance programme.

7.2.QUALITY EVALUATION OF RSV AGENTS

Since radiolabelled particles are intended for administration to humans, it is imperative that they undergo strict QC measures. Basically, it involves several specific tests and measurements that ensure the following aspects of radiolabelled particles:

- Purity
- Potency
- Product identity
- Biologic safety
- Efficacy

No discussion about RSV is complete without mentioning QC issues. It is the key factor that underpins its success, survival and strength. It is primarily divided into 3 parts:

- (1) QC of the particle
- (2) QC of the radionuclide
- (3) QC of the radiolabelled particle

7.2.1. QC of the particle

7.2.1.1. Determination of the particle density

The density (ρ) is an elementary physical property of the particle and is defined as the ratio of its mass (m) to its volume (V):

$$(2) \quad \rho = \frac{m}{V} [\text{kg m}^{-3}]$$

The SI unit of density is kg m^{-3} . However, g cm^{-3} is another unit commonly used in laboratories. Its conversion is: $1 \text{ g cm}^{-3} = 1000 \text{ kg m}^{-3}$.

Density determination by pycnometer is a very precise method. The pycnometer (from the Greek puknos, meaning 'density', also called pycnometer or specific gravity bottle), is a flask with a close-fitting ground glass stopper with a fine hole through it. This fine hole releases a spare liquid after closing a top-filled pycnometer and allows for obtaining a given volume of measured and/or working liquid with a high accuracy. A given mass of the particle is added to the pycnometer, which is then weighed, thus giving the weight of the particle. A photograph of a pycnometer is shown in Figure 26.

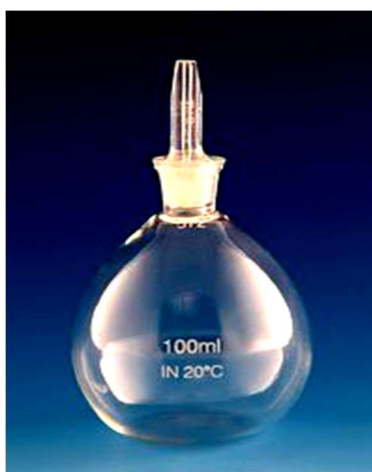


FIG. 26. Photograph of a pycnometer (courtesy of Mr. Jalilian)

The pycnometer is then filled with a liquid (water) of known density where the particle is completely insoluble. The weight of the displaced liquid can then be determined, and thence the specific gravity of the particle. The weight of the pycnometer must be measured together with the inserted solid particle m_0+m_s . We add water and determine the weight m_{water} (weight $m_0+m_s+m_{\text{water}}$).

First, it is essential to determine the weight of the pycnometer together with inserted object m_0+m_s . Then water is added and its weight m_{water} is determined (measured weight minus m_0+m_s). The volume of added water V_{water} can be obtained as:

$$(3) \quad V_{\text{water}} = \frac{m_{\text{water}}}{\rho_{\text{water}}}$$

The volume of the measured particle V_s is the difference between the volume of water that fills the empty pycnometer V and volume V_{water} .

Density of measured object ρ_s can be then calculated as:

$$(4) \quad \rho_s = \frac{m_s}{V_s}$$

It is essential that the particle used in RSV should have a density of approximately 0.7 to 2.0 gm/mL, preferably from 0.7 to 1.3 gm/mL. Its density should be such that the particulate matter of a suspension will not tend to settle the liquid form vehicle in which it is dispersed. Particles used in RSV should be suspendable in pharmaceutical acceptable vehicles.

Sieve analysis is the oldest and most widely known method used to characterise particle size distributions [506]. The particle size distribution is defined via the mass or volume. The process divides the particulate material into size fractions by passing the material through a number of sieves of different mesh sizes and then used to determine the mass fraction of particles within each size range.

The particles are vibrated through a series of sequentially decreasing sieves using a single, or combination of horizontal, vertical or rotational motion in accordance with the chosen method. This causes a relative movement between the particles and the sieve; depending on their size the individual particles either pass through the sieve mesh or are retained on the sieve surface. Particles under motion will eventually orientate to present their 2 smallest dimensions to the sieve mesh opening and pass to the next sieve of smaller nominal opening. The likelihood of a particle passing through the sieve mesh is determined by the ratio of the particle size to the sieve openings, the orientation of the particle and the number of encounters between the particle and the mesh openings. Upon completion of the sieving process the weight of the sieves is measured and compared to the weight of the sieves before addition of the sample. This gives the mass of the material on each sieve. Through addition of the mass fraction on each sieve, from the smallest to the largest sieve size, a cumulative mass distribution of test sample is obtainable.

Sieving analysis of dry particle as per USP General Test 786 Method is as follows [507]:

- Tare each test sieve to the nearest 0.1 g;
- Place an accurately weighed quantity of test specimen on the top (coarsest) sieve and replace the lid;
- Agitate the nest of sieves for 5 min;
- Carefully remove each sieve from the nest without losing material;
- Reweigh each sieve and determine the material weight on each sieve;
- Determine the material weight in the collecting pan in a similar manner;
- Reassemble the nest of sieves and agitate it for 5 minutes;
- Remove and weigh each sieve as previously described; and
- Repeat these steps until the end point criteria are met (the weight on any of the test sieves does not change by more than 5% of the previous weight on that sieve).

When the analysis is completed, the analyst reconciles the material weights. The total losses must not exceed 5% of the weight of the original test specimen. If particles retained on any sieve are aggregates (rather than single particles), then the use of dry sieving is not likely to be an easily reproducible method. At that point, the analyst could consider the use of Method II as an alternate technique [507]:

- Modify the lid and collecting pan of the sieve nest to permit the addition of a liquid onto the surface of the top sieve and the collection of the liquid from the pan;
- Select a liquid in which the test specimen is insoluble and modify the sieving method as follows;
- Thoroughly disperse the dried test material in the liquid by gentle agitation and pour this dispersion onto the top sieve;
- Rinse the dispersion equipment with fresh liquid and add the rinsing to the top sieve;
- Feed the sieving liquid through a suitable pumping mechanism to the nozzle(s) in the lid and collect the sieving liquid from the pan in a suitable container;
- Continue the wet-sieving process until the emerging liquid appears to be free of particles;
- Remove each sieve from the sieve nest and dry each sieve to constant weight at the same temperature as that previously described; and
- Determine the weight of the dried material on each sieve.

One must remember that the particle diameter information obtained using analytical sieving represents the minimum square aperture through which the particle can pass [507]. Details of the particulate shape influence the separation of particles by sieving because particles will pass through openings on the basis of their cross-sectional diameter.

7.2.1.2. Dynamic Light Scattering Method

Dynamic light scattering (DLS) method is a preferred method for particle sizing owing to its short analytical time, robustness, high precision, reproducibility, wide measurement range and flexibility of operation using liquid, spray and dry dispersion. When a laser beam is passed through liquid suspensions containing particles in Brownian motion, it experiences fluctuations in its intensity due to light scattering. In the DLS instrument, measurements of this fluctuation of intensity at a given scatter angle are used to infer the particle size or the ‘hydrodynamic diameter’ of the suspended particles. The DLS instruments measure the fluctuations in the intensity of the scattered light with time in order to generate an exponentially decaying autocorrelation function. This function is then analysed for characteristic decay times, to determine the diffusion coefficient unique to the scattering suspensions in conjunction with the Stokes-Einstein equation, the hydrodynamic radius.

The primary advantage of the DLS method is that it provides an absolute measurement without any further information about the composition and the optical properties of the particles in suspension [481]. The lower limit of the instrument depends on the laser power and signal-to-noise ratio that can be as low as 2 nm. The data obtained using the instrument is usually in two formats depending on the type of algorithms used for the inversion of the autocorrelation function. A Gaussian distribution is typically used to represent unimodal dispersions. The used algorithms provide information about the mean particle size, widths and peak modes of the particle size distributions. The intensity-based data, collected by the instrument, can be reliably reduced to a volume-weighted PSD.

One of the disadvantages of the DLS method is that samples in some cases may require significant dilution for accurate size measurements, which can be problematic for measurement of droplet sizes of emulsions. Figure 27 depicts the schematic components of a DLS system.

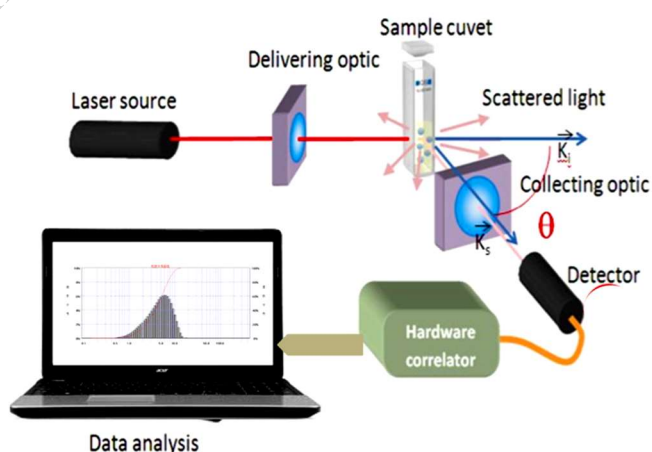


FIG. 27. Schematic diagram of a typical DLS system (Courtesy of Mr. Dash)

7.2.1.3. Scanning Electron Microscopy

An electron microscope is a type of microscope which uses a particle beam of electrons to illuminate a specimen and create a highly-magnified image. Electron microscopes have much greater resolving power than optical microscopes and can obtain much higher magnifications of up to 2 million times, while the best optical microscopes are limited to magnifications of several thousand times. Both electron and light microscopes have resolution limitations, imposed by the wavelength of the radiation they use. The greater resolution and magnification of the electron microscope is because the wavelength of an electron, i.e. De Broglie wavelength is much smaller than that of a photon of visible light.

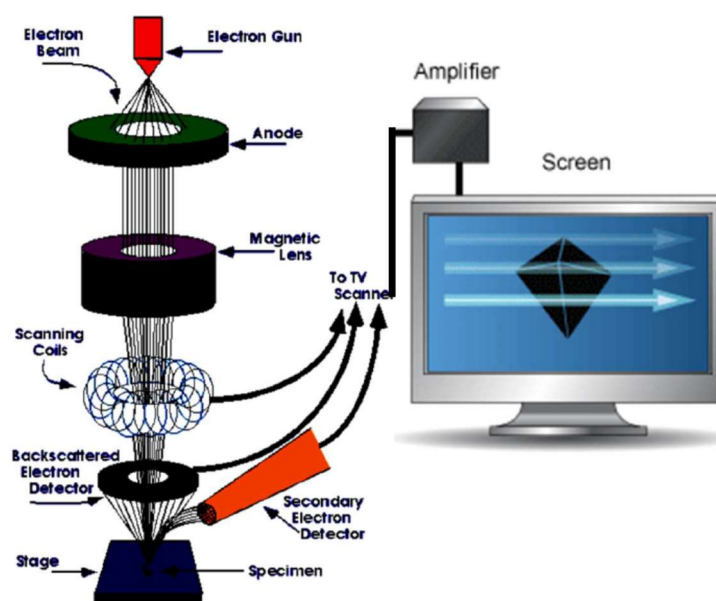


FIG. 28. Schematic diagram of typical scanning electron microscope (Courtesy of Mr. Dash)

Figure 28 shows the schematic diagram of a typical electron microscope. The scanning electron microscope is a type of electron microscope that images the sample surface by scanning it with a high-energy beam of electrons in a raster scan (it is the rectangular pattern of image capture and reconstruction in television or computer that then highlights on the screen) pattern. The electrons interact with the atoms and hence make up the sample producing signals that contain information about the sample's surface topography, composition and other properties.

7.2.2. QC of radionuclides

7.2.2.1. Radionuclide purity

Radionuclide purity is defined as that percentage of radioactivity of the radionuclide of interest to the total radioactivity of the radioactive preparation. The purity of the radionuclide is based upon the percentage of the radionuclide present in the desired radionuclide (free from contaminants) and determines whether other radionuclides that are not of interest are present in the solution. Such radionuclide impurities arise during the radionuclide production; hence,

they are dependent on the production method–route. Any other radionuclide other than the one of interest is considered to be an impurity [508]. Radionuclidic purity is an important quality parameter and it is mandatory that the radionuclide impurities to be within the stipulated limits.

7.2.2.2. Determination of the nature and energy of the radiation

Determination of the nature and energy of the radiation emitted could be carried out using several procedures including construction of an attenuation curve and the use of spectrometry. The attenuation curve offers the scope for analysis of beta radiation.

Gamma(γ) ray spectrometry: gamma (γ) ray spectrometry is mostly used for identification of γ rays and detectable X rays. The measured energy of a γ ray corresponds to the type of element and its isotope, while the number of counts corresponds to the abundance of the radioactive source present in the measured sample with some little considerations. The success of gamma ray spectrometry technique requires information on the photo-peak efficiency of the detector as well as in the counting geometry for each photon energy. Figure 29 depicts the gamma ray spectrum for ^{177}Lu obtained from a high purity germanium detector.

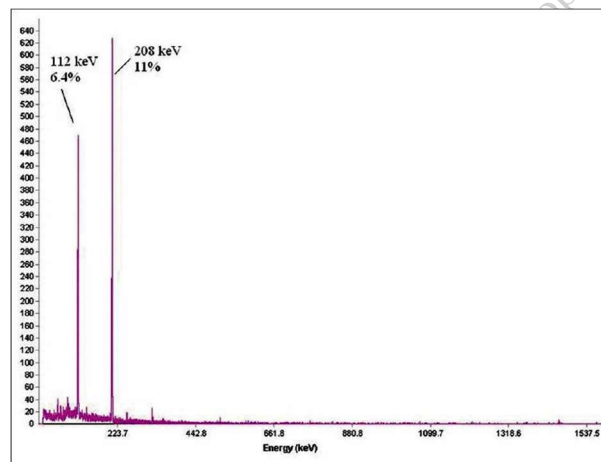


FIG. 29. Gamma ray spectrum for ^{177}Lu [192]

The preferred detector for γ and X ray spectrometry is a high-purity germanium. High purity germanium detector is the most sensitive and efficient device, and it is widely used in determining activity of radionuclides from higher order down to pCi level [509].

The gamma detector needs to be calibrated using standard sources owing to fact that detection efficiency is a function of the energy of the γ and X rays as well as the form of the source and the source-to-detector distance. The detection efficiency is generally measured using a calibrated source of the radionuclide to be measured or, for more general work, a graph of efficiency against γ and X ray energy may be constructed from a series of calibrated sources of various radionuclides.

The detector efficiency, E , at a given photopeak energy for a given geometry is determined by using a known quantity or concentration (for a volume geometry) of a γ emitting radionuclide, as follows:

$$E = \frac{C}{A \times B}$$

(5)

Where:

- C = net count rate, cpm, (integrated counts in the photopeak above the base line continuum divided by the counting time in minutes);
- A = activity of radionuclide added to the given geometry container (dpm); and
- B = the γ ray abundance of the radionuclide being measured (gamma/disintegration).

The γ and X ray spectrum of a radionuclide which emits γ and X rays is unique to that nuclide and is characterized by the energies and the number of photons of particular energies emitted per transformation from one energy level to another energy level. This property contributes to the identification of radionuclides present in a source and to their quantification.

The isotopes indicated by the γ spectrum are determined as follows:

- Identify all photopeak energies;
- Integrate the photopeak regions of the spectrum and subtract the area under the base line continuum to determine the true photopeak area;
- Radionuclides are identified by their appropriate photopeak, and ratios to each other when more than one gamma photon is emitted by an isotope in the sample; and
- Radionuclide impurity are identified by detecting peaks other than those expected.

Calculation of the radionuclide concentrations of the sample is as follows:

$$A = \frac{C}{B \times E \times V}$$

(6)

Where:

- C = net count rate, cpm, in the peak area above base line continuum;
- B = the gamma ray abundance of the radionuclide being measured (gammas/disintegration);
- E = detector efficiency (counts/gamma) for the particular photopeak energy being considered;
- V = volume of sample aliquot analysed.

Gamma spectrometry offers the scope to establish the rate of the decay of radioactivity using the peaks to diminish in amplitude as a function of the $T_{1/2}$. If in a sample, a radioactive impurity with a different $T_{1/2}$ is present, it is possible to detect the latter by identification of the characteristic peak or peaks, which amplitudes decrease at a different rate from that expected for the particular radionuclide. A determination of the $T_{1/2}$ of the additional peaks by repeated measurements of the sample will help to identify the impurity. Due to differences in the half-lives of the different radionuclides that can be present in a solution, the radionuclidic purity

changes with time. The requirement of the radionuclidic purity must be fulfilled throughout the period of validity.

7.2.2.3. Attenuation curve

Determination of energy of beta energy for pure beta emitters is carried out from the attenuation curve when spectrometer for β rays is not available or for β/γ emitters when gamma spectrometer is not available.

This method essentially consists of estimating the maximum energy of β radiation (beta max) which provides only an approximate value. The source, suitably mounted to a fixed geometry, is placed in front of the thin window of a Geiger-Müller counter or a proportional counter. The source is protected as described above. The count rate of the source is then measured. Between the source and the counter are placed, in succession, at least six aluminium screens of increasing mass per unit area. The position and geometry of the detector, foils and the source must be the same during this measurement. Within such limits that with a pure beta emitter this count rate is not affected by the addition of further screens. The screens are inserted in such a manner that constant geometrical conditions are maintained. A typical attenuation graph of β emitting radionuclide is shown in Figure 30.

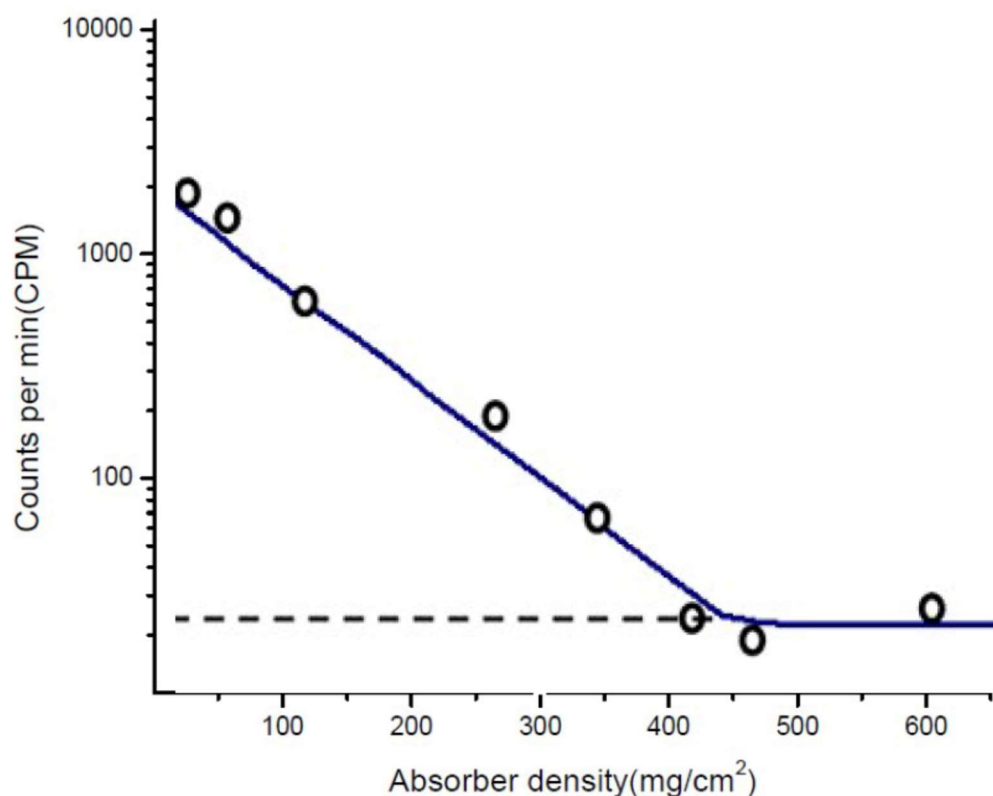


FIG. 30. Attenuation graph of beta emitting radionuclide (courtesy of Mr. Dash)

A graph is drawn in which the mass per unit area expressed in milligrams per square centimetre as the abscissa, and the logarithm of the count rate as the ordinate for each screen examined. A

graph is drawn in the same manner for a standardized preparation. The mass attenuation coefficients are calculated from the median parts of the curves, which are practically rectilinear.

The mass attenuation coefficient μ_m , expressed in square centimetres per milligram, depends on the energy spectrum of the beta radiation and the nature and the counting geometry. It therefore allows beta emitters to be identified. It is calculated using the equation:

$$(7) \quad \mu_m = 2.303 \frac{\log A_1 - \log A_2}{m_1 - m_2}$$

- m_1 = mass per unit area of the lightest screen;
- m_2 = mass per unit area of the heaviest screen, m_1 and m_2 being within the rectilinear part of the curve;
- A_1 = count rate for mass per unit area m_1 ;
- A_2 = count rate for mass per unit area m_2 .

The mass attenuation coefficient μ_m , thus calculated, does not differ by more than 10% from the coefficient obtained under identical conditions using a standardized preparation of the same radionuclide. The range of beta particles is an additional parameter which can be used for the determination of the beta energy. It is obtained from the graph described above as the mass per unit area corresponding to the intersection of the extrapolations of the descending rectilinear part of the attenuation curve and the horizontal line of background radioactivity.

Liquid scintillation counting (LSC) may be used to obtain spectra of α and β emitters. Due to the low penetrative power of beta radiation, the detection efficiency of beta emitters is quite low, and the quantification of beta emitting isotopes is carried out by using LSC. The best possible contact is achieved when the sample is dissolved in the scintillation solution. By counting the photons produced in the reaction of beta particles with the scintillator, the quantification of beta emitting isotopes can be easily carried out. In LSC, the radionuclide is mixed with a cocktail, which consists of a solvent and scintillator (fluor), where the decay energy will be transferred to the cocktail, and converted to photons, by counting the photons using a PMT (photomultiplier tube), where the activity of radionuclides is measured. A digital picture of the energy distribution of the isotope is obtained using a multi-channel analyser, which is a memory that stores the electrical pulses from the PM tubes of LS counter. Beta spectrum of $^{90}\text{Sr}/^{90}\text{Y}$ taken in LSC coupled to a multi-channel analyser is shown in Figure 31.

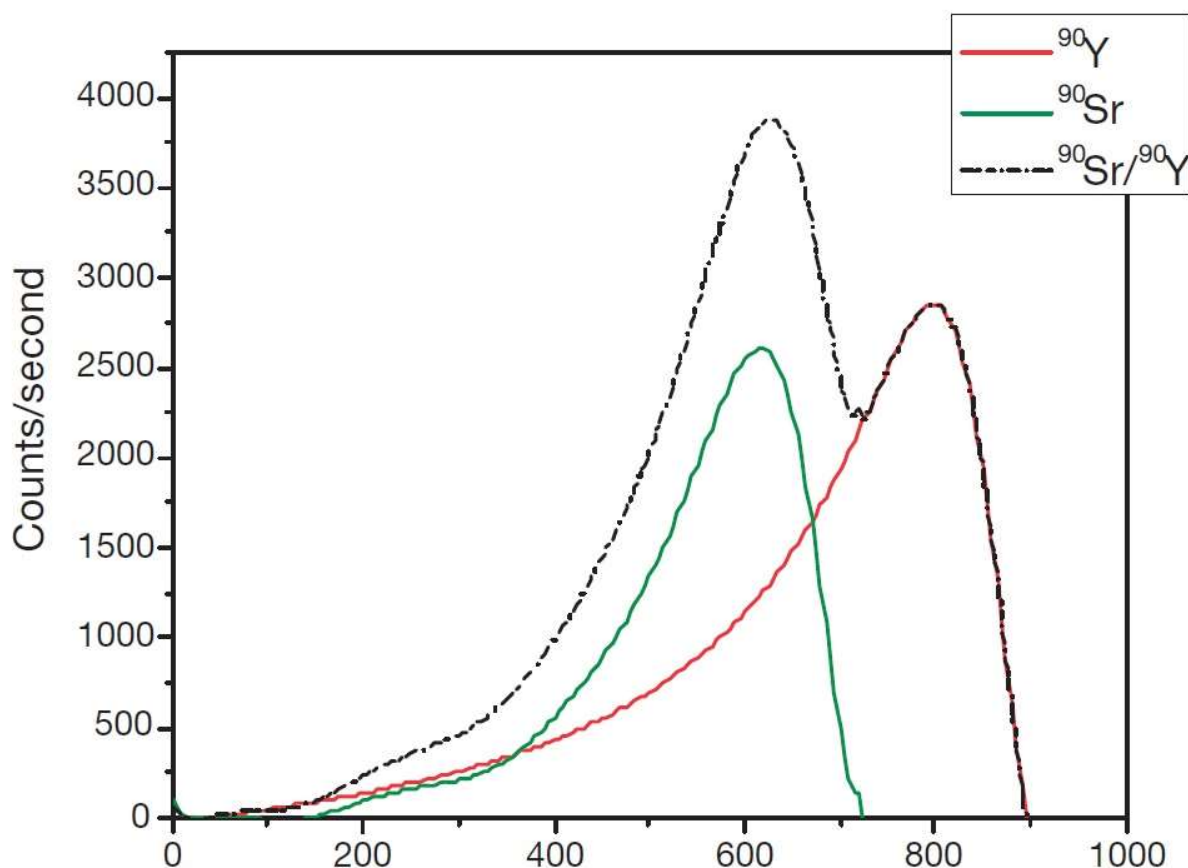


FIG. 31. Spectra for the $^{90}\text{Sr}/^{90}\text{Y}$ taken in a LSC coupled to multi-channel analyser⁶

7.2.2.4. Radiochemical purity

The ratio—expressed as a percentage—of the radioactivity of the radionuclide of interest in a stated chemical form, to the total radioactivity of that radionuclide present in the preparation, is referred to as ‘radiochemical purity’. Considering the perceived need to determine the radiochemical purity of a radionuclide, it is essential to separate different chemical substances containing the radionuclide and estimate the percentage of radioactivity associated with the declared chemical substance. The origin of radiochemical impurities may be during: the radionuclide production step; subsequent chemical processing; incomplete preparative separation; and chemical changes during storage. The requirement of the radiochemical purity must be fulfilled throughout the validity period.

Radiochemical purity can be determined by using analytical techniques by including paper chromatography, thin-layer chromatography, instant thin-layer chromatography, electrophoresis, size-exclusion chromatography, and liquid chromatography. Instant thin-layer chromatography assay uses specific cellulose backed silica gel chromatography strips as a solid phase. This method is easy to use, rapid and can be incorporated easily in a routine quality

⁶ Figure 31 available at INTERNATIONAL ATOMIC ENERGY AGENCY, Therapeutic Radionuclide Generators: $^{90}\text{Sr}/^{90}\text{Y}$ and $^{188}\text{W}/^{188}\text{Re}$ Generators, Technical Reports Series 235, IAEA, Vienna (2009).

control program. Thin-layer and paper chromatography are also commonly used. As very small quantities of the radioactive material applied, a carrier may be added while undertaking the analysis. Subsequent to the development of the chromatogram, the support is dried, and the positions of the radioactive areas are sensed by autoradiography or by measurement of radioactivity over the length of the chromatogram by using suitable collimated counters or by cutting the strips and counting each portion. The positions of the spots or areas permit chemical identification by comparison with solutions of the same chemical substances (non-radioactive) using a suitable detection method. Detection of the radioactivity in the strip can be carried out in a number of ways.

The percentage of activity in each section can then be determined. For example, if a strip is cut in two sections 'A' and 'B', then the percentage activity in section A is given by:

$$(8) \quad \%A = \frac{A \times 100}{A + B}$$

The strip can be imaged under a gamma camera and regions of interest can be drawn around the areas of radioactivity from which the percentage of counts in each region can be determined. Although this method offers the advantage of imaging the whole chromatography strip enabling artefacts to be seen, it is not practicable for most hospital departments due to the cost of camera time. The strip can be imaged using a radiochromatogram scanner which uses a sodium iodide detector to detect the radioactive emission. If the scanner is linked to an integrator, then quantification of the peaks can be carried out. One of the major limitations to paper and thin layer chromatography methods of determining RCP is the resolving power of the methods.

7.2.2.5. High Performance Liquid Chromatography

High performance liquid chromatography (HPLC) has a higher sensitivity and resolving power than simple TLC and PC methods. HPLC separation is based on the hydrophilic/lipophilic properties of the components of a sample used. The detectors used are either radioactive or UV or refractive index which can be connected in series allowing simultaneous identification of compounds. It is pertinent to pointed out that HPLC does not detect colloidal contaminants and that this should be estimated using TLC methods.

7.2.3. QC of radiolabelled particles

The flow properties such as syringeability and injectability of the radiolabelled particles suspension are the major determinants that govern its success in RSV:

- Syringeability describes the ability of the suspended radiolabelled compound to pass easily through hypodermic needle on transfer from the vial prior to injection. Increase in the viscosity, density, particle size and concentration of solids in suspension hinders the syringeability of suspension; and
- Injectability refers to the performance of suspension during injection and includes factors such as pressure or force needed for injection. Evenness of flow, aspiration qualities, and freedom from clogging.

The syringeability and injectability of suspension are closely related to the viscosity and particle characteristics of the suspension (as shown in Figure 32):

- Clogging or blockage of syringe needles while administering a radioactive particle suspension may occur because of a single large particle or an aggregate that blocks the lumen of the needle or because of a bridging effect of the particles; and
- Drainage refers to the ability of the suspension to break cleanly away from the inner walls of the primary container-closure.

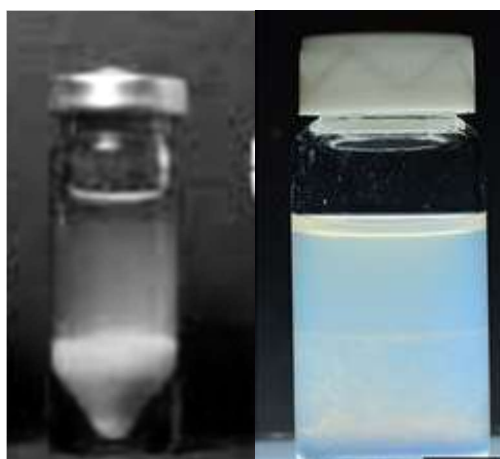


FIG. 32. Photograph of a radiolabelled particles suspension

The number of particles and their sizes amenable for RSV applications in a preparation could be determined with several methods, such as with autoradiography or phase-contrast microscopy if the sample is placed on a haemocytometer grid [510]. Alternatively, transmission electron microscopy may be used.

Stability studies

Radiolabelled particles must be stable until the time of administration. A procedure prior to administration is as follows: radiolabelled particles must be kept at room temperature or at 37°C for 2 and 24 hours after radiolabelling in (2 mL each) saline solution (0.9 % NaCl), ascorbic acid (pH 5), human serum and human synovial fluid diluted 1:1 with saline (to reduce viscosity). In every case the percentage of bound activity must be measured.

Approximately 1 mg of the particles are to be placed in a 10-mL vial, and 2 mL of each medium is to be added. The vials will be stoppered and placed on a rocking platform for gentle agitation, then immersed in a water bath incubator maintained at 37 °C for 2 and 24 hours. At various times, the tubes are to be removed and 2 mL of saline is to be added; the tubes will be then shaken and centrifuged at 5,000 rpm for 5 min. Three aliquots of 1 mL each are removed from each test tube with a volumetric pipette and placed in three different 10-mL vials so that the geometry was the same in all the samples. The vials are then to be counted in a NaI(Tl) well type counter. The release of activity from the radiolabelled particle should be less than 5%.

The long-term particle size stability of radiolabelled particles can be checked with gel filtration [511], photon correlation (PC) spectroscopy [511, 512] and microfiltration [512]. The

radiochemical stability can be checked with, e.g., paper chromatography, thin-layer chromatography, high-pressure liquid chromatography (HPLC), gel filtration and electrophoresis.

7.2.3.1. Size of radiolabelled particles

Since batch-to-batch differences in radiolabelled particle size sometimes, routine quality control of radiolabelled colloids is essential. This is primarily focused on the determination of particle size together with checking the radiochemical purity. In this method, either the particle-size or the activity-size distribution is obtained.

Electrophoresis: It is possible to separate colloid particles carrying charge by electrophoresis. Lim et al. [513] developed an elaborate technique to measure the size and charge distributions of colloid particles by combining electrophoresis and laser light scattering measurements.

Gel filtration: Colloid preparations may be eluted through a chromatographic bed in a column in order to separate particles of different sizes following the method reported by Persson et al. [514] on filtration technique for colloids in which the colloid sample is applied at the top of the column and eluted with 10 mL of isotonic saline. The column is sealed afterwards and scanned using a slit-collimated NaI(Tl) detector. The scanning profile obtained provides qualitative information on the size distribution as well as the presence of radiolabelled impurities. This technique could be used for routine quality control of radiolabelled particles. The method described by Billingham and Jette [515] for determining the activity-size distribution of colloids can also be used.

Scanning electron microscopy: it can be used to determine the size distribution, particle shape, concentration, and chemical composition. In this method, the radioactive particle sample is usually spread on a polycarbonate filter and allowed to dry [511]. Low-Z particles are then coated with a thin layer of gold foil not only to increase the image contrast, but also to prevent heat effects. With a freeze-fracture technique it is possible to eliminate the risk of volatilization of particles [515].

Transmission electron microscopy: it can be used to determine the size distribution, particle shape, particle concentration, and chemical composition. Before undertaking the analysis, the radioactive particle sample is spotted onto or nebulized on a plastic-coated grid and allowed to get dry or partially dry. This method suffers from the drawback that there is the possibility that the particles may change or sublime due to the vacuum in the microscope and the heat of the electron beam, which encounters difficulties for analysis of the preparations containing stabilizers and contaminants [516]. In spite of this drawback, Warbick et al.[516] found this method preferred choice for determining size of radioactive particles.

Photon correlation spectroscopy: Photon correlation spectroscopy technique involves the illumination of a particle solution with a laser in which the light scattered at 90° is detected in a photomultiplier. As the particles move and diffuse in the solution due to the Brownian motion, the scattered light will give rise to a diffraction pattern. The rate at which this intensity pattern changes is inversely proportional to the particle size. A computer is used to calculate the average particle size and a polydispersity index, which is an indication of the width of the size distribution [512].

Ultra-filtration: It is essentially a pressure-driven process in a liquid flow through a membrane [517]. The technique is based on the separation of particles and molecules according to the molecular weight cut-off value of the membrane. In this method, the membrane retains most particles above its retention rating and permits most smaller particles, along with the solvent to flow through it. There is a possibility that some percentage of the particles get adsorbed on the surface of the membrane and create a 'gel layer' which in turn may have a higher retention than the membrane itself. In order to circumvent this phenomenon, it is essential to establish the 'gel-layer' by conducting a pre-filtration step before consistent results could be obtained.

Microfiltration: This method makes use of polycarbonate membrane filters of well-defined pore sizes for microfiltration [518]. The commercially available Nuclepore[®] polycarbonate membranes with 17 different pore sizes, ranging from 0.01 μm to 12 μm could be employed for this method. In this method, a sample of radioactive colloid is allowed to pass through a membrane (held in a filter holder) followed by washing it with a 2 mL distilled water. The fraction of activity passing the filter can then be determined by radioactivity measurements on the filter, and it filtrates by using a radioisotope calibrator or a well type NaI(Tl) detector.

Ultracentrifugation: Ultracentrifugation technique could also be used for sizing colloids. In this method, a sample of radioactive colloid is layered on a sucrose gradient and is then spun in an ultracentrifuge with the intent to separate the gradient into fractions. Each fraction is then measured for radioactivity by using a radioisotope calibrator or NaI(Tl) detector. The success of the technique resides on the effective calibration of the radioactive detector.

Microscopy: Phase contrast microscopy or light microscopy is an optical-microscopy technique that converts phase shifts in light passing through a transparent specimen to brightness changes in the image. In a phase-contrast microscope the phase difference between light that is diffracted by a specimen, and the light that is direct and undeflected is one-quarter of a wavelength or less. By placing an appropriate mask in the back focal plane of the objective to provide selective filtering of the diffracted light, this phase difference increased by another quarter wavelength. Waves that differ in phase by half a wavelength cancel one another. In places in the phase image where this occurs, no light is transmitted. As a result, phase differences caused by variations in the specimen appear as intensity variations in the image. This may be used for sizing radioactive particles. It is a fast and simple technique and it gives a rough estimate of the particle size of these types of colloids.

Coulter[®] Counter: The Coulter method of sizing and counting particles is based on measurable changes in electrical impedance produced by nonconductive particles suspended in an electrolyte. In a Coulter[®] counter, radioactive particles suspended in an electrolyte are allowed to pass through a small aperture between electrodes, across which an electric current flow. In the sensing zone, each particle displaces its own volume of electrolyte. Volume displaced is measured as a voltage pulse; the height of each pulse being proportional to the volume of the particle. As fluid containing radioactive particles is drawn through each aperture, each particle displaces electrolyte in the aperture and thus produces a pulse proportional to its displaced volume. Each pulse is counted and sized in order to obtain the size distribution. The quantity of suspension drawn through the aperture is precisely controlled to allow the system to count and size particles for an exact reproducible volume.

7.2.3.2. Sterility

Radiolabelled particles for parenteral administration must be prepared with precautions designed to exclude microbial contamination and to ensure sterility. In the production of sterile radiolabelled particles, the aim must be that in a million units at the most one living microorganism may be found. With a view to ensuring a low microorganism count before the sterilization procedure, the method of production and the sterilization procedure needs to be regularly controlled microbiologically. Suitable sterilization methods are autoclaving (heating in saturated steam under a suitable temperature-time ratio, e.g. 120°C for 20 minutes) and dry sterilization (dry heating with a suitable temperature-time ratio, e.g. 160°C for 2 hours, or 180°C for 30 minutes). While selecting the method of sterilization, care must be taken to ensure that it has no adverse effect on the quality of product [2].

7.2.3.3. Apyrogenicity

Bacterial endotoxins (pyrogens) are polysaccharides from bacterial membranes. They are water soluble, heat stable, and filterable. If they are present in a preparation and administered to a patient, they can cause fever and leukopenia in immune suppressed patients. To minimise the chances that pyrogens are present it is important that preparations are manufactured and dispensed under aseptic conditions, and that all used consumables and equipment have been heat treated and known to be pyrogen free [519].

The limulus amoebocyte lysate (LAL) test is used for the detection of pyrogenic endotoxins. In the past, the LAL test was considered to be only an alternative method to the rabbit pyrogen test [520]. In the new edition of the European Pharmacopoeia [521] and Supplement 2001 [522], the LAL test is already mentioned to be of equal value as the rabbit pyrogen test. Analogously, the LAL test is classified at the same level as other national pharmacopoeias. For example the United States Pharmacopoeia XXIV [523], the British Pharmacopoeia [524] and the Czech Pharmacopoeia [525] and its Supplements.

Presently, the six following methods are described in the current European Pharmacopoeia [526]:

- Method A: Gel-clot method: limit test
- Method B: Gel-clot method: semi-quantitative test
- Method C: Turbidimetric kinetic method
- Method D: Chromogenic kinetic method
- Method E: Chromogenic end-point method
- Method F: Turbidimetric end-point method

The gel-clot technique (method A and B) allows detecting or quantifying endotoxin and is based on clotting of the lysate in the presence of endotoxins. The concentration of endotoxins required to cause the lysate to clot under standard condition is the labelled lysate sensitivity. Both kinetic methods (method C and D) make use of the linear regression of the logarithm of the response on the logarithm of the endotoxin concentration [526]. The end-point method (method E and F) are based on the quantitative relationship between the endotoxin concentration and the quantity of chromophore (method E) released at the end of incubation period, respective of the turbidity of the reaction mixture [522].

In situations where it is not possible to carry out these tests before releasing the batch for clinical use due to the short half-life of the radionuclide used in the preparation, the test is then regarded as a control of the production quality [526].

The injection should not contain more than $\frac{175}{V}$ I.U. of endotoxins per millilitre in which V is the maximum recommended administered total dose in milliliters.

Note that Endotoxin is measured in Endotoxin Units per millilitre (EU/mL). One EU is equal to one International Unit (IU) of endotoxin.

7.3. DOCUMENTATION

7.3.1. Documentation

The aim of documentation is to account traceability of each radioactive particle preparation and provide an audit to trace an individual product for suspected defect. It guarantees that all personnel involved in the manufacture of RSV agents are intimately aware of this information necessary to decide suitability of the radioactive particle release in that batch for patient use [504]. The instructions as well as standard operating procedures (SOPs) of radioactive particle preparation should be written and independently approved by the production in charge. A specification should be available for each material/chemical/radioisotope used as well as for the final dispensed radioactive particle.

General requirements [504]

- Good documentation constitutes the backbone of success of the quality assurance system. A written procedure mitigates errors arising from spoken communication, and offers the tracing of activities accomplished;
- Documents must be designed determinedly, prepared diligently, reviewed thoroughly, and distributed;
- It is obligatory that the prepared document should be approved, signed and dated by the appropriate authorised persons;
- Documents including the title, nature, and purpose should be well-defined and methodically written in a clear-cut fashion. Documents containing instructions should be defined systematically and be easy to follow. The style and language of documents should commensurate their intended use;
- It is crucial to review the documents periodically and should be up-to-date to comply with new editions of the national pharmacopoeia or other official compendia. During the process of document revision, utmost care must be taken to preclude inadvertent use of superseded documents;
- Hand-written documents should be avoided. In the situation where documents require data entry, it is crucial to provide sufficient space to incorporate such entries;
- In the event of any correction made to a document or record, it must be signed or initialled and dated. Whenever necessary, the reason for amending the document must be recorded;
- Records must trace all activities related with radioactive particle preparation at the time it was done;

- Critical records must be stored at a secure place having limited accessibility to authorized persons. Additionally, adequate care must be taken to protect the records from loss, destruction, or falsification, and from damage due to fire, water, among others, while kept for storage;
- Critical records for regulatory compliance for day to day activities must be duplicated on paper, microfilm, or electronically, and stored in a secure location in a separate building located away from the originals;
- While recording the date, it may be carried out either by electromagnetic or photographic means, where detailed procedures pertaining to the adopted system must be available. In case where documentation is followed through electronic data processing methods, only authorized persons are permitted to enter or modify data in the computer in which access is controlled by passwords or other suitable methods, and entry of critical data must be checked individually;
- It is equally important that during the period of custody, the extracted data can be readable within an appropriate period of time; and
- If data is altered, it must be noticeable.

7.3.2. Preparation procedures

In light of the perceived need to achieve regulatory compliance, it is crucial to have a full documentation system offering traceability of radiopharmaceuticals for RSV. A list of the most common types of documents, along with a brief description of each is depicted below [504]:

- (1) SOPs: step-by-step instructions for performing operations related to the preparation of radioactive particles;
- (2) Batch records: it represents a document prepared by production personnel for a particular product manufactured in the department. It contains step-by-step instructions for the tasks related to production activities.
- (3) Test methods: documents relating to the step-by-step instructions for testing chemicals, materials, radionuclides, and other production-related tasks and activities. The test procedure contains forms that have to be filled in at the end of the procedure to ensure inspection and checking of all QC activity by document. It makes sure that the product fulfill its requirement for use in RSV.
- (4) Specifications: documents that account the mandatory requirements of the radiolabelled particles must be fulfilled before being released for clinical use. The purpose of this documentation is to compare the test results of the QC department with the approved specifications and to decide whether they pass the test; and
- (5) Logbook: it is a bound collection of forms arranged in a chronological order used to record the operation, maintenance, and calibration of a piece of equipment, preventive maintenance and repairs, and unexpected events/deviations for manufacturing equipment.

Considering the perceived need to ensure the quality standards of each radiolabelled particle, sometimes it is essential to change the product specifications, manufacturing or control procedures. Maintaining written records of such modification/alteration is essential. Written procedures should be in place to justify such modification/alteration, and documented appropriately [504]:

- Special attention should be given to undertake a review of a representative number of batches either approved or rejected, and a summary of the records associated with the batch must be documented; and
- There should be established written procedures to review and update regarding complaints, recalls, and returned or salvaged radiolabelled particles. Based on the related investigations, corrective and preventative actions should be taken to allow trend analysis.

All production, quality control, and product distribution must have mandatory records for regulatory compliance and should be retained for at least 1-year post expiration date of each batch. This is intended to trace the history of each manufactured batch [504]. In case of APIs, all records must be retained for at least 3 years after the batch is completely distributed for clinical use to cover the potential maximum shelf-life of the product using this API.

There must be systems in place to maintain records of the followings [504]:

- The name of the laboratory where the radioactive particles have been manufactured:
 - Identity and quantity of radioisotopes as well as carrier particles received from each batch;
 - The name of the supplier where radioisotopes and carrier particles have been availed;
 - Control number(s) or any identification number of the radioisotopes and carrier particles assigned by the supplier;
 - The number allocated with date on the receipt of radioisotopes and carrier particles at the manufacturing site;
- Test certificate on the receipt of radioisotopes, carrier particles and chemicals;
- Records to identify the radioisotopes and carrier particles used for making radioactive particles; and
- The decision taken to reject radioisotopes, carrier particles and chemicals.

7.3.3. Batch records

Batch production records constitute a written document of each production batch, prepared during the production of radioactive particles. It contains the following: a sequential data pertaining to each chemical and radioisotope used for production; complete information related to the production; and control of each batch of radiolabelled particles. It constitutes the documentation pertaining to the step by step manufacturing process of each batch. The batch production record needs to be checked before the delivery of products to ensure that it is the accurate version. If the batch production record is gathered from a discrete part of the master document, that document should comprise a reference to the current master production document being used [504].

Prior to the preparation of radioactive particles, there should be a checklist of all equipment and workstation prepared to ensure that they are clear of previous products and suitable for use. Cleaning of the equipment should be checked and documented appropriately. Batch and date of cleaning with a signature is also mandatory. Data entry of each batch should be made in chronological order to ensure traceability. Recording of the batch number, including product code, date and time of production, and batch size, either in a logbook or by electronic data processing system, is to be carried out immediately [504].

All essential information of each significant step in the batch production process must be recorded. This include the following [504]:

- Dates and times (when appropriate);
- Characteristics of major equipment used for formulation of radiolabelled particles (e.g. reactors, synthesizer, etc.);
- Precise characteristics of each batch, including activity content of the radionuclide, SA, quantity used, quantity produced, and batch numbers of carrier particles used during the preparation of radiolabelled particles;
- Actual radiolabelling yield recorded under optimized experimental conditions;
- Signatures of the persons performing and supervising the task;
- Any deviation from the written procedure must be properly noted and investigated by the appropriate authority to ensure that the quality of the product remains unaltered;
- Test results prior to product release for clinical use;
- All analysis results of each batch of the product must be documented. If needed, it may permit recall of any batch;
- Release or rejection of the batch must be duly signed by the responsible personnel with the date; and
- All essential information of the production record review.

Accurate reviewing of production batch records and quality control records is mandatory as part of the approval process of batch release. Any deviation from the batch specifications should be thoroughly scrutinized. Investigation including both the conclusion and follow-up action in the form of written record should be made. As part of the approval process of batch release, it is crucial to review the production and quality control records. Any deviation from the product specifications of a batch should be scrutinized scrupulously. This practice should be extended to other batches of the same product. The investigation made including the conclusion and follow-up action should be in the form of written record [504].

The following information along with date, time and signature of the responsible person should be recorded at the time of each action taken [504]:

- The product name, the batch number and the activity content of the products to be packed, as well as the quantity actually attained and its reconciliation;
- The date(s) and time(s) of the packaging operation;
- Packaging process's date(s) and time(s);
- The name of the person responsible for packaging;
- The initials and signatures of the operators of different significant steps; and
- The checks made to ensure that packaging instructions are followed meticulously.

7.3.4. Staff training

Well-qualified employees to perform radioactive particle preparation are an essential part of GMP [527]. As such, requirements for qualifications, training and development of all employees involved in radioactive particle preparation must be met to ensure that employees can aptly perform their assigned tasks according to their position. The best way to accomplish this is through training programmes tailored to each employee's job profile. This should not just end with an induction programme but continue with annual training plans and periodic

retraining to ensure that an employee's knowledge and behaviour is maintained at the required level. Various types of training programmes are conducted and documented. Training is conducted for each category of employees on the following topics:

- Basics of cGMP
- Glossary of cGMP
- Quality management system
- Process and documents

Training should be planned, scheduled, conducted and documented using a very systematic approach. Training is conducted as classroom training. The training is followed by an assessment and is documented.

- (1) **SOP training:** all employees working in a radiological laboratory must undergo training on the procedures of the respective functions. SOP training is also given to employees from cross functions wherever applicable. Refresher training is carried out whenever there is a major procedural change on the preparation of radiolabelled particles. These trainings are not only assessed, but also documented;
- (2) **External training:** the concerned head of the department of a radiological laboratory usually nominates people for external training, depending on the type and need of the training. The nominee submits a copy of all the training material pertaining to technical training to the QA or the training department;
- (3) **Specific training:** specific training is conducted in accordance with identified training. Specific training may be either on the job or classroom training, and it is documented;
- (4) **On the job training:** on the job training is carried out in the radiological laboratory, wherever applicable. It is assessed by the trainer with an assessment or a demonstration of the radiological procedure by the trainee and the same is documented in the assessment record;
- (5) **Safety training:** the radiological laboratory identifies those who need to have radiological safety training, which may be given individually or to a group of employees in the same or related occupations. The topics approached will be defined according to the existing radiological risks and complexities. These should cover: the knowledge of mechanisms of radioactive materials' exposure, including radionuclides, biohazards and process equipment. It also includes the appropriate use of radiological protection items and how to proceed in an emergency;
- (6) **Job-change training:** job change training may be organized and accomplished after reviewing the employee's training record and training requirements for the new job position. It should be based on a training plan for the employee about the analysis of the employee training record v/s the training requirements for the new job is prepared; and
- (7) **Training to contract/temporary employees:** this type of training possesses a special challenge for most departments as they are transient. Temporary employees in the production areas or quality control laboratories must be trained appropriately as their work can impact the quality of the product. They should be educated and trained robustly to get desired results without any deviations.

7.3.5. Validation of Training

Employees after training must be evaluated to ensure that they have learnt and are qualified for the job. Validation provides assurance that the training program is meeting expected standards and assures that the trainees have achieved the skills and knowledge [528]. Assessment and evaluation of training are carried out through oral examinations, written examinations (using paper or computer systems), simulations (using cold samples), and performance-based assessments. Snap tests –surprise tests– are conducted in various radiological departments on several topics including radiological safety, CGMP compliance, QA/QC, among others. With a view to check the awareness and adherence to the systems and procedures, snap tests are conducted at regular intervals. Snap tests can be recorded with a form which can be documented for further evaluation. Self-assessments are used frequently in self-study and computer-based courses to give the trainee a chance to evaluate how much they have learned. Evaluation should be appropriately graded to ensure that the objectives set for the training are met and they form a basis for the review and next training activity.

The minimum qualifying marks for the cGMP, refresher cGMP, SOP training and Snap Test assessments shall be 75%. A training certificate should be issued to successful employees. Only they should be allowed to perform their assigned duties and responsibilities independently [111].

7.3.6. Retraining

Retraining or additional training is necessary to those employees who have not qualified in the training course.

7.3.7. Periodic Review of Training

The top management team of the department should review the training program with personnel department periodically to ensure that the plan has been completed for satisfactory performance of the functions employees expected to perform. Training, documentation and retention training records should provide the evidence that the training was carried out. The training records should be archived as specified in the document management SOP's. The department heads should ensure updating the training records. All training documents should be retained for a period of five years.

8. A STANDARD OPERATING PROCEDURE FOR RSV

8.1. INFORMED CONSENT

As for any medical treatment with potential hazards, a patient's informed written consent is mandatory, which is more pronounced in case of invasiveness and additional use of radiation. Informed consent includes:

- Verbal and written information about the procedure;
- Its benefits and risks; nature of the treatment;
- Joint specific choice of the radionuclide;
- Its side effects;
- Instructions for the next 48 hours after administration; and
- An outline discussing therapy efficiency and questionnaire including specific questions on subjective symptoms, history of disease, medication with the signatures of the patients and the doctor has to be documented (Annex II).

The patient should be informed about the invasive nature of RSV and about the accompanying complications of joint puncture such as infection, local haemorrhagia, and the risk of iatrogenic and/or non-iatrogenic extra-articular distribution of the radiopharmaceutical [1]. In addition, patients have to be informed about the RSV mechanism, indications, contraindications, nature of radioactive procedure and alternative treatment modalities, such as surgical synovectomy [1]. A sample of informed consent has been shown in Annex I.

Patients should be well informed about the immobilisation of 48 hours after the treatment and the complications resulting from immobilisation such as thromboembolic event. They should also know about the delayed response of RSV of up to 1 month with further improvements from 3 to 6 months, advancement of joint inflammation of about 60% to 80%, and the possibility of retreatment in case of non-response [1]. Patients also should be told about a temporary increase in inflammation and pain following the treatment. Information about possible side effects, complications and precautions should be written in a detailed and complete written informed consent, including [1]:

- Procedure, mechanism, indications, contraindications, benefits and risks;
- Alternative treatment options;
- Treatment with radioactivity and radiation exposure;
- Complications by puncturing a joint;
 - Infection
 - Local hemorrhagia
- Risk of radionecrosis (very rare);
- Risk of pyrexia or allergy (very rare);
- Initially a passage feels increasing pain due to radiation synovitis;
- Delay in response up to one month;
- Final improvement up to 6 months after RSV;
- Overall improvement of approximately 60-80%;
- Theoretical future risk of malignancy comparable to routine diagnostic radiological and nuclear medicine procedures;
- Risk of thromboembolism due to 48 hours immobilization after RSV (if necessary prophylactic antithromboembolic precautions);
- Necessity to repeat RSV in non-responder to the first RSV after a period of 6 months;
- Patients must be informed about follow-up examination and response evaluation from 3 to 6 months after RSV; and
- RSV does not require withdrawal of biological therapy, since it is not associated with increased risk of infection [37].

8.2. DIAGNOSTIC

A complete history of the disease must be evaluated, and all patients' documents related to it, including previous treatments, should be provided at the presentation. Important information such as clinical symptoms, duration of synoviopathy, duration and doses of medication, previous treatments etc. Clinical examination of the involved joints with respect to swelling, hyperthermia, pain and range of motion. Most of patients referred to RSV have usually experienced a long history of antiphlogistica medication or intraarticular injection of glucocorticoid with short time or insufficient response, and in some cases surgical synovectomy [1].

Recent imaging results (not older than 3 months) such as planar X-rays, MRI or bone scan with [^{99m}Tc] phosphonate of the joint should be evaluated to confirm the indication of RSV. Planar X-rays do not show sign of synovitis, but any morphological abnormalities can be visualized. In some cases, to clarify the uncertainty, CT scan or MRI can be helpful. A bone scan with blood pool imaging is considered as a predictor of response to RSV in patients with synovitis [131, 132]. An increased periarticular activity in the blood pool phase and the intensity of the blood pool are correlated with patient response to RSV [529]. However, the prerequisite of RSV response is an adequate intra-articular injection, and distribution and retention of the radiopharmaceutical to achieve the highest radiation to the synovialis [530]. Bone scan in 3-phase technique is a conventional, cheap gold standard for detection of metabolic abnormalities in soft tissue in and around the joint such as synovitis and can discriminate those from degenerative disease. High resolution bone scan from the affected site can exactly localize the joints that can benefit from RSV, especially in case of patient's subjective pain perception if multiple neighbouring joints are affected. Comparison of scan in blood-pool and mineralization phase can discriminate between the inflamed and degenerative component of the joint. De novo disease with exclusively inflamed feature in the perfusion and blood-pool phases, and with no degeneration in the mineralization phase are extremely rare. In general, almost all joints examined by RSV reveal in the bone scan a mixed inflamed and degenerative feature. This is mostly due to selection bias of patients with long history of disease referring to RSV treatment after multiple refractory local treatments and surgeries. Ultrasound of the joint can evaluate and estimate the joint fluid and the synovial thickness [1].

8.3. FACILITIES

According to the European Association of Nuclear Medicine's guidelines and country specific regulations [132], the application of radiopharmaceuticals with beta emitters should be performed in a dedicated room intended for handling open sources of ionizing radiation, suitable for sterile injection procedures and approved for the use of beta emitters as required by the national regulatory committees of the atomic law and by specialized nuclear medicine staff [37]. An appropriate aseptic technique is mandatory, with adequate sterilization of the treatment site and use of sterile utensils, drapes and gloves [37].

A C-arm radiographic device should be present. Around the application site, typically on and underneath the C-arm detector, tissue has to be laid out to absorb unintentionally spilled droplets of beta emitter. In addition, separate plastic waste bags have to be provided exclusively for contaminated waste to meet safety requirements for storage and later discharge. If in-patient treatment is required by national legislation, this should take place in an approved facility with appropriately shielded rooms and en-suite bathroom facilities.

Joint puncture must be performed by an experienced physician where all means should be taken to ensure the exact intraarticular position of the needle tip, complete intra-articular injection and distribution of the radiopharmaceutical. Extra-articular application and/or leakage could result in extensive complications and necrosis of healthy tissues [304]. Extraarticular or par-injection of radiopharmaceuticals can be avoided by using imaging guidance [131, 132]. In case of large and medium-sized joints such as the knee or shoulder, ultrasonographic guided joint puncture can be used. However, fluoroscopic guided arthrography with application of contrast media can be more accurate in treating small joints of the hands and feet [304].

8.4. PREPARATION OF PATIENTS

- Double check the identity of the patient and medical history, medications and allergies;
- Define clearly the indication for RSV of the proposed joint. Imaging of the joint can be performed with a scintigraphy, MRI, and/or ultrasound. It should be presented and clearly clarify the presence and extension of synovitis in the proposed joint for treatment [286];
- Before the procedure, patients should empty the bladder to avoid immediate post-therapy mobilisation, during and following the RSV procedures;
- All treatments with radiopharmaceuticals in women of childbearing ages, pregnancy and breastfeeding should be excluded; and
- If needed, the RSV procedure should be explained for the patient and the family.

8.5. INSTRUMENTATION

- (1) Activimeter
- (2) Fluoroscope
- (3) Instrumentation for decontamination

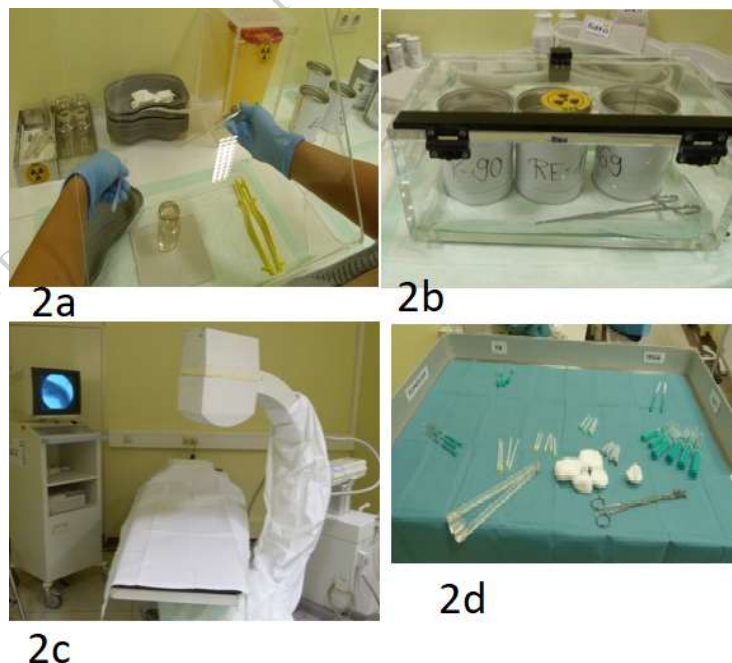


FIG. 33. (2a): Preparation of radiopharmaceutical. (2b): small containers for radioactive waste. (2c+2d): preparation of workspace (courtesy of Farahati).

It is important to prepare and store the radiopharmaceuticals in a safe place to prevent contamination. Access to RSV-rooms should be restricted to authorized persons only. The number and name of attendants should be limited to the operating personal and should be documented in the study protocol for each session. All operating personal must fulfil all approved certifications and SOPs. They should wear convenient and advisable radiation dosimeters, and wear trunk-monitors for the trunk between the waist and the neck. For working with beta emitters is essential to carry an extremity monitor on the left index finger for right-handed, and a right index finger for left-handed to monitor the high exposed short-range radiation. They should stay as far as possible away from the C-arm. Figure 33 shows a simple preparation of the equipment needed and used in the procedure.

8.6. UTENSILS

- 70% alcohol to clean with gauze or swabs;
- Sterile isotonic solution for injection (e.g. 0.9% saline);
- Anaesthetics (e.g. Lidocaine);
- Sterile gauze;
- Sterile tools;
- Glucosteroids;
- Contrast media;
- 20 to 22 gauge needle;
- 1, 5, 10 ml syringes; and
- Radiopharmaceuticals preferably in 1 ml syringe in a plexy shield.

8.7. CONSIDERATIONS ON THE RECEIPT AND HANDLING OF RADIOPHARMACEUTICALS

Receipt and handling of radiopharmaceuticals is tied to strict approval by authorities, depending on the country's specific regulations. These imply locality, radiation protection, handling procedures and staff. Usually approval for handling and storage of a maximum amount of beta emitting radionuclide activity is granted, allowing for sufficient radiopharmaceutical activity to treat the expected number of patients and joints during the day of delivery. Radiation protection requires supervision regarding contamination and exposure surveillance. First step after receipt of the ordered activity is the distribution into portions suitable for administration into the joints.

Detection and imaging of beta emitting radionuclides is difficult. In general, dose calibrators are used to measure the Bremsstrahlung of the radionuclides indirectly. For this purpose, the dose calibrator have to be configured specifically to ensure a constant geometry of the holder for the syringe with the beta emitter [1]. The activities are drawn from the delivered glass vial preferably with an insulin syringe. The insulin syringe has the advantage of a subscale allowing for a good judgement of the activity volume drawn, which is useful for reducing the number of probe measurements and exposure to radiation. Table 3 shows the recommended dose and penetration of radiopharmaceuticals for each joint.

TABLE 3. CHARACTERISTICS OF RADIOPHARMACEUTICALS FOR RADIOSYNOVIORRHESIS [1,132,148]

RADIONUCLIDE (particle)	Vol. MI	PARTICLES (m)	HALF-LIFE (d)	B-MAX E. (mev) soft tissue /cartilage	PENETRATION β -RADIATION (mm)	GAMMA-E (kev)	JOINTS
Yttrium-90 (Citrate)	<2	3-6	2.7	2.2	3.8-11 / <8.5	---	Knee
Re-186 (Colloid/Sulphide)	<1	5-10	3.7	1.07	1.2-3.7 / <3.1	140	Shoulder
Er-169 (Citrate)	<0.2	3-8	9.4	0.34	0.3-1.0 / <0.7	---	PIP
Au-198		2.7	0.96		1.2-3.6	411	Knee
P-32 (Chromic)		10-20	14	1.7	2.6-7.9	---	Knee
Ho-166 (FHMA)		5-10	1.2	1.8	2.2-8.7	81	Knee
Dy-165 (FHMA)		3-10	0.09	1.3	1.4-5.6	95	Knee

FHMA: ferric hydroxide macroaggregates; HA: hydroxyapatite

It is beneficial to handle the syringes and vials with suitable grippers following the principle of keeping distance between fingers and beta emitters to avoid Bremsstrahlung. Importantly, plexy shielding must be used with syringes or vials to avoid directly touching their surface with beta emitters behind. Studies were carried out by the German Bundesamt für Strahlenschutz showing dose rates of 9mSv/s at the syringes tip filled with 185 MBq ⁹⁰Y, whereas the rear (empty) end measured 0.36 mSv/s. Therefore, holding the syringe near the tip with two fingers is to be strictly avoided. Appropriate shielding material for beta emitting radionuclides is acrylic plastic. Fingertip doses up to 22.1 μ Sv/MBq were observed by others without using appropriate shielding, as compared to 0.4 μ Sv/MBq by using a clamp and acrylic shield. Hence, it is imperative to use strict aseptic procedures according to guidelines for joint puncture, and to ensure before the procedure that all needed materials are prepared, available and reachable during the puncture procedure. Insulin syringe is frequently used because it is more convenient for intraarticular injections (especially for small joints) with subscale of radioactivity for exact judgement of the activity volume. Syringes and vials with suitable grippers keep distance between fingers and beta emitters to avoid Bremsstrahlung, especially in case of ⁹⁰Y. Additionally, use of plexy shielding for syringes or vials avoid the direct touch of beta emitters with the hand and fingers and can dramatically reduce the radiation exposure. Figure 34 shows shielding parts for safe handling of the radiopharmaceuticals for RSV procedure to keep distance and avoid contamination by directly touching beta emitters

Technicians and doctors should use thermos-luminescence finger dosimeters. Transport of syringes and vials must be done in electron catching acrylic boxes. These can be put inside of portable lead boxes to additionally shield gamma radiation. Use of nitril or vinyl instead of latex gloves have to be enforced. Latex gloves do not protect from skin contamination with the potential consequence of high local doses. By following these principles, the staff should not have finger doses exceeding the sensitivity threshold of the official finger dosimeters.



FIG. 34. Plexy shielding for syringes and vials (courtesy of Farahati)

The activity of radiopharmaceuticals should be estimated by calculating the volume. To avoid confusion, all vials and syringes should be labelled clearly with the name of the patient, birthdate, the name of radiopharmaceuticals, activity and volume (e.g. 185 MBq – [^{90}Y] citrate; Meier Maria 1.1.1956). If necessary, it would be beneficial to record the quality control, the administered radioactivity, date and time of all administered medications in a permanent medical record. Permanent observation of patients is mandatory to check the possible complications of RSV procedure and medications.

8.8.PUNCTURE

- (1) Double check identification of patient, the joint and the side proposed for RSV, the indications and informed consent. Puncture of joint should be performed in accordance with local guidelines for joint puncture. It should be performed by a nuclear medicine specialist or can be performed by a skilled physician (e.g. orthopaedics) in the presence of a nuclear medicine physician. The nuclear medicine physician is responsible for all the procedure and should inject the radiopharmaceutical by his own after securing the intra-articular position of the needle. Figure 35 shows the disinfection of the patient organ as well as coverings;
- (2) Check the proposed joint for RSV before procedure for any injury, infection, and other possible risks;
- (3) Check and palpate the possible injection site, injection target and the angle of the needle to insert the tip of the needle intraarticular by the first shot to avoid multiple insertion pain. Multiple insertions may also lead to more leakage of radiopharmaceuticals from the joint cavity;
- (4) Shorten and remove the hair over the puncture area, but do not shave (it may cause skin injury). Take a comfortable positioning for joint puncture with the best view of the patient and C-arm monitor;
- (5) Cover cuts in the skin of the hands with adhesive plaster before procedure and wash the hands.

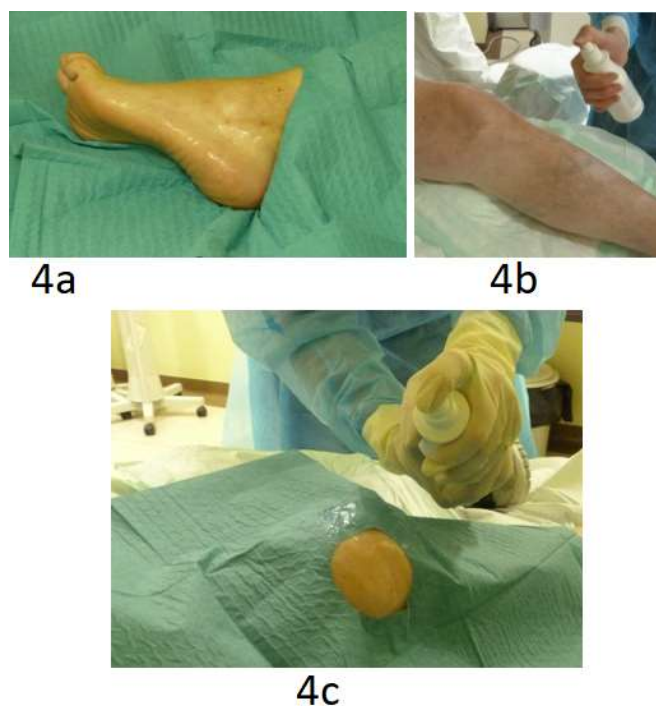


FIG. 35. (4a-c): extensive disinfection of the puncture site. (4c): sterile drape for knee (courtesy of Farahati).

- (6) Use aseptic technique and personal protective equipment, laboratory coat or a surgical gown, disposable sterile gloves, surgical mask, and avoid any connection or touching of non-sterile areas;
- (7) Cover the joint carefully with sterile drape under sterile conditions;
- (8) The joint should be punctured with a needle gauge appropriate to the joint's size by simultaneously infiltrating and anaesthetizing the skin over the puncture area with local anaesthesia (e.g. Lidocaine 1%). Excess joint fluid should be aspirated prior to injection of the radiopharmaceutical [37]; and
- (9) For medium and small joints usually gauge 22 is used. We attach a hose to the needle and a small syringe with 50% contrast media. Still on the skin's surface the needle is targeted at the joint gap while doing a single X ray shot with the C-arm when appropriate. Single shot mode ensures minimizing radiation exposure. X ray focus should be adopted as much as possible and useful.

After detection and confirming the homogenous intra-articular position of the needle by aspiration of synovial fluid or by fluoroscopy, while still touching the skin, inject as much as necessary an amount of contrast media, followed by a single X ray shot to document needle position and visualize the intra-articular distribution of the contrast media. The puncture procedure can be laborious for the physician and painful for patients, especially in case of finger or toe joints in patients with progressive rheumatoid arthritis with close or untraceable intra-articular space. After documentation, the contrast media and excess synovial fluid should be aspirated as much as possible. Then, the syringe containing the radiopharmaceutical is coupled to the needle and the activity is administered. This procedure ensures a minimum of exposure time and a maximum of distance between fingers and beta emitter. It also ensures a determined joint puncture and safe placement of the needle without any radiation hazard.

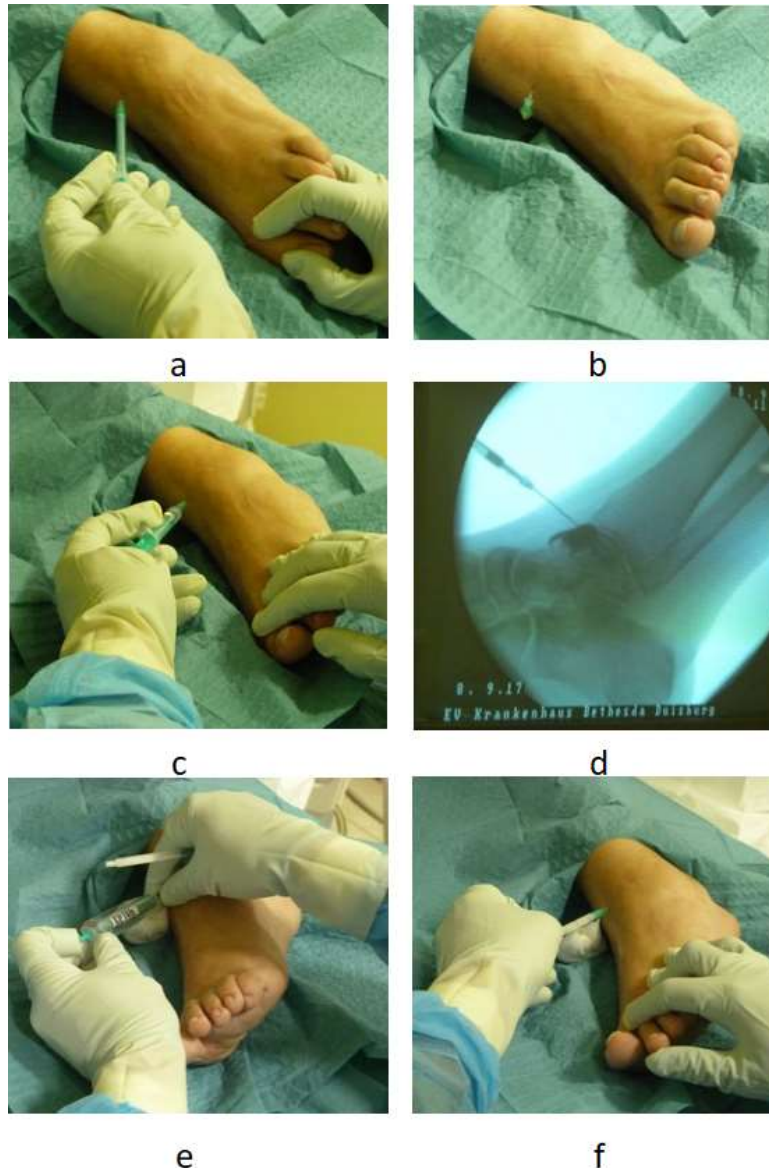


FIG. 36. Ankle and knee: (a) puncture and local anaesthesia; (b) Conforming of needle position 7: (b) by aspiration; (c) with contrast agent; (d) by fluoroscopy; (e) injection of radiopharmaceutical; (f) injection of corticosteroid. (courtesy of Farahati).

Long-acting glucocorticoids can be injected to:

- Bridge lag phase of onset of RSV effect;
- Avoid/lower the risk of radiation-induced synovitis;
- Lower the grade of hypervascularity and/or hyperpermeability diminishing leakage;
- Spread well in the distally located inter carpal compartments in the wrist joint; and
- Adjust the corticosteroid dose to the joint size (2-4 mg Finger joints, 10 mg middle size joints, and 20-40 mg Knee).

After the application of the radiopharmaceutical, the needle can be flushed with saline/corticosteroids/local anaesthetics solution during withdrawal to reduce the risk of skin necrosis. A brief visual overview of the procedure is demonstrated in Figure 36 and 37.

Additionally, after RSV application is it advisable to immobilize the treated joint for at least 48 hours to reduce the risk of radioactive leakage to para-articular tissues. In the case of lower limb joint treatment (hip, knee, ankle), the patient is recommended to avoid walking, thus requiring assistance of third parties [1]. Finally, to control the appropriate performance of the RSV, post-therapeutic imaging can be performed. Planar scintigraphy of the treated joint reveal clearly the distribution of radioactivity inside the joint cavity up to several days following RSV [1]. For one week after RSV, the patient should refrain from any kind of strenuous activity, rehabilitation or physical therapy of the treated joint. Four to six months after RSV women in reproductive age should avoid pregnancy [37, 131, 132].

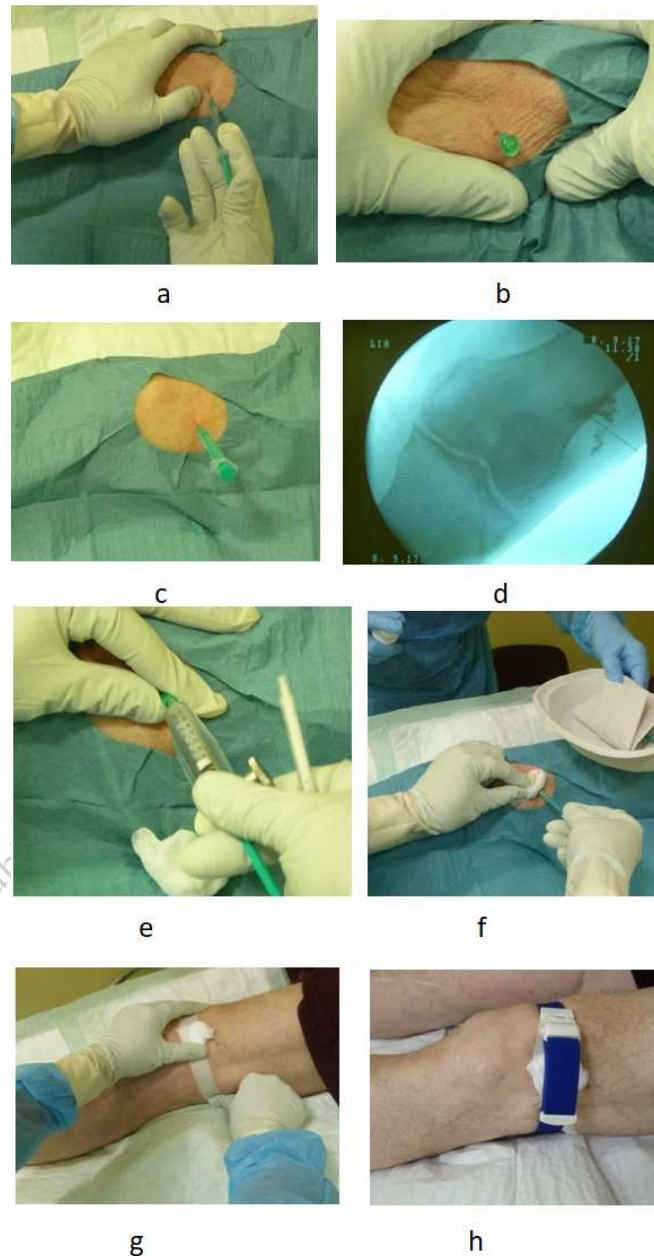


FIG. 37. Ankle and Knee: (a) puncture and local anaesthesia; Conforming of needle position: (b) by aspiration; (c) with contrast agent; (d) by fluoroscopy; (e) injection of radiopharmaceutical. (f) injection of corticosteroid. (g+h) tourniquet (courtesy of Farahati).

8.9. POST-RADIOSYNOVECTOMY PROCEDURES

- Position the patient by using supportive materials and immobilizers;
- Scan treated joint and adjacent lymph nodes with a scintillation camera (using bremsstrahlung energy window and photo-peak) or Geiger Muller Counter for ^{32}P ;
- Indicate appropriate anatomic landmarks for imaging;
- Review images to ensure that the required information has been acquired with appropriate quality;
- Document the intra-articular distribution of the radiopharmaceutical in the joint and exclude any extra-articular transport of radiopharmaceuticals to the adjacent lymph nodes;
- Immobilise the treated joint for 48 hours with a splint to reduce lymphatic leakage rate;
- Radiation induced synovitis with increased pain and effusion should not be drained during the first 4 weeks after RSV;
- Instrumentation for contamination;
- Decontamination; and
- Use prophylactic cool-pad for pain relief.

After finishing the RSV treatment, all procedures including the information on proper puncture, application of radiopharmaceuticals and applied co-medications should be documented and securely stored in an archive (in Germany for 30 years). All possible risks and hazards and risky issues or safety conditions to the supervisor should also be documented, including:

- Monitor the personal contamination after leaving the RSV-room;
- Monitor background contamination, disposals, and equipment before and after RSV;
- Monitor and document the body contamination following an incident and decontaminate;
- Attend all proper training courses;
- Identify clearly radioactive material at any time with radioactive warning tape; and
- Mark on the radiopharmaceutical with information about the activity and date.

8.10. POST-RADIOSYNOVECTOMY IMAGING

After radionuclide injection, a distribution scan should be acquired with a gamma camera to document successful intra-articular injection and proper distribution within the joint. It is recommended to do a follow-up that is usually performed by the referring physician in close collaboration with the nuclear medicine specialist at 4 weeks, 3 months, and 6 months. An early check-up for side effects or other complications is recommended from three to seven days after treatment to assess the response to RSV. Figures 38 demonstrates imaging examples to follow up the injection.



FIG. 38. Post-RSV imaging of the knee by scintigraphy reveal periarticular distribution of Y-90-citrate in knee joint (courtesy of Farahati).

8.11. FOLLOW-UP

- Patients should be revised four to six days after injection to evaluate, respond, report, and document the early side effects;
- Clinical examination should be performed to assess the therapeutic success; and
- Follow-up with the collaboration of an attending rheumatologist.

The patient should be informed about the immobilisation of the joint after RSV treatment for at least 48 hours. Early pain after RSV can be treated with antiphlogistics. Patients should be given clearly all recommendations and information to avoid unnecessary radiation exposure to family members and the public. These rules vary by country. For example, women should avoid pregnancy after treatment for at least four to six months [1]. Nevertheless, such risks are hypothetical, since excretion of the intraarticular radionuclides via urine or bowel are negligible. Furthermore, increased observation of hygienic measures is strongly encouraged.

Patients who receive treatment in multiple joints may be helped if they receive in-patient treatment over 48 hours and if the facility has a therapeutic ward to host these patients. The nursing personnel in nuclear medicine facilities should have the appropriate radiation safety knowledge. If significant medical conditions are noticed, such as acute radiation lesions, contingency plans should be provided to treat these cases as a medical emergency. Under no circumstances medical personnel unfamiliar with such measures should take planned action, whereas radiation exposure concerns should not interfere with prompt medical treatment. The follow up of a regular RSV includes a patient evaluation after six to eight weeks after treatment. In case of positive treatment response, this can be renounced. Four to six months after treatment, a clinical examination is recommended, or in some countries like Germany is mandatory. Re-evaluation can also be done interdisciplinary, involving the rheumatologist or orthopaedic surgeon as the physicians primarily take care of these patients [1]. Depending on the response, a second treatment may be envisioned.

8.12. OUTCOME

Many studies were published reporting results of RSV in patients treated for different indications. Studies reaching evidence-based medicine in level 1a and featuring randomized and double-blinded, controlled multicentre trials are rare. The success rates reported a range from 40% to 90% for the different joints and different underlying diseases [11, 16, 378, 469, 531–534]. Deutsch et al. [10] summarize the results of 72 studies carried out between 1975 and 1992 in patients with rheumatoid arthritis. After one-year follow-up, the results of treatment have been classified from 60% to 80% of patients as good or excellent. Efficacy of RSV in patients with osteoarthritis or other diseases not caused by rheumatoid arthritis have been studied in more detail. In these patients, similar results have been observed with response rates between 40% and 80% [531, 535].

In a study it was investigated the time to remission after RSV and the effect of underlying diseases, type of joint and duration of illness, as well as age and gender on the success rates of RSV in 97 patients with 174 treated joints [531]. After six months, the probability of pain release of more than 20% amounted to 78% and was significantly dependent on the age of the patient ($p=0.02$) and the duration of illness ($p=0.05$) [1]. However, no influence of gender ($p=0.17$), underlying disease ($p=0.23$) and type of the joint ($p=0.69$) was found [531]. Hence, RSV is effective in rheumatoid arthritis and in activated osteoarthrosis with reactive synovitis and effusion.

Another study evaluated the effectiveness of RSV in relation to joint type and underlying disease by both self-assessment of patients and scintigraphic assessment to determine conditions under which RSV might be preferable to the sole intra-articular corticoid injection [530]. The group included 136 patients who had treated 424 joints, 313 with RA and 111 with OA. The subjectively estimated success rates for the small, medium-sized, and large joints were ranging from 79% to 89% in both RA and OA. The scintigraphically determined response rates ranged from 69% to 81%, being higher in patients with RA than in patients with osteoarthritis. Based on the study, it is recommended switching earlier to RSV.

Several prospective double blind studies have evaluated the efficacy of RSV [11, 377, 417]. In a double blind, randomised, placebo-controlled, international multicentre study patients with rheumatoid arthritis with recent ineffective corticosteroid injections into their finger joints were treated [378]. This study reached the highest level of evidence. Eighty-five finger joints of forty-four patients were treated with either [^{169}Er] citrate or saline solution. Results of an evaluation six months later in their intent-to-treat approach showed a significant effect of [^{169}Er] citrate compared to placebo for the principal criteria decreased pain or swelling ($P = 0.04$) and decreased pain and swelling ($P < 0.01$). Mobility was also significantly increased ($P = 0.04$). These results clearly confirm the clinical efficacy of [^{169}Er] citrate RSV of RA diseased finger joints after previous inefficient intra-articular corticosteroid therapy. Consequently, known efficacy of RSV is becoming a positive viable alternative to treat chronic synovitis in RA and secondary to inflammatory arthropathies [1]. The advantages of RSV compared with surgical synovectomy include equivalent results, lower costs, ambulatory procedure, and repeatability [52, 61]. In patients developing chronic effusions after arthroplasty (e.g. of the knee), RSV is able to stop effusions effectively [536].

According to the review of Deutsch, nine studies reported good to excellent results in 60% to 80% of patients with haemophilia [10]. Concordant data of Siegel reported significantly

decreased incidence of bleeding in 70% to 80% of the patients. This resulted in a considerable reduction of costs for treatment in comparison to the conventional surgical approach which makes the intensive use of clotting factors in those patients mandatory [61]. Furthermore, promising new agents are currently under preliminary biological evaluation, such as ^{177}Lu and ^{175}Yb hydroxyapatite particles [438]. These agents seem to be viable alternatives to ^{169}Er based agents, coming from a feasible and cost-effective production route.

8.13. RADIATION PROTECTION

Virkkunen M. et al. [537] reported the first adverse effect of RSV after intra-articular application of ^{198}Au . Extra-articular irradiation to the lymphatic and venous system after RSV can be resulted by leakage of the radiopharmaceutical from the joint. Wide range of leakage for different radiopharmaceuticals are reported in the literature. In general, the rate of leakage after RSV is reported to be approximately 10%; however, some reports are as high as 48%. Wide range of leakage can cause iatrogenic or non-iatrogenic diseases. The extra-articular injection is the major iatrogenic cause of leakage and depend on experience and learning curve of the physician. Non-compliance is the major cause of non-iatrogenic leakage and can result in 40% leakage from the joint [538]. Thus, immobilisation of the treated joint after each RSV is essential to reduce the leakage and optimize the RSV results.

Increased leakage can also result from a small size of labelled particle. One week after RSV, 6% of the activity is taken up in the lymph nodes and 2% in the hepatosplenic system [176]. Higher leakage rate of 14% is reported for [^{169}Er] colloid [539], and lower leakage was observed after RSV of knee joints with ^{165}Dy and [^{32}P] chromic phosphate [371, 540] resulting in doses to the lymph nodes between 0.5 and 2.4 Gy. Probably the ten times larger particle size of chromic phosphate as compared to colloid particles of ^{90}Y is the reason for the different leakage rates. Higher leakage rates can be also result from instability of the radiopharmaceutical. RSV with 200 MBq ^{90}Y is reported to result in a whole body radiation: doses between 9 and 99 mSv and gonadal dose of 0.1-0.2 mSv [541]. Increased chromosomal aberrations after RSV of knee joint with ^{90}Y are reported by Daker in 1979 [542] and ^{186}Re is reported to increase the dicentric lymphocytes. However, in other studies no chromosomal aberration is reported when using ^{169}Er and ^{32}P [395, 542] or ^{165}Dy . Figure 39 shows an inflamed knee joint before and after treatment [543].



FIG. 39. Immobilization of (a) left upper ankle and (b) left knee (courtesy of Farahati)

8.14. CONCLUSION

RSV has been used for decades to treat patients with hemarthropathy, rheumatoid arthritis and recently in osteoarthritis. Yet, there are only a few controlled studies with clear-cut evidence regarding the clinical results using different radiopharmaceuticals and the effects of internal irradiation with respect to different pathophysiologies and stages of disease. In addition, discrepancies with regard to expertise, selected criteria, diagnostic work, and radiopharmaceuticals used in different countries, make a comparison of published data on this topic difficult [1]. Studies with proper inclusion criteria and with appropriate expertise, are needed to justify the roll of RSV as an alternative minimal invasive therapy option for patients with synoviopathy with distinct underlying pathologies. Several clinical studies have already indicated that years of improved symptoms and delay to surgical option can be achieved by RSV when conservative therapy has failed [536]. In addition, recent reports suggest that radiosynoviorthesis can do more than synovitis [31].

Ideally, RSV should be employed before progressive radiological signs of joint destruction occur. However, it is unusual to have referred patients for RSV having not previously been treated by a general physician, orthopaedic or rheumatologist. Most patients have already had symptoms for many months, despite prolonged conservative treatment, multiple application of intra-articular corticosteroid, and in many cases prosthesis surgery. In other words, RSV is unfortunately considered by specialists for musculoskeletal diseases as the last option.

The major advantages of RSV include little or no need for hospitalization, no physical therapy, low costs, the possibility of repeated administration, and results are comparable to those of surgical synovectomy. In patients with chronic synoviopathy secondary to rheumatoid arthritis or activated arthrosis, the results of RSV are reported to be positive. RSV is considered as the initial procedure of choice for the treatment of patients with refractory hemarthrosis in haemophilia. RSV can reduce joint effusions after implantation of prosthesis effectively. The radiation dose to the gonads is low and the morbidity rate for tumours induced by whole-body radiation is negligible. Additionally, an increased risk for cancer after RSV has not been reported [1]. However, leakage of the radionuclide along the needle track can result in serious radiation necrosis to the skin with later scarring [131, 132]; thus, irrespective of different radiopharmaceuticals and techniques used, immobilisation of the treated joint after RSV is mandatory [1].

Despite modern modalities for diagnosing arthropathy, bone scan remains the only imaging technique that assesses the bone metabolism through the whole body, offering overall available modality with a high sensitivity at an affordable cost. Using bone scan in a 3 phase mode of perfusion, blood pool and mineralisation phases enables the clinician to detect inflammation with a high sensitivity and to discriminate it from localisation and extent of the degenerative joint compartment [544].

Open and arthroscopic surgical synovectomy and radionuclide synovectomy are the options in patients with HA and RA with hypertrophic and exudative joint disease who fail to response to systemic therapy and local corticosteroids. Outcomes are reported to be similar for all three procedures, decreasing the frequency of effusion (as seen in Fig. 40 below) and joint bleeding from 70% to 100 % [390, 545], and pain relieve and reduction in synovitis in 60% to 80 % of RA [1]. However, with respect to cost-effectiveness and minimal invasiveness [547], RSV is

the treatment of choice, especially in low income countries, and should be the therapy of choice in multi morbid patients with high risk for operation.



FIG. 40.RSV of knee Joint with 185 MBq [^{90}Y] citrate before (a) and 6 months (b) after the treatment (courtesy of Farahati)

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In case of rejection:

I do not consent to the proposed procedure. I have been advised that this may make the treatment of the condition considerably more difficult, with detrimental consequences for my health.

Location, Date, Time	Patient	Doctor
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ANNEX II: MEDICAL QUESTIONNAIRE (ANAMNESIS)

A standard Medical questionnaire (Anamnesis) to be filled by patients prior to RSV procedure.

Age: _____ Years

Height: _____ cm

Weight: _____ kg

Have you had a Radiosynoviorthesis or other treatments/examinations with radioactive materials before? If yes, when and where	<input type="checkbox"/> yes	<input type="checkbox"/> no	Anticoagulation Therapy , Warfarin (Marcumar) / ASS / Plavix	<input type="checkbox"/> yes	<input type="checkbox"/> no
Corticoid	<input type="checkbox"/> yes	<input type="checkbox"/> no	Arthroscopy / Operation	<input type="checkbox"/> yes	<input type="checkbox"/> no
Diabetes / Insulinpflichtig	<input type="checkbox"/> yes	<input type="checkbox"/> no	Total endoprosthesis _ left / right	<input type="checkbox"/> yes	<input type="checkbox"/> no
KM-Allergie	<input type="checkbox"/> yes	<input type="checkbox"/> no	Allergic to local anaesthesia	<input type="checkbox"/> yes	<input type="checkbox"/> no
Do you have any allergies for example? against Proteins, Contrast media, Latex Medication, certain food?	<input type="checkbox"/> yes	<input type="checkbox"/> no	Have you had a radiological examination with contrast media in the last months? If yes, when and where?	<input type="checkbox"/> yes	<input type="checkbox"/> no
Have you had X-Rays or radiological examinations of the joint? If yes, when and where?	<input type="checkbox"/> yes	<input type="checkbox"/> no	Have you had a joint or cartilage disease like Osteoporosis, Gout, Joint infection, Hemarthrosis? (Bleeding in the joint)	<input type="checkbox"/> yes	<input type="checkbox"/> no
Do you have any thyroid diseases (Hyper- or Hypothyroidism, Struma nodosa)?	<input type="checkbox"/> yes	<input type="checkbox"/> no	Do you have a coagulation disorder? For example, frequent nosebleeds or bruises without? Do you suffer from trauma or another blood disease?	<input type="checkbox"/> yes	<input type="checkbox"/> no
Do you have any chronic infections? (Hepatitis, HIV-Infection, TBC)?	<input type="checkbox"/> yes	<input type="checkbox"/> no	Do you have any heart diseases?	<input type="checkbox"/> yes	<input type="checkbox"/> no
Have you had a Thrombosis or vascular disease?	<input type="checkbox"/> yes	<input type="checkbox"/> no	Have you had any Radiotherapy? If yes, in which organ and when?	<input type="checkbox"/> yes	<input type="checkbox"/> no

Are you pregnant?	<input type="checkbox"/> yes	<input type="checkbox"/> no	Are you breastfeeding?	<input type="checkbox"/> yes	<input type="checkbox"/> no
Do you have any one attending home with you to help with post-operation care?	<input type="checkbox"/> yes	<input type="checkbox"/> no			

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ABBREVIATIONS

BAT	N,N'-bis(2-mercaptoethyl)ethylene-diamine
CO ₂ -DADS	N,N'-bis (mercap- toacetamido)-2,3-diaminopropanate
cGRPP	current Good Radiopharmaceutical Production Practice
Chitin	poly-β-(1-4)-N-acetyl D-glucosamine
Chitosan	poly-β-(1-4)-2-amino-2-deoxy-D-glucose
DLS method	Dynamic Light Scattering
DTPA	Diethylenetriaminepentaacetic acid
GMP	Good Manufacturing Practice
HA	Hydroxyapatite [Ca ₁₀ (PO ₄) ₆ (OH) ₂]
HPLC	High Performance Liquid Chromatography
LAL	Limulus Amebocyte Lysate
LSC	Liquid Scintillation Counting
NCA	No-carrier-added
OA	Osteoarthritis
P.I.	Post Injection
PLA	Poly lactic acid
QA	Quality Assurance
QC	Quality Control
RA	Rheumatoid Arthritis
RSV	Radiosynovectomy
SA	Specific Activiy
SOPs	Standard Operating Procedures
TEM	Transmission electron microscopy
α-HIBA	α-hydroxy-isobutyric acid

CONTRIBUTERS TO DRAFTING AND REVIEW

Dash, A.	Bhabha Atomic Research Centre, India
Farahati, J.	Bethesda, Duisburg, Germany
Giammarile F.	International Atomic Energy Agency
Jalilian, A.	International Atomic Energy Agency

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