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# Microsponge: A Novel Tool for Topical Drug Delivery of Anti Rheumatoid Drugs

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***Authors' contributions***

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

Microsponge is developing field of technology which can achieve goal of site specific as well as controlled drug delivery. Physicochemical properties of microsponge like Particle size, particle size distribution, porosity, surface morphology plays a major role in selection of type of dosage form and route of administration for delivery of drug. Microsponge is also emerged as novel tool for delivering of drug by topical route. Topical route is having added advantage of formulation flexibility, greater patient compliance, improved safety and efficacy of formulation and aesthetic properties. Rheumatoid Arthritis is immunomodulatory disease which requires long term treatment for management of disease. Available oral formulation may cause liver toxicity upon long term use. Topical route can be suitable alternate route for delivery of drug with enhanced stability of drug, reduced side effects, and reduced frequency of administration. Due to porous and spongy structure of Microsponge, it has the capacity to entrap large amount of dose and can modify drug release too.

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## 1. INTRODUCTION

Arthritis is an immunomodulatory disease that mainly causes inflammation of the joints which can affect a single or multiple joints. It affects mainly geriatric patient but sometimes also observed in young age children. Further, it develops mainly in female patient compared to that of male patient [1,2].

Rheumatoid arthritis (RA) is an auto immune disease that causes pain and swelling of joints, preferably affecting synovial membrane (Fig. 1). Clinical manifestation also involves stiffness, restricted movement of joints, redness etc. It requires a long term treatment [3-6]. Since there is no causative cure available to treat arthritic condition, Disease Modifying Anti Rheumatoid Drugs (DMARDS) are used for symptomatic relief [7-10].

Currently used DMARDS; Methotrexate, Leflunomide, Hydroxychloroquine, Sulphasalazine etc. are available as oral dosage forms. Long term administration of Oral formulation of drugs causes liver toxicity. Topical drug delivery system can be used as alternative route. Varieties of formulations can be used to deliver the drug for topical application[11-13]. Some commonly used topical formulations are cream, ointment, lotion, gel, emulgel, organogel etc. Gel is most convenient dosage form to be used topically as it contains aqueous based vehicle, highly compatible with skin, with greater rate of permeability through skin [14-16].

Microsponges are porous, spherical microsphere, capable of encapsulating high drug content. Due to large porous surface, it is capable to release drug for a longer period of time, in a controlled manner [17-19]. It is also stable for a wide range of pH and temperature [20]. Microsponges are also compatible with low dose of drug and also capable for uniform distribution of drug with a minimal dose and thereby also affects release rate of drug [21]. Microsponge can be used as a carrier for local as well as systemic drug delivery. Both hydrophilic and lipophilic drug can be incorporated and delivered through chosen route of administration. Research work for microsponge has been reported for sustained drug delivery, solubility enhancement, gastroretentive drug delivery, for topical drug delivery [22-25]. Few marketed preparations are also available for topical delivery of drug like cream, lotion, gel, powder etc. Microsponge provides a wide range of formulation flexibility depending on physicochemical characteristics of the drug [26-28].

Most of the drugs available are poorly water soluble causing difficulty in development of dosage forms. To enhance water solubility of drug, solubility enhancement approaches can be used. Microsponge based topical drug delivery also offers additional advantage of localized and site specific drug delivery. It also bypasses first pass hepatic metabolism as well as side effects upon oral administration of drug [29-32].

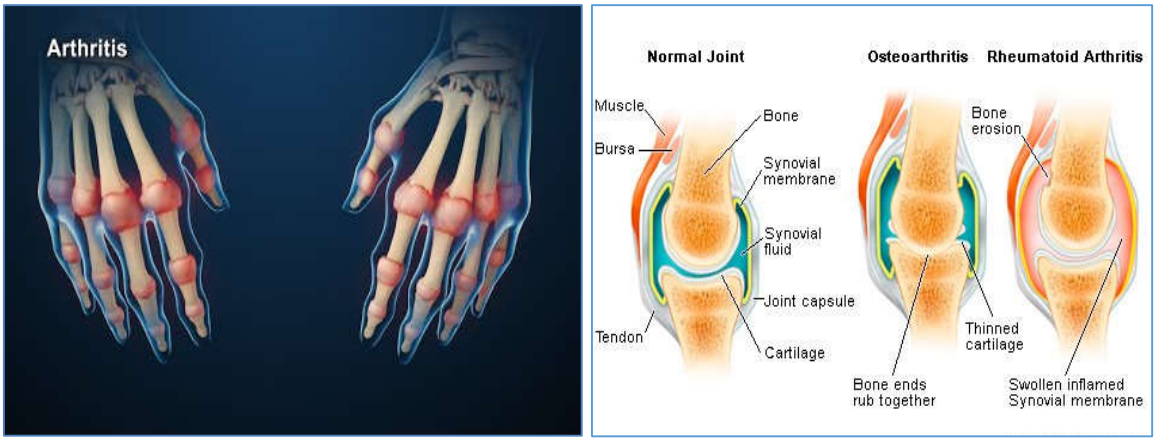


**Fig. 1. Schematic representation of rheumatoid arthritis**
**(Source of image:https://www.medicinenet.com/arthritis/article.htm)**

Advantages [20]

- Extended release
- Improved product elegancy
- Flexibility to develop novel products forms
- Improved oil control as it absorbs oil up to 6 times its weight without drying
- Enhanced product performance
- Improved formulation flexibility
- Microsponge system are non-irritating, non ,mutagenic, non-allergic
- Improved thermal, physical and chemical stability

Disadvantages

- Require long time to the reaction
- No confirm uniform structure
- Require vigorous washing to remove organic solvents
- Probable entrapment of unreacted solvent traces
- Require reflux condition
- Reproducibility is less
- Process condition like change in temperature, solvent addition and evaporation may
- influence the stability of core material
- May lead to cracking or shrinkage

Characteristics of microsponge drug delivery system [20]

- Microsponges show acceptable stability over pH ranging from 1 to 11 and at high temperatures
- Microsponges have high entrapment efficiency up to 50 to 60%
- The average pore size of micro sponges in small in a way to prevent the penetration of bacteria, thus they do not need sterilization or addition of preservatives
- Microsponges absorb oil up to 6 times their weight without drying
- Microsponges exhibits good compatibility with various vehicles and ingredients
- Microsponges possess free flowing properties
- Microsponges are non-allergenic, on-irritating, non-mutagenic and non-toxic

Polymers used to prepare Microsponge

- Ethyl Cellulose
- Carbopol
- Eudragit S100
- Eudragit RS100
- Eudragit RSPO

## 2. METHODS OF PREPARATION OF MICROSPONGE

### 2.1 Liquid – Liquid Suspension Polymerization Technique

In this method, monomers and other excipients are dissolved in a solvent. Solvent is selected in such a way that it is immiscible with external phase i.e. water. Solution containing monomer is than allowed to disperse in external aqueous medium containing surfactant. Dispersion of immiscible phase in aqueous phase results in formation of suspension with fine droplets. Polymerization of monomer present in suspension is promoted by catalyst, temperature or radiation (Fig. 2). Polymerization continues till the process completely utilizes monomer. Upon evaporation of solvent; porous, spongy Microsponge precipitates out which are required to be washed to remove impurity. Further, microsponges are separated from reaction media and subjected for drying [20,33,34].

### 2.2 Quasi-emulsion Solvent Diffusion

Microsponges can also be prepared using quasi emulsion solvent diffusion method. This method involves preparation internal organic phase and external aqueous phase. Inner phase can be prepared by dissolving polymer and drug simultaneously in common organic solvent with specified condition of stirring and temperature. Outer phase is prepared by dissolving surfactant in aqueous phase. Dropwise addition of internal phase to external phase results in formation of fine droplets dispersed in external phase. Complete evaporation of Organic solvent yield formation of tiny, porous Microsponge (Fig. 3). Isolated microsponges are then subjected to washing and subsequent drying [35-37].

In both discussed method of preparation, drug can be incorporated at the time of preparation if it can withstand supposed experimental condition. In case, if drug is thermolabile in nature, microsponges are pre-formed without drug. Drug is incorporated by soaking miacrosponges in saturated solution of drug for 24-48 hrs.

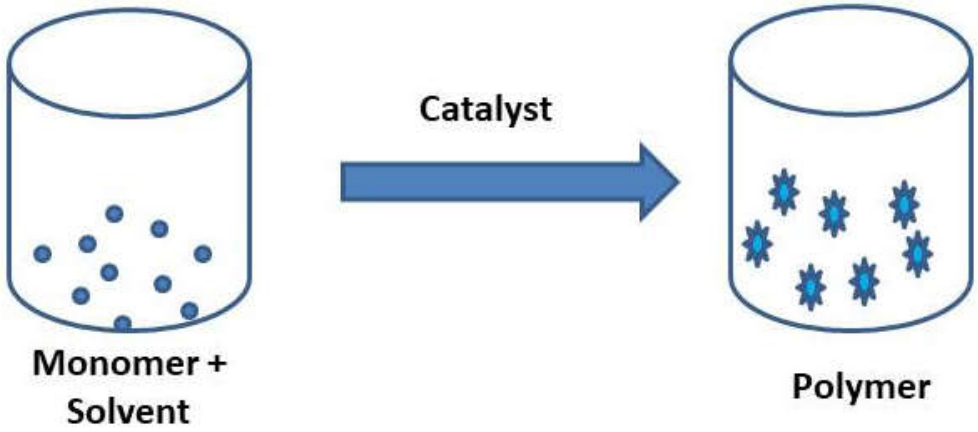


**Fig. 2. Schematic representation for Liquid liquid suspension polymerization technique**

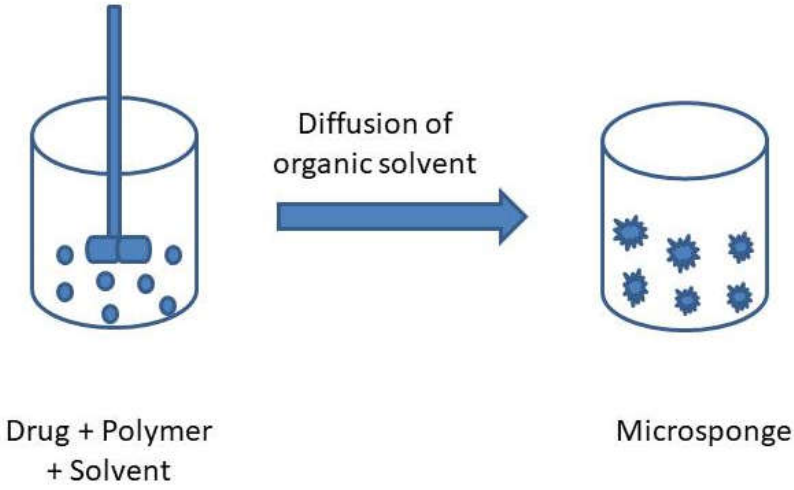


**Fig. 3. Schematic representation for Quasi-emulsion solvent diffusion technique**

## 3. CHARACTERIZATION OF MICRO-SPONGE

### 3.1 FTIR Spectrum

Fourier Transform Infrared Spectrophotometer is used to study drug-excipients compatibility. Previously dried drug and excipients are subjected to Spectrophotometer and spectrum is recorded in wavelength range 4000-400 $cm^{-1}$. Recorded spectrum is subjected to analysis for compatibility. Each drug and excipients are having identical spectrum due to the presence of identical functional groups and intermolecular forces involved between the molecules. Standard spectrum can be verified with test and difference can be identified [38,39].

### 3.2 Differential Scanning Calorimetry (DSC)

DSC is performed to study thermal behaviour of drug, polymer and other excipients. DSC is also used to check compatibility between drug and excipients. Study is carried out by compressing dry solid sample between two aluminium pans. Further, it is subjected to gradual heating with constant purging of nitrogen flow rate. Thermogram obtained using this procedure is studied for accessing amorphous or crystalline nature of components to be studied [40,41].

### 3.3 Microscopic Analysis

Optical microscopy can be carried out by using lab scale microscope. Slide can be prepared by Sprinkling a thin layer of dried Microsponge and observed under Optical microscope using standard magnification. Particle size and Particle size analysis can also be performed. Further, optical microscope can be connected with camera to capture the photograph of prepared Microsponge [42,43].

### 3.4 Scanning Electron Microscopy (SEM)

Scanning electron microscopy is performed to study three dimensional surface morphology of prepared microsponge. SEM uses a probe which can scan only conductive material. Hence, prepared microsponge is prepared by coating with electro conductive metal under specified condition of vacuum. Scanning probe moves over the surface of Microsponge and depicts image, from which topographical study of Microsponge can be performed [44,45].

### 3.5 X-ray Diffraction Study (XRD)

XRD is used to study physicochemical structure of given sample. Sample of Microsponge was subjected to equipment. Short wavelength radiation, X-ray is imparted to sample under specified condition of voltage. Diffracted radiation is recorded on diffractogram. Upon, analysing diffraction pattern, it can be concluded that weather structure of sample is amorphous or crystalline in nature. Further, from study, it can also be concluded that during processing, physical structure of drug or Microsponge has been changed or not [46,47].

### 3.6 Percentage Yield

Amount of drug, Polymer and other excipients forms a total theoretical mass of Microsponge. Practical mass of Microsponge is actually weight of Microsponge obtained after experimental process to prepare Microsponge. Percentage yield for Microsponge can be calculated using following formula [48,49].

$$\% = [\text{particle mass of microsponges} / \text{Theoretical mass}] \times 100$$

### 3.7 Drug Content and Encapsulation Efficiency

Drug content is determined by dissolving accurately weighed quantity of Microsponge in solvent with continuous stirring. Solvent is selected in such a way that it can dissolve drug as well as polymer. Hence, most of the content would dissolve in chosen solvent. After filtration, drug content from the solution can be analysed by using suitable analytical technique.

Drug content and encapsulation efficiency can be calculated using following formula [50,51].

$$\text{Actual drug content (\%)} = [\text{M actual drug} / \text{M obtained}] \times 100$$

$$\text{Encapsulation efficiency} = [\text{M practical} / \text{M theoretic}] \times 100$$

where, M actual is the actual drug content in weighed quantity of microsponges,
M obtained is the weighed quantity of powder of microsponges

### 3.8 *In vitro* Drug Release Study

In vitro drug release study can be performed by using Franz diffusion cell. It uses two compartments, namely donor and acceptor compartment. Both compartments are separated by dialysis membrane. Accurately weighed quantity of Microsponge is placed in donor compartment containing small amount of diffusion media, acceptor compartment is also filled with diffusion medium. Whole assembly is set on magnetic stirrer. Acceptor compartment is continuously stirred and maintained at $37^0$c to simulate human body condition. At regular interval of time, aliquots are collected from acceptor compartment and replaced with fresh diffusion medium to maintain sink condition. Collected aliquots are filtered and diluted with suitable volume of diffusion media and analysed using specific analytical technique. From obtained data, % drug release and drug release kinetic can be studied [52,53].

### 3.9 Stability Study

Stability study can be performed to check the effect of environmental conditions or storage conditions on formulation of Microsponge. Optimized formulation of Microsponge can be observed up to 1 month for short term accelerated stability study.

A condition of stability study is temperature and relative humidity (40±2 ºC/75%±5%RH) as per ICH (International Conference on Harmonization) guidelines. Upon completion of stability study,

collected samples can be subjected to analysis for various parameters [54-56].

## 4. CONCLUSION

Microsponges are versatile dosage form that can offer the incorporation of wide range of drug and dose of drug to be incorporated. High porosity of Microsponge imparts rapid drug release. Modified polymer can also be used to have sustained/ controlled drug delivery also. Compared to currently available treatment of Rheumatoid arthritis as Oral formulation, Microsponge can be designed to deliver the anti rheumatoid drug for topical application. This can have added advantage for site specific drug delivery. Furthermore, topical delivery can enhance efficacy, safety of dosage form. Future perspective for development of Microsponge for topical application can be promising route for management of arthritis.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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