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Advancements in arthritis treatment: a review of Microsponge Drug delivery systems

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Abstract

Rheumatoid arthritis is distinguished by chronic synovitis, systemic inflammation, and autoantibodies (especially against rheumatoid factor and citrullinated peptide). Genetic factors account for approximately 50% of the risk of developing rheumatoid arthritis. In developed countries, smoking is the most significant environmental risk. This condition is especially common in women and the elderly. For decades, drug administration for acute or chronic diseases has relied on different dosage forms such as tablets, capsules, creams, and injectable. However, the need for multiple daily doses often leads to fluctuating drug levels, causing toxicity and inefficiency. This challenge, along with issues like Frequent administration and erratic absorption has spurred the development of Sustained drug delivery systems. To overcome the symptoms of arthritis a flexible medication delivery option is provided by microsponge technology, which was initially developed for topical uses before being investigated for oral administration more recently. Microsponges release active chemicals into the skin in a regulated and time-dependent manner. Topical treatments fail to enter the systemic circulation and have a number of drawbacks, including an offensive smell, greasiness, and skin irritation. The microsponge delivery technology solves this issue.

These little but powerful carriers, which take the form of microscopic porous spheres, have an exceptionally large surface area that functions as a dynamic canvas for the effective encapsulation of medicinal substances.

Key words : Arthritis, Microsponges, microporous bead, Topical drug delivery, cutaneous.

[2,3]Associate Professors

Arthritis is a condition characterized by joint immobility and severe pain. Pain is often persistent and concentrated in the affected joint. Inflammation surrounding the joint, joint damage from disease, and the daily strain on the joint. contribute to this pain. Additionally, muscle strains from vigorous movements against rigid and painful joints can exacerbate symptoms, as can fatigue. Arthritis impacts body movements and can arise from various tissue and organ disorders. It affects individuals of all ages, leading to swelling, redness, pain, and limited mobility in the affected area.

In rheumatoid arthritis, distal joints are typically affected, leading to joint deformities characterized by bending. Conversely, in osteoarthritis, proximal joints are commonly involved, resulting in joint deformities marked by bending.

These days, one of the most significant challenges facing the pharmaceutical company adeptly managing the rate of active pharmacological substances are delivered to particular, pre-specified parts of the human body. As a result, scientists are working hard to design and create a variety of controlled-release medication delivery methods. The principal aim of these initiatives is to augment the efficacy of pharmacological interventions and foster increased patient adherence[45]. The patented Polysponge Delivery System comprises porous microspheres crafted from polymeric materials These are minute, spherical particles reminiscent of sponges. and are made up of several interconnected gaps inside a non-collapsible framework. Their extensive porous surface enables the controlled release of active ingredients[46]. The pore volume varies between 0.1 and 0.3 cm^3/g. and The surface has the capability of being adjusted between 20 and 500 m^2/g^3. Applied topically, the active components can be used in a highly concentrated form or in conjunction with a liquid carrier. On the other hand, there are certain limitations to this direct application. First, the volatile active ingredient might evaporate quickly with direct application; Second, applying the active ingredient in a very pure form can frequently cause a sharp rise in blood plasma levels, which can have major negative effects like toxicity and/or allergic reactions[43]. Because of this, it would be ideal to have a delivery composition or system that could distribute active ingredients to the skin in a controlled and extended manner following application. Such delivery methods should ideally also regulate any potential toxicity related to the active ingredient[34]. Microsponges are made of Non-compressible structures with permeable surfaces that allow for the controlled dissemination of active substances. The drug delivery system based on microsponges dispenses its active ingredient in response to skin contact and on a timed schedule[29] The foundation of Microsponge Systems is a small polymer-based microsphere that may be used to carries or Entraps an extensive range compounds. These microspheres can subsequently be added to a prepared product, including a gel, cream, liquid, or powder formulation[34].

Types of arthritis :

The world has different forms of arthritis. The most common kind is caused by joint damage, infection, or aging. Other arthritis types include rheumatoid arthritis, psoriatic

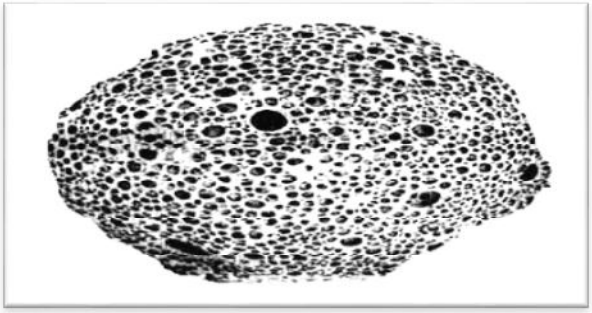
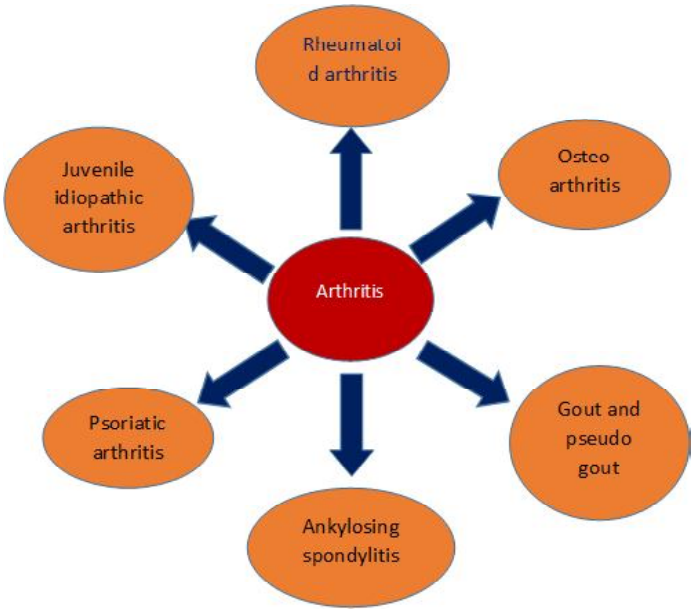


Figure 1. Porous microsponges[15]



arthritis, and autoimmune illnesses in which the body attacks itself. Due to the joint infection Septic arthritis is caused. The most common complaint of those with arthritis is pain, which can be localized to the neck, back, hip, knee, or foot. Arthritis pain is caused by inflammation around the joint, as well as disease-related joint degeneration

Treatment :

For the treatment of arthritis, both Ayurvedic and allopathic treatments are available. First, let's discuss the Ayurvedic herbs used in arthritis.

Ayurvedic Herbs :

1. ***Nirgundi :***

   Nirgundi (*Vitex negundo*) has been traditionally used in Ayurvedic medicine for treating arthritis due to its anti-inflammatory and analgesic properties.

Nirgundi leaves are often used in various forms such as decoction, oil, or paste for arthritis relief. The leaves contain compounds like flavonoids and alkaloids, which possess anti-inflammatory and pain-relieving effects.

Figure 2. Nirgundi herb

2. ***Ajwain (Trachyspermum ammi):***
Ajwain, also known as carom seeds, is commonly used in traditional medicine for its potential benefits in arthritis. Ajwain contains compounds with anti-inflammatory properties that may help reduce inflammation in the joints, which is a key factor in arthritis pain.

3. ***Dashmool***
Dashmool, a combination of ten medicinal roots, is commonly used in Ayurveda for arthritis. It is known for its anti-inflammatory and analgesic properties, helping to alleviate joint pain and inflammation.

4. ***Shallaki***
Shallaki, also known as *Boswellia serrata,* is commonly used in Ayurvedic medicine for arthritis. It is believed to have anti-inflammatory properties that help reduce inflammation and pain associated with arthritis.

Figure 3. Shallaki
(a medicinal tree)

5. ***Ginger (Zingiber officinalis) :***
Ginger is commonly used to alleviate arthritis symptoms. It contains compounds with anti-inflammatory properties that can help reduce pain and swelling in arthritic joints.

- Allopathic treatment often provides faster relief and are prescribed based on specific symptoms and conditions. Additionally, allopathic medicines can target inflammation and pain more effectively, leading to better management of arthritis symptoms.so We often prefer allopathic medication over Ayurvedic remedies.

Non-Steroidal anti-inflammatory drug :

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to alleviate pain, reduce inflammation, and lower fever. They are available in tablet form and also as topical treatments like creams, gels, or lotions applied to specific areas of the body.

Control Release Preparation of NSAIDS

Conventional tablets like aspirin typically require high doses to achieve their effects in

the treatment of rheumatoid arthritis, it shows highly marked gastrointestinal side effects. This drug has suddenly rise or decline of plasma concentration in blood due to their short time that it takes for elimination and plasma concentration. Hence, the SR or CR commenced the drug's short half-life causes unpredictable plasma concentrations throughout the day during prolonged therapy, but it remains efficacious under these settings. There has also been considerable interest in SR or CR pills containing NSAIDs with short elimination half-lives. These SR or CR preparations were created with the goal of prolonging the therapeutic benefits of NSAIDS.

Mechanism of Action of NSAIDs :

Anti-Inflammatory Effect

NSAIDs exert their anti-inflammatory effects by inhibiting prostaglandin G/H synthase, or cyclooxygenase, the enzyme that catalyzes the transition of arachidonic acid to prostaglandins and thromboxane. NSAID inhibits the cox therefore the synthesis of prostaglandin ultimately stop.This enzyme has two forms: cox1 and cox2. Selective inhibition of cox2 reduces Gl negative effects. NSAIDs activate endothelial cells and induce the production of cell adhesion molecules, which aid in the targeting of circulating cells to inflammatory areas. NSAIDs may reduce expression of these cell adhesion molecules, as well as directly inhibit neutrophil activation and function.

COX 1 ⟹ is a constitutive that is necessary of our body
COX 2 ⟹ when cox2 is working it causes generally pain, inflammation.

Attributes of materials entrapped within Microsponges :

The following specifications must be met by actives that can be trapped in microsponges.

- ✓ In order to mitigate aesthetic concerns, the solubility of concentration of constituent within the carrier should be restricted to 10-12 %w/w [27]
- ✓ It must be completely miscible in monomer or able to be made miscible by adding a quantity of solvent that is not miscible in water.
- ✓ During formulation, it is imperative that not raise the viscosity of the mixture and be inert to monomers.
- ✓ It is important that the microsponges' spherical structure remains intact[17]

Characteristics of Microsponge :

- ✓ The following attributes of microsponges are listed[17] :
- ✓ Formulations for microsponges remain unaffected across the pH range of 1 to 11
- ✓ It is possible to utilize a wide range of vehicles and substance incorporating microsponge formulations
- ✓ As the typical pore diameter of microsponge formulations is approximately 0.25μm, it is self-sterilizing and too tiny for bacteria to pass through.
- ✓ Compositions for microsponges can be cost-effective and have a free flowing nature.

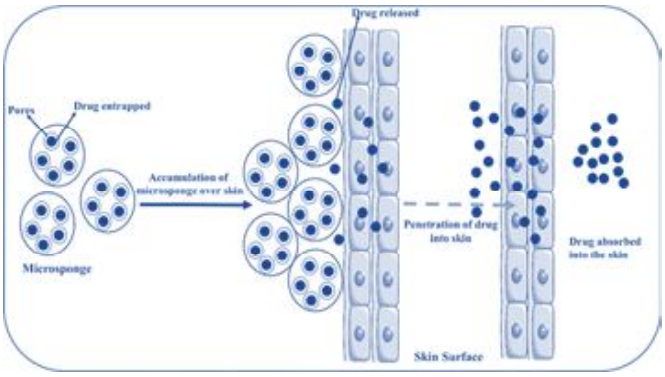


Figure 4. Mechanism of drug release[13]

Advantages [1,36,37,11] :

- Enhanced formulation elegance
- MDS permits the addition of poorly miscible items.
- Prolonged dispensed
- Formulas with less discomfort[41]
- Prolonged release, sustained activity until 12 hours
- Increases stability[33]
- Enhances material processing, such as the ability to turn liquids into powders[34].
- Increases therapeutic efficacy.

o *Advantages compared to microencapsulation and liposomes :*

Generally, microcapsules lack the ability to govern the pace at which active ingredients release. The active ingredients inside the microcapsules will leak out once the wall breaks in contrast to the previously mentioned system, the microsponge system has lot of advantages, such as stability from pH range 1-11 and for temperature till up to 130 °C, and an average pore size of 0.25 µm where bacteria are unable to penetrate. Liposomes have a worse payload, are more difficult to manufacture, and have less microbiological and chemical stability.

o *Benefits as compared to ointment :*

Because ointments are generally thick, sticky, and unpleasant, patients tend not to use them as prescribed. For therapy to be effective, these vehicles need a high concentration of active drugs, which causes adverse responses in substantial users.

o *Benefits over conventional formulations:*

Conventional topical medication formulations target the outer skin layer, quickly forming a dense layer of active ingredients that is rapidly absorbed. Microsponge technology, however, reduces irritation and prevents over-accumulation of ingredients in the dermis and epidermis, maintaining efficacy without compromise.

Limitations

1. The use of organic solvents as porogens presents a risk to the environment and could be quite combustible.

2. Even if the restrictions appear severe, they are easily surmountable with the right quality

control techniques combined with process standardization and optimization, such as post-manufacturing washing.[31,37]

3. Microsponges can be effectively transformed into tablets intended for the colon by utilizing pectin[44] or calcium pectinate as a matrix forming[35]. However, microsponges by themselves are unable to prevent the release of the primary component into the upper portion of the gastrointestinal tract.

Dispersion Process :

Microsponges are prepared to release a specific amount of material and active ingredient gradually and it can be affected by various parameters that are mention below[20]

1. Variation in temperature[11,19]
2. Pressure
3. pH triggered system[20]
4. Solubility[10,22]

Microsponge fabrication[25,40]:

- *Liquid-liquid suspension polymerization:*

The liquid-liquid suspension polymerization technique involves dissolving active chemicals and monomers in a solvent solution, dispersing additives like surfactants, then introducing a catalyst or applying radiation to initiate polymerization, resulting in porous microspheres[36]

The different processes involved in creating microsponges are summed up as

- choosing a monomer or monomer mixture.
- As polymerization progresses, chain monomers are formed.
- Ladder formation brought forth by chain monomer cross-linking.
- The process of folding the monomer ladder results in spherical particles. Agglomeration of microspheres causes bunches of microspheres to develop.
- The formation of microsponges by bunch binding.

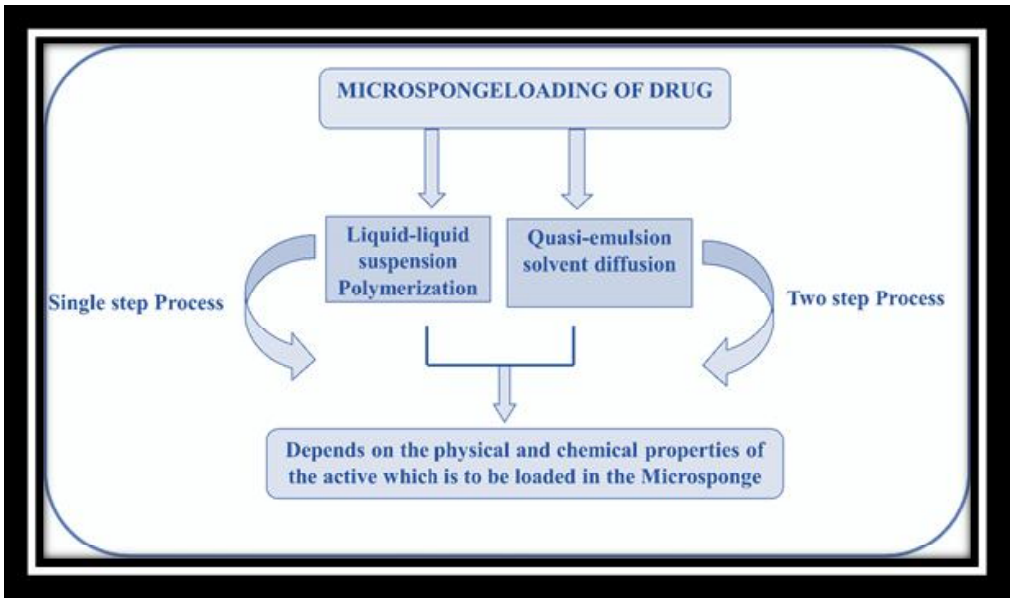


Figure 5. Microsponge fabrication[14]

- *Quasi-emulsion solvent diffusion process:*

The simulated emulsion solvent diffusion method involves dissolving Eudragit RS 100 in ethyl alcohol for the inner phase, adding medication, and sonication at 35°C [23]. A PVA solution in water serves as the outer phase. After stirring for 60 minutes, the mixture undergoes filtration to eliminate microsponges, which are then weighed after drying for 12 hours at 40°C to ascertain the production yield determine production yield[24,36].

Criterion for assessment of Microsponges include:

Particle size determination :

Microsponges can be produced Powders that flow freely and have appealing aesthetic attributes with desirable aesthetic qualities by controlling particle sizes during polymerization. Key variables affecting Particle size comprises the ratio of medication to polymer. and emulsifying agent concentration. Increasing the drug-to-polymer ratio results in smaller particles, while higher emulsifying agent content lead to the development of macroscopic microsponges[7,30,50]

Morphological and surface topographical analysis :

The choice of solvent matrix utilized for the core phase and the temperature maintained throughout preparation both affect the microsponges surface shape. Any circumstance or solvent combination that causes the polymer to precipitate quickly produces a surface that is either less porous or non-porous[9].

Drug incorporation efficiency and manufacturing yield :

Incorporation of drugs into microsponges can be achieved via active loading, a two-step process, or passive loading, a one-step process. Passive encapsulation is simpler, more practical, and more effective compared to active incorporation. Increasing drug-to-polymer ratio[26] and reducing particle size enhance Drug incorporation efficiency and manufacturing yield[18]

$$\text{Loading efficiency} = \frac{\text{Actual drug content in microsponges}}{\text{Therotical Drug Content}}$$

$$\text{Production yield} = \frac{\text{Practical Mass of Microsponges} \times 100}{\text{Therotical Mass}}$$

Research on compatibility :

FT-IR and TLC assess drug compatibility with reaction adjuncts. For DSC, 5 mg Samples undergo weighing procedures into sealed aluminum pans, warmed at 5°C/ min under nitrogen, from 25 to 430°C [12,47]

Resiliency :

The final formulation's hardness is determined by the resilience of the microsponges, impacting their collapse and drug release ability. Optimizing stiffness through interlinking adjustment is essential, but drug release patterns do not reliably indicate microsponge robustness. The best method for assessing robustness remains undetermined[2,48].

Dissolution analysis :

Microsponge dissolution is assessed using a dissolution apparatus with a stainless steel basket (5 μm mesh) rotating at 150 rpm

under Saturation conditions. Samples are collected at intervals from the medium for analysis using appropriate technique[3].

Other in-vitro studies include[38]

- ***FTIR***

The FTIR spectra of both the drug and Eudragit RS-100 were obtained. The FTIR spectra of drug and Eudragit RS-100 were recorded using FTIR spectrometer. This was recorded in potassium bromide disc. From FTIR we check the compatibility between drug and polymer[5].

- ***Differential scanning calorimetric (DSC) analysis :***

Samples were weighed accurately and put into aluminum and sealed for thermal analysis. Every sample was heated between 40 and 430 degrees Celsius at a rate of 20 degrees Celsius per minute.

- ***Statistical analysis :***

Using Graph Pad stat software, the results from each experiment were statistically analyzed for that Student t-test and one-way analysis of variance (ANOVA) were used. Significance was judged to be indicated by $P < 0.05$.

Applications of Microsponge systems :

Three main methods for microsponge systems:[4,32,41,49]

1. As active components are released from reservoirs over a longer period of time.
2. As receptacles for absorbing unwanted substances including extra skin oil, or
3. As closed receptacles that keep substances away from the skin for surface-level effects

Traditional topical formulations may rapidly release active components, risking adverse effects beyond the skin's surface[8] Microsponge technology offers extended release rates, potentially Minimizing adverse effects while preserving therapeutic effectiveness[8]

The use of active agents

1. Sunscreens: Excellent defense against sun-related ailments and sunburns even at elevated concentrations, along with less irritation make sunscreens a long-lasting product.

2. Anti-acne products, such as benzoyl peroxide, continued to be effective while causing less skin sensitivity and irritation[28].

3. Anti-inflammatory: Persistent action that reduces allergic reactions on the skin.

4. Antifungals: Active ingredients released gradually.

5. Antidandruff agents, Ingredients like zinc pyrithione and selenium sulfide reduce irritation and odor, extending safety and effectiveness.

6. Antipruritic: More prolonged and enhanced action.

7. Rubefacients: Extended use with less irritation, oiliness, and smell.

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