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Review Article

Role of Microsponge Drug Delivery Systems In Improving Therapeutic Outcomes In Rheumatoid Arthritis

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A B S T R A C T

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disorder characterized by progressive synovial inflammation, joint destruction, pain, and functional disability. Conventional drug therapy used in the management of RA often requires frequent dosing and is associated with systemic adverse effects, which may reduce patient compliance during long-term treatment. Therefore, the development of novel drug delivery systems capable of providing controlled and sustained drug release with reduced toxicity is of significant interest.

Microsponge drug delivery systems (MDS) are porous, polymeric microspheres possessing a large surface area and interconnected void structure that enable efficient entrapment and controlled release of therapeutic agents. These systems offer several advantages such as prolonged drug release, improved stability, reduced irritation, enhanced formulation flexibility, and improved patient compliance. Microsponges can be prepared using various techniques including liquid–liquid suspension polymerization, quasi-emulsion solvent diffusion, water-in-oil-in-water emulsion solvent diffusion, porogen addition, lyophilization, and ultrasound-assisted methods. Drug release from microsponges can be regulated by external factors such as pH, temperature, pressure, and solubility gradients.

The present review focuses on the fundamentals of microsponge drug delivery systems, their methods of preparation, mechanisms of drug release, in-vitro characterization, recent advancements, and pharmaceutical applications with special emphasis on their potential role in the management of rheumatoid arthritis. Microsponge-based formulations represent a promising approach for improving therapeutic efficacy while minimizing adverse effects, thereby offering a suitable strategy for long-term treatment of rheumatoid arthritis.

Keywords: Microsponge drug delivery system; Rheumatoid arthritis; Controlled release; Polymeric microspheres; Targeted therapy

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INTRODUCTION:

Micro-sponge drug delivery systems (MDS) are spherical, porous, polymeric and patented delivery systems that are used for prolonged topical administration. They are spongy tiny like spherical articles of 5 – 300 µm The surface and pore volume can be varied from 20 to 500 m2/g and 0.1 to 0.3 cm-3/g, respectively. Due to their non-collapsible structure made of interconnecting voids, they are inert and stand in a high degree of shear and hence can be used in the manufacturing of powders, lotions, and creams[1,2]

Microsponges are patented polymeric delivery systems consisting of porous microspheres that can entrap a wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, and anti-infective, anti-fungal, and anti-inflammatory agents. Like a true sponge, each microsphere consists of a myriad of interconnecting voids within a non-collapsible structure, with a large porous surface. The microsponge technology was developed by Won in 1987, and the original patents were assigned to Advanced Polymer Systems, Inc. This company developed a large number of variations[3,4]

MDDS can reduce irritation there by improving patient's compliance. These have the ability to improve formulation flexibility and can facilitate extended release formulations. However, Absorption of residual monomers may cause a toxic effect. The preparations of microsponge mostly use organic solvents and some may be highly inflammable and they can cause environmental hazards.

Microsponges are porous microsphere-based polymeric delivery devices. These particles have a broad porous surface and are spherical, like sponges. Additionally, they might alter drug release favourably, lessen adverse effects, and increase stability. The numerous benefits of microsponge technology make it a flexible drug delivery system. Before being mixed into a manufactured product like a gel, cream, liquid, or powder, microscopic polymer-based microspheres known as "Microsponge Systems" can suspend or entrap a variety of compounds. Most exterior surfaces are porous, which over time allows materials to flow out of the sphere. In recent years, oral use of the porous, polymeric microspheres known as microsponges has increased. Microsponges are designed to effectively administer a pharmaceutical active ingredient at the lowest dosage while also enhancing stability, minimising adverse effects, and adjusting drug release[4,5].

Rheumatoid arthritis

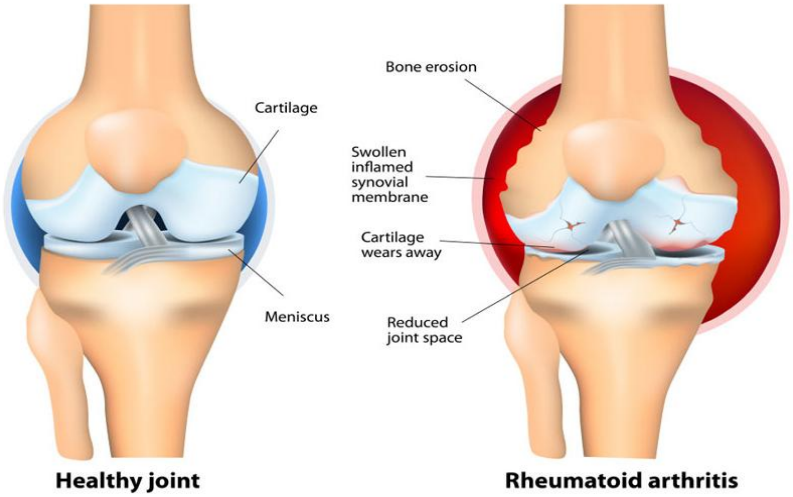

Figure 1: Pathogenesis of Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, symmetrical, inflammatory autoimmune disease that initially affects small joints, progressing to larger joints, and eventually the skin, eyes, heart, kidneys, and lungs. Often, the bone and cartilage of joints are destroyed, and tendons and ligaments weaken [1]. All this damage to the joints causes deformities and bone erosion, usually very painful for a patient. Common symptoms of RA include morning stiffness of the affected joints for > 30 min, fatigue, fever, weight loss, joints that are tender, swollen and warm, and rheumatoid nodules under the skin. The onset of this dis- purposes requiresRheumatoid arthritis (RA) is a chronic, symmetrical, inflammatory autoimmune disease that initially affects [6,7]

Anatomy

RA primarily affects joints, but it also affects other organs in more than 15–25% of cases.Associated problems include cardiovascular disease, osteoporosis, interstitial lung disease, infection, cancer, feeling tired, depression, mental difficulties, and trouble working.

Joints

A diagram showing how rheumatoid arthritis affects a joint Hand deformity, sometimes called a swan deformity, in an elderly person with rheumatoid arthritis

Arthritis of joints involves inflammation of the synovial membrane. Joints become swollen, tender, and warm, and stiffness limits their movement. With time, multiple joints are affected (polyarthritis). Most commonly involved are the small joints of the hands, feet and cervical spine, but larger joints like the shoulder and knee can also be involved.Synovitis can lead to tethering of tissue with loss of movement and erosion of the joint surface, causing deformity and loss of function.The fibroblast-like synoviocytes (FLS), highly specialized mesenchymal cells found in the synovial membrane, have an active and prominent role in these pathogenic processes of the rheumatic joints.

RA typically manifests with signs of inflammation, with the affected joints being swollen, warm, painful, and stiff, particularly early in the morning on waking or following prolonged inactivity. Increased stiffness early in the morning is often a prominent feature of the disease and typically lasts for more than an hour. Gentle movements may relieve symptoms in the early stages of the disease. These signs help distinguish rheumatoid from non-inflammatory problems of the joints, such as osteoarthritis. In arthritis of non-inflammatory causes, signs of inflammation and early morning stiffness are less prominent. The pain associated with RA is induced at the site of inflammation and classified as nociceptive as opposed to neuropathic.The joints are often affected in a fairly symmetrical fashion, although this is not specific, and the initial presentation may be asymmetrical

[8,9].

Skin

The rheumatoid nodule, which is sometimes in the skin, is the most common non-joint feature and occurs in 30% of people who have RA.It is a type of inflammatory reaction known to pathologists as a "necrotizing granuloma". The initial pathologic process in nodule formation is unknown but may be essentially the same as the synovitis, since similar structural features occur in both. The nodule has a central area of fibrinoid necrosis that may be fissured and which corresponds to the fibrin-rich necrotic material found in and around an affected synovial space.

Surrounding the necrosis is a layer of palisading macrophages and fibroblasts, corresponding to the intimal layer in synovium and a cuff of connective tissue containing clusters of lymphocytes and plasma cells, corresponding to the subintimal zone in synovitis. The typical rheumatoid nodule may be a few millimetres to a few centimetres in diameter and is usually found over bony prominences, [9]

Lungs

Lung fibrosis is a recognized complication of rheumatoid arthritis. It is also a rare but well-recognized consequence of therapy (for example with methotrexate and leflunomide).

Caplan's syndrome describes lung nodules in individuals with RA and additional exposure to coal dust.

Exudative pleural effusions are also associated with RA. [10]

Heart and blood vessels

People with RA are more prone to atherosclerosis, and risk of myocardial infarction (heart attack) and stroke is markedly increased Other possible complications that may arise include: pericarditis, endocarditis, left ventricular failure, valvulitis and fibrosis.Many people with RA do not experience the same chest pain that others feel when they have angina or myocardial infarction. To reduce cardiovascular risk, it is crucial to maintain optimal control of the inflammation caused by RA (which may be involved in causing the cardiovascular risk), and to use exercise and medications appropriately[10,11]

Blood

Various mechanisms can cause anaemia in rheumatoid arthritis, which is by far the most common abnormality of the blood cells. The chronic inflammation caused by RA leads to raised hepcidin levels, leading to anaemia of chronic disease where iron is poorly absorbed and also sequestered into macrophages. The red cells are of normal size and colour (normocytic and Normochromic). [11]

Kidneys

Renal amyloidosis can occur as a consequence of untreated chronic inflammation. Treatment with penicillamine or gold salts such as sodium aurothiomalate are recognized causes of membranous nephropathy.[12]

Liver

Liver problems in people with rheumatoid arthritis may be from the underlying disease process or the medications used to treat the disease. A coexisting autoimmune liver disease, such as primary biliary cirrhosis or autoimmune hepatitis may also cause problems.[13]

Neurological

Peripheral neuropathy and mononeuritis multiplex may occur. The most common problem is carpal tunnel syndrome caused by compression of the median nerve by swelling around the wrist [12]

Method of preparation

Liquid-- suspension polymerization

Liquid-- suspension polymerization is based on freeradical suspension polymerization technique. In the methodreported by Grochowicz et al., the reaction was carried outin a round bottom three necked flask fitted with a stirrer, awater condenser and a thermometer. A solution ofnon-polar drug and the monomer(s) was prepared, to whichaqueous phase containing surfactant and dispersant wasadded. Polymerization was initiated by activating the monomersby catalysis or increased temperature or adding an initiator.Water insoluble pore forming diluents may also beadded to the reaction mixture . When the drug is sensitive the polymerization conditions, two-step process can beused .Polymerization leads to the formation of ladders as a result ofcross-linking between chain monomers. Folding of monomer ladder lead to the formation of spherical particles and theiragglomeration resulted in formation of bunches of microspheres.Binding of these bunches formed microsponge. After polymerizationthe liquid is diffused out leaving microsponges. Thougha convenient method, major disadvantage of this process isprobable entrapment of unreacted monomeric residues.[14,15].

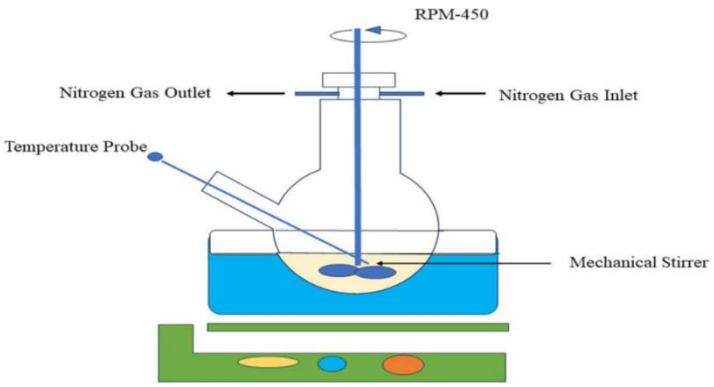

Figure 2: Liquid- Suspension Polymerization

Quasi-emulsion solvent diffusion

This process involved formation of quasi-emulsion of two differentphases similar to emulsions. The internal phase ofdrug--polymer solution made in a volatile solvent like ethanolor acetone was added to external phase comprising the aqueouspolyvinyl alcohol (PVA) solution with vigorous stirring.Stirring lead to the formation of emulsion globules calledquasi-emulsion globules. Solvent was then extracted outfrom these globules to form insoluble microparticles. Followingsufficient stirring, the mixture was then filtered to separatethe microsponges . The microsponges were thendried in an air heated oven. Conceptually, the finely dispersed droplets of the polymeric solution of the drug(dispersed phase) get solidified in aqueous phase via counterdiffusion of organic solvent and water out of and into thedroplets . The diffused aqueous phase within the dropletsdecreased the drug and polymer solubility resulting in theco-precipitation of both the components and continueddiffusion of the organic phase results in further solidification,producing matrix-type porous microspheres. In comparisonwith liquid-- suspension polymerization method, thismethod offered the advantage of less exposure of the drug tothe ambient conditions, low solvent residues in the productbecause the solvent get extracted out due to its solubility in Aqueous media or due to its volatile nature [14,15].

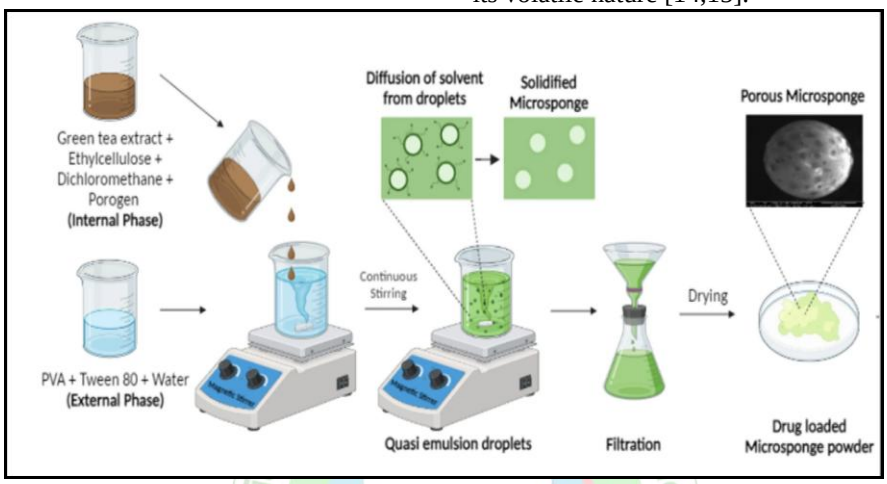

Figure 3: Quasi-Emulsion Solvent Diffusion

Water in oil in water (w/o/w) emulsion

Solvent diffusion this novel technique was developed to prepare biodegradable porous microspheres. In this method, an internal aqueous phase containing an emulsifying agent like span, polyethyleneimine and stearyl amine was dispersed in organic polymeric solution. Thereafter, this w/o emulsion was again dispersed in external aqueous phase containing PVA to form a double emulsion. This method has the advantage of entrapping both water-soluble and water-insoluble drugs. It can also be used for entrapping thermolabile materials like proteins. Some authors also described the xanthan gum as emulsifier to stabilize the internal w/o emulsion.[15,16]

Addition of Porogen

In this technique, internal aqueous phase of water in oil in water (w/o/w) emulsion was replaced by a porogen like hydrogen peroxide or sodium bicarbonate. For this, the porogen was dispersed in the polymeric solution to form a uniform dispersion system which was redispersed in aqueous phase containing PVA. An initiator was then added to the w/o/w emulsion and the organic solvent was allowed to evaporate to leave the microparticles. The effect of incorporating hydrogen peroxide resulted in the formation of evenly distributed and interconnected pores with diameters ranging from 5 to 20 µm [17,18].

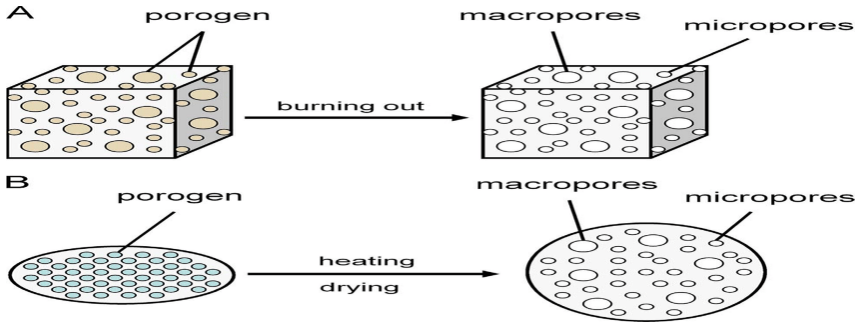

Figure 4: Addition of Porogen

Oil in oil emulsion solvent diffusion

In contrast to w/o/w method, oil in oil (o/o) emulsion was prepared using volatile organic liquid as the internal phasethat was allowed to evaporate slowly at a controlled ratewith continuous stirring. As reported the technique used dichloromethane as the solvent for internal phase,

polylactideglycolic acid as polymer and a mixture of fixed oil (corn ormineral) and dichloromethane containing span 85 as external phase. The internal phase was added drop wise to the dispersion medium with continuous stirring to get the microspongesThis technique was utilized for development of hydroxyzine HCl-loaded Eudragit RS-100 microsponges using acetone as dispersing solvent and liquid paraffin asthe continuous medium.Selection of the organic solventand external phase depend on the physicochemical propertiesof drug and the polymer used for fabrication of microsponges.[18]

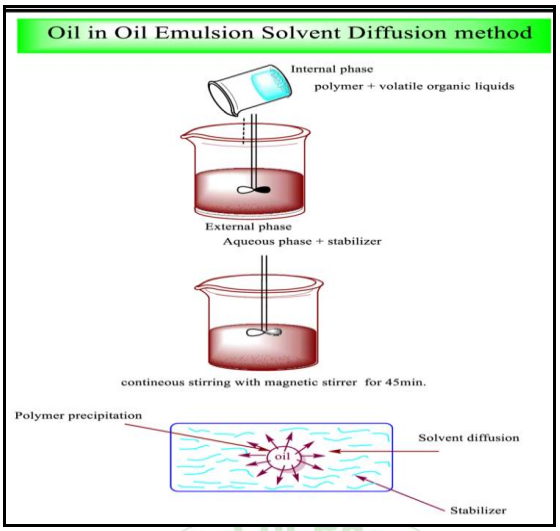

Figure 5: Oil in oil emulsion solvent diffusion

Lyophilization

Lyophilization as technique was used for converting themicrospheres prepared by gelation technique, to porousmicrospheres. In this methodology, the microspheres wereincubated in the solution of chitosan hydrochloride andthen lyophilized Quick removal of solvent led to formationof pores in the microspheres. This method is quick anrapid but has the disadvantage of producing cracked orshrunken microparticles due to quick elimination of solvent.[19]

Vibrating orifice aerosol generator method

Vibrating orifice aerosol generator (VOAG) was first reportedfor the preparation of lipid bilayer mesoporous silica particles.The method involved synthesis of porous particles byevaporation-driven surfactant templating in microdropletsby a VOAG method. For the preparation of core particle Tetraethylorthosilicate, ethanol, water and dilute hydrochloricacid were refluxed to prepare stock solution. This stock solutionwas diluted with the solvent containing surfactant andstirred to allow the formation of monodisperse droplets usingVOAG. The microspheres produced were encapsulated inthe liposomes. These encapsulated particles can be utilized fortargeted drug delivery of actives.[18,19]

Ultrasound-assisted production

This method was developed by modifying the liquid—liquidsuspension polymerization, to utilize b-cyclodextrin (b-CD)as monomer and diphenyl carbonate as cross-linking agentto synthesize the nano sponges. Size control of the microparticleswas accomplished by heating and sonication of thereaction mixture. The reaction mixture was allowed to cooland the product obtained was milled to give rough particlesthat were washed with distilled water and then by ethanol .The porous microparticles of cross-linked b-CD can serveas carrier for efficient loading of drugs. However, thismethod has the disadvantage of entrapment of residues of the cross-linking agents that can be potentially toxic.[19,20]

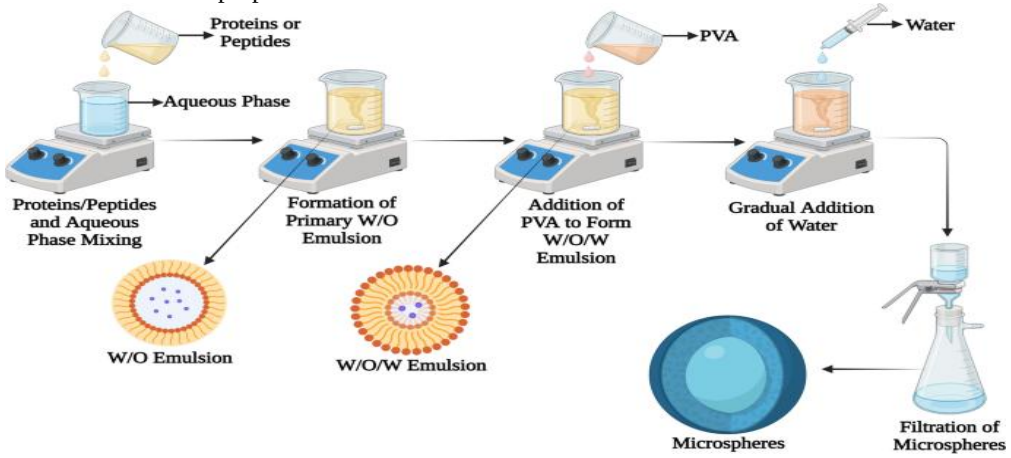

Figure 6: Ultrasound-assisted production

Mechanism of Drug Release

In reaction to a variety of outside stimuli, microsponges can be programmed to produce a specific amount of active substances over a while.

1. **pH Triggered System**

   You can change the covering on the microsponge to start the pH-based release of the active. This has several uses for drug delivery.

2. **Temperature Release**

   Temperature is one factor that can act in the release of active materials from microsponges. At room temperature, some of the compounds retained inside the Microsponge, like emollients and sunscreens, maybe too viscid to naturally distribute onto the skin. viscosity may drop as an outcome of being warmed by the body's warmth, the sun, or another heat source, increasing the flow rate. [21,22]

3. **Pressure Release**

   When pressed or squeezed, the microsponges system releases liquid or active components, refilling the skin's supply of the substance that has been trapped there. The sponges' capability to release water and the resilience of the microsponges could also affect how much is released. [23]

4. **Solubility**

   In the occurrence of water, microsponges comprising water-soluble compounds such as sterilizers and deodorants will release the substance. Diffusion, while taking into account the ingredient's partition coefficient among the micro sponges and the external system, can also initiate the[21-26]

Current trend of Microsponges drug delivery system:

Microsponges presently have the greatest advantages in the area of topical and cosmetics products but with the advancement of time few new advancement have been identified the modification of Microsponges like nanoferrosponges, nanosponges and porous microbeads. After hyper cross linked of nanosponges with cyclodextrins forms alpha Cyclodextrines, Beta cyclodextrines and gamma cyclodextrines . Limited researches have been discovered like ethyl cellulose Nano sponges have been prepared for skin disorders by combining with hydrogel formulations. Ferrosponges also known as magnetic sponges like hydrogels produced by using in-situ magnetic nanoparticles using different concentration of gelatins. Nanoferrrosponges were prepared by polymer coprecipitation with magnetite .[30,31,32]

Advances in technology developed by adapting the methods to form nanosponges and porous micro pellets include Cyclodextrin (CD) based nano-sponges for drug delivery. These advanced drug delivery systems are utilized for oral administration of various drugs such as dexamethasone, flurbiprofen, doxorubicin hydrochloride, itraconazole, This This β-CD molecule is cross-linkedby reacting the β-CD with biphenyl carbonate and these form the nanosponges as advanced formulation.[32,33]

Researchers have observed that the addition of a cytotoxic substance as the carrier system in the formulation that can be increased the drug potency and can be used in targeting the cancer cells and also as carriers for the delivery of gases.[34]

Topical anti-inflammatory gels of naproxen entrapped in Eudragit based microsponge delivery system have recently become available. In recent research, naproxen containing Eudragit RS-100, Carbopol and PVA has been developed by quasi-emulsion method. Design and *in vitro* characterisation of betamethasone microsponge loaded topical gel is a recentdevelopment in betamethasone microsponges formulation for topical anti-inflammatory action by using Quasi-emulsion method. Recent research has also made available,[33,34]

microsponge formulation containing controlled release risperidone used in the treatment of schizophrenia and schizoaffective disorders. Formulation, optimisation, development, and evaluation of microsponge gel of fluconazole has also been prepared [35]

Microsponges were successfully prepared by a quasi-emulsion solvent diffusion method using Eudragit Rs 100 and PVA with distilled water and liquid–liquid suspension polymerisation method. These have a potential for improved stability, enhanced formulation flexibility reduction in side effects while maintaining their therapeutic efficacy [36]

Application of Microsponges

1. **In Topical Preparation**

   Due to market demand, Industrial Producibility and short application of dermatological products, Microsponges in the topical preparation are widely used. As Microsponges are porous in nature due to this property microsponges loaded antiperspirants, deodorant and sunscreens are widely marketed .Various drug loaded Microsponges were prepared and evaluated for topical preparation like Curcumin loaded microsponges were formulated using QESD technique and polyvinyl alcohol and ethyl cellulose as carrier and Acyclovir microsponge loaded emulgel are formulated to improve the transdermal application using DOE approach and Oxiconazole nitrate loaded microsponges were prepared and evaluated for topical preparation to enhance the solubility of drug . [37,38]

2. **For Anti-Acne preparation**

   The bacteria causing acne is Propionibacterium acne. Hyper secretion of Sebum from distorted follicles results in Acne. Benzoyl peroxide, azelaic acid and salicylic acid are localized topical agent used in the prevention of Acne. Various preparations were formulated for Acne treatment like: Miconazole nitrate loaded microsponges were prepared and evaluated using quasi emulsion solvent diffusion method and Dapsone loaded microspongewere prepared and evaluated for treating the microbial property and preparation and analyzation of Havan Ash loaded microsponges for the treatment of Acne using Quasi emulsion solvent diffusion method[38,39]

3. For Skin Cancer

In the white skinned peoples skin cancer is commonly occurred disease. In general ratio approx. one million Americans per year were affected from skin cancer . Generally two types of skin cancer were defined namely: Melanoma and Non Melanoma .Tacrolimus loaded microsponges were prepared to cure the skin disorders .[41,42,43]

In vitro characterisation

1. Micromeritics of microsponges

The porosity and its descriptive parameters (total intrusion volume, bulk and apparent densities, pore area, pore diameter and porosity) were determined using mercury intrusion porosimeter (AutoPore IV 9500, Micromeritics, USA). Blank and drug loaded microsponges were submerged under a pool of mercury in a calibrated cell within a vacuum chamber. Mercury intrusion volume was measured by gradually increasing the cell pressure, which allowed the mercury to forcefully penetrate the pores of the microsponges[40].

2. Thermal analysis

To study thermal behaviour, differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) were conducted. DSC thermograms of ketoprofen, unloaded micro-sponges and drug-loaded formulations were recorded using DSC 1 Star (Mettler-Toledo, Leicester, UK). Whilst Thermobalance Mettler TG50 (Mettler-Toledo Ltd., Leicester, UK) was used for TGA. An accurately weighed quantity (4-8 mg) of samples was sealed and pierced in flat-bottomed aluminium crucibles and heated at a rate of 10 °C/min,from 25-150 °C for DSC and 25-500 °C for TGA, under continuous dry purge of liquid nitrogen flowing at a rate of 50 mL/min.[41]

3. X-ray Diffraction (XRD)

X-ray diffraction patterns were recorded using X-ray diffraction system (PAN alytical X 'Pert Powder) between 5 to 50° at 2θ angle. The XRD instrument was equipped with a Cu Kα radiation source (1.5406 Å) with a generator voltage and current of 30 kV and 10 mA, respectively.

4. Fourier Transform Infra-red Spectroscopy (FT-IR)

FT-IR spectra of ketoprofen, EC, HPMC, Tween80, PVA and microsponge formulations were recorded over wavelength range of 4000 to 500 cm-1 at a resolution of 4 cm-1 using an ATR FT-IR spectrometer (Alpha Bruker).

5. Scanning Electron Microscopy (SEM)

Formulations were evaluated for morphology by a JEOL model JSM-6060LV scanning electron microscopy (Japan). Samples were lightly spread over specimen stubs, and a sputter coater (SC7620) was used for coating the surface of the material with AuPd for high qual images. Samples were carefully prepared to ensure particles are not crushed. Images were captured at multiple magnifications.[42]

CONCLUSION

Microsponge drug delivery systems offer a promising strategy for the management of rheumatoid arthritis by providing controlled and sustained drug release, reducing dosing frequency, and minimizing systemic adverse effects. Their unique porous structure enhances drug stability, therapeutic efficacy, and patient compliance. With continued research and technological advancements, microsponge-based formulations have the potential to become effective alternatives to conventional RA therapies for long-term treatment.

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