MICROSPONGES: TOPICAL PREPARATION AND ITS APPLICATIONS

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ABSTRACT

Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge-like spherical particles with a large porous surface. Moreover, they may enhance stability, reduce side effects and modify drug release favorably. Microsponge technology has many favorable characteristics, which make it a versatile drug delivery vehicle. Microsponge Systems are based on microscopic, polymer-based microspheres that can suspend or entrap a wide variety of substances, and can then be incorporated into a formulated product such as a gel, cream, liquid or powder. The outer surface is typically porous, allowing a sustained flow of substances out of the sphere.

Microsponges are porous, polymeric microspheres that are used mostly for topical use and have recently been used for oral administration. More and more developments in delivery systems are being integrated to optimize the efficacy and cost-effectiveness of the therapy. Microsponge technology offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility. In addition, numerous studies have confirmed that microsponge systems are non-irritating, nonmutagenic, non-allergenic, and non-toxic. Microsponges are being used currently in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products. One of the best feature of microspone is it is self-sterilizing. This review is based on method of preparation and applications of microsponges.

INTRODUCTION

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 of the technique and applied those to cosmetic as well as OTC and prescription pharmaceutical products. At the present time, this interesting technology has been licensed to Cardinal Health, Inc.\textsuperscript{[1]} Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge-like spherical particles with a large porous surface. Moreover, they may enhance stability, reduce side effects and modify drug release favorably. Microsponge technology has many favourable characteristics, which make it a versatile drug delivery vehicle.\textsuperscript{[2,3]} Microsponge has been increasingly investigated to reach the aim in recent years. Microsponges are a polymeric delivery system consisting of porous microspheres, and they may enhance the rate of dissolution of poorly water-soluble drugs by entrapping such drugs in microsponge pores.\textsuperscript{[4]} These pores are very small, and the drug can be reduced to microscopic particles in these pores, which significantly increase the surface area of the drug and increase the rate of solubility. Hence, this system may improve the efficacy and bioavailability of some poorly soluble drug.\textsuperscript{[5]} A topical conventional delivery drug suffers some problems such as aesthetically unappealing, greasiness and stickiness that often leads to lack of patient compliance. In the formulation point of view, uncontrolled evaporation of active ingredient, unpleasant odour and incompatibility of drugs with the vehicles are the notable drawbacks faced by Pharmaceutical scientists.\textsuperscript{[6]} Thus, huge demand for novel drug delivery systems. Microsponges drug delivery (MDS) is one of the potential and promising drug delivery systems to encounter those hurdles. Moreover, it may improve stability, reduce side effect of active ingredients from topical formulations, further it helps to modify drug release favorably.\textsuperscript{[7]}

Microsponges are also designed to deliver active ingredients efficiently at minimum dose and to enhance stability, reduce side-effects, and modify drug release.\textsuperscript{[8,9]}

**Advantages of microsponges**

1. Microsponge formulations are stable over range of pH 1 to 11.
2. Microsponge formulations are stable at the temperature up to 130\degree C.
3. Microsponge formulations are compatible with most vehicles and ingredients.
4. Microsponge formulations are self sterilizing as their average pore size is 0.25\textmu m.
5. Microsponge formulations have higher payload (50 to 60\%), still free flowing and can be cost effective.
6. Microcapsules cannot usually control the release rate of actives. Once the wall is ruptured the actives contained within microcapsules will be released. Whether MDS can do it.
7. Liposome suffers from lower pay load, difficult formulation, limited chemical stability and microbial instability, whether MDS have wide range of chemical stability and easy to formulation.

8. Microsponges are microscopic spheres capable of absorbing skin secretions, therefore reducing oiliness and shine from the skin.\textsuperscript{10}

**Benefit of microsponge drug delivery system**

2. Extended release.
3. Reduced irritation and hence improved patient Compliance.
4. Improved product elegance.
5. Improved oil control as it can absorb oil up to 6 times its weight without drying.
6. Improved formulation flexibility.
7. Improved thermal, physical, and chemical stability.
8. Flexibility to develop novel product forms.
9. Microsponge systems are non-irritating, non-mutagenic, non-allergenic and non-toxic.\textsuperscript{11,12}

**CHARACTERISTICS OF MICROSPONGE**

- Microsponges formulations are stable over range of pH 1-11;
- Microsponge formulations are stable at temperature up to 130°C;
- Microsponge formulations are self-sterilizing as their average pore size 0.25 µm where bacteria cannot penetrate;
- Microsponge formulation have higher payload (50-60%), still free flowing and can be cost effective.\textsuperscript{13}

The Microsponge technology is a proprietary system of microparticles that can entrap a very wide range of pharmaceutical and cosmetic active ingredient to enhance their performance in topically applied dermatological products. This technology has been introduced in topical drug products to ensure the controlled release of active drug into the skin in order to reduce systemic availability and reduce local cutaneous reaction to active drug.

Drugs explored in Microsponge drug delivery system are

- Salicylic acid
- Retinol
Tretinoin
- Ketoconazole
- Trolamine
- Flurbiprofen
- Dicyclomine
- Paracetamol
- Ketoprofen
- Benzoyl peroxide
- Fluconazole
- Ibuprofen

Structure of microsponges

Fig1. Structure of Microsponges

Methods of preparation of Microsponges

Micro sponge’s drug delivery system can be prepared in two ways, one-step process or by two-step process that is liquid-liquid suspension polymerization and quasi emulsion solvent diffusion techniques based that is based on physicochemical properties of drug to be loaded.

1. Liquid-liquid suspension Polymerization

The porous microspheres are prepared by suspension polymerization method in liquid-liquid systems. In this method the monomers which are immiscible are first dissolved along with active ingredients in a suitable solvent monomer and are then dispersed in the aqueous phases which consist of additives like surfactant, suspending agents to facilitate formation of suspension.\textsuperscript{[14,15]} The polymerization is then activated by increasing temperature or irradiation or by addition of catalyst. The polymerization process continues the formation of a reservoir.
type of system with spherical structure. After the polymerization process the solvent is removed leaving the spherical structured porous microspheres, i.e., microsponges.\textsuperscript{[2,13]}

Fig 2. showing preparation of microsponges by liquid liquid suspension polymerization.

2. Quasi-emulsion solvent diffusion

Porous microspheres (microsponges) were also prepared by a quasi-emulsion solvent diffusion method (two-step process) using an internal phase containing polymer such as eudragit which is dissolved in ethyl alcohol. Then, the drug is slowly added to the polymer solution and dissolved under ultra-sonication at 35°C and plasticizer such as triethylcitrate (TEC) was added in order to aid the plasticity. The inner phase is then poured into external phase containing polyvinyl alcohol and distilled water with continuous stirring for 2 hours. Then, the mixture was filtered to separate the microsponges. The product (microsponges) was washed and dried in an air-heated oven at 40°C for 12 hr.\textsuperscript{[14,15]}

Fig 3: showing preparation of microsponges by quasi-emulsion solvent diffusion
3. Polymerization

The porous microspheres are prepared by suspension polymerization method in liquid-liquid systems. In their preparation, the monomers are first dissolved along with active ingredients in a suitable solvent solution of monomer and are then dispersed in the aqueous phase, which consist of additives (surfactant, suspending agents, etc. to aid in formation of suspension). The polymerization is then initiated by adding catalyst or by increasing temperature or irradiation. The various steps in the preparation of microsponges are summarized as:
- Selection of monomer or combination of monomers
- Formation of chain monomers as polymerization begins
- Formation of ladders as a result of cross linking between chain monomers
- Folding of monomer ladder to form spherical particles-

Agglomeration of microspheres.

The polymerization process leads to the formation of a reservoir type of system, which opens at the surface through pores. In some cases an inert liquid immiscible with water but completely miscible with monomer is used during the polymerization to form the pore network. After the polymerization the liquid is removed leaving the porous microspheres, i.e., microsponges. Impregnating them within preformed microsponges then incorporates the functional substances. Sometimes solvent may be used for faster and efficient incorporation of the active substances. The microsponges act as a topical carriers for variety of functional substances, e.g. anti acne, anti inflammatory, anti purities, anti fungal, rubefacients, etc. [16,17]

4. Emulsion solvent diffusion method

In this method 2 phases are used in different proportion of organic and aqueous(ethyl cellulose and polyvinyl alcohol). The dispersed phase having ethyl cellulose and drug get dissolved in dichloromethane(20 ml) and a definite amount of polyvinyl alcohol added to 150 ml of aqueous continuous phase. Then, the mixture is stirred properly at 1000 rpm for 2hr. The required microsponges were collected by the process of filtration and kept for drying in oven at 40ºc for 24hr. microsponges which are dried were strored in dessicators and ensurity of removal of residual solvents is done.[18]

5. Microsponges prepared from hyper-cross linked β-cyclodextrins

Prepared from β-cyclodextrins act as microsporous materials performed their work as carriers for drug delivery. Due to this 3-d networks are formed which may be a roughly spherical
structure about the size of a protein having channels and pores in the internal part. Reacting cyclodextrin with a cross linker such as di-isocianates, diaryl carbonates, carbonyl di-imidazoles etc. Sponges size is controlled according to porosity, surface charge density for the attachment to different molecules. microsponges are synthesized in neutral or acidic form. They consist of solid particales and converted in crystalline form. Capacity of microsponges to encapsulate drug having different structures and solubility. They are used to increased aqueous solubility of poorly-water soluble drugs.\textsuperscript{19,20}

Evaluation Parameters of Microsponges
Various evaluation tests were performed to evaluate the prepared formulations of microsponges

1. **Percentage Yield**: The prepared microsponges of all batches were accurately weighed. The percentage yield of microsponges was calculated by using following equation \( \% \) Yield \( = \) Actual weight of product/total weight of product \( \times \) 100.\textsuperscript{21,22}

2. **Morphology and surface topography of microsponges**: Prepared microsponges can be coated with gold–palladium under an argon atmosphere at room temperature and then the surface morphology of the microsponges can be studied by scanning electron microscopy (SEM). SEM of a fractured microspone particle can also be taken to illustrate its ultra-structure.\textsuperscript{23,24}

3. **Determination of loading efficiency and production yield**: The loading efficiency (%) of the microsponges can be calculated according to the following equation Loading efficiency \( = \) Actual Drug Content in Microsponges / Theoretical Drug Content X 100

4. **Theoretical Drug Content**: The production yield of the micro particles can be determined by calculating accurately the initial weight of the raw materials and the last weight of the microspone obtained.
Production Yield\( = \) Practical mass of Microsponges \( \times \) 100.\textsuperscript{25,26}

5. **Morphology and particle size studies**: The morphology and surface characterization of the microspone formulation were evaluated by SEM analysis using JSM 840A SEM analyser after the sample had been gold sputtered coated with 25nm gold film thickness.\textsuperscript{27,28}
6. **In vitro dissolution studies**: In vitro dissolution studies were carried out using USPXXI dissolution assembly (basket type) in 900 ml of pH7.4 saline phosphate buffer solution at 370± 5°C and rotated at 50 rpm. Specified amount of aliquots were withdrawn at hourly intervals up to 8h. The samples were assayed at 222 nm.\(^{29}\)

7. **Stability studies**: The stability studies are carried out according to guidelines given by International Council of Harmonization (ICH guidelines). In view of the potential utility of coated, uncoated & Ethyl cellulose microsponge formulation, stability studies were carried out. The formulation was tested for stability at 50 ± 2 0 C, 250 ± 2 0C/ 60±5 RH, 400±2 0 C/ 75±5 RH. Formulations were stored in glass bottles/vials and were evaluated after 15, 30, 45 days.

8. **Drug-polymer compatibility studies**: The sample of drug, excipients and mixture of drug with excipients (binary (1:1) powder mixtures prepared by trituration of drug with the individual excipients) was sealed in vials and kept at room temperature for not less than one month and then samples were analyzed by DSC and FTIR.\(^{30}\)

9. **X-ray diffraction studies**: X-ray diffractometry (XRD) of the BFZ, polymer and BFZ microsponges of optimized batch were performed by a diffractometer at TIFR to observe the physical state of BFZ in the microsponges. The instrument details are as follows,

   Manufacturer : Panalytical
   Model : Xpert PRO MPD
   Anode : Copper K-alpha
   Wavelength : 1.5405 angstrom
   Power: 45KV and 40mA Detector: Xcelerator with diffracted beam monochromator.\(^{31}\)

10. **In-vitro diffusion study of Microsponge Gel**: The in vitro release of microspongic gel was performed by the membrane diffusion technique a sample of 1g of the preparation was spreaded on a cellophane membrane previously soaked overnight in the release medium. The loaded membrane was firmly stretched over the edge of a glass tube of 2 cm diameter; the membrane was tied up with a rubber to prevent leakage. Tubes were then immersed in the dissolution vessel which contained 50 ml of the release medium, phosphate buffer pH 5.5, and maintained at 37°C ± 0.5°C. The shafts were rotated at 50 rpm and aliquots each of 2 ml were withdrawn from the release medium at specified time intervals. Withdrawn samples were replaced by equal volumes of fresh release medium.
The samples were assayed spectrophotometrically at specific $\lambda_{\text{max}}$ and the concentration of the drug was determined from the previously constructed calibration curve. The in vitro diffusion studies were recorded for a 10 hour period.[32]

**Drug release mechanism of microsponge**

The active ingredient is added to the vehicle in an entrapped form. As the microsponge particles have an open structure (they do not have a continuous membrane surrounding them), the active is free to move in and out from the particles and into the vehicle until equilibrium is reached, when the vehicle becomes saturated. Once the finished product is applied to the skin, the active that is already in the vehicle will be absorbed into the skin, depleting the vehicle, which will become unsaturated, therefore, disturbing the equilibrium. This will start a flow of the active from the microsponge particle into the vehicle, and from it to the skin, until the vehicle is either dried or absorbed. Even after that the microsponge particles retained on the surface of the stratum corneum will continue to gradually release the active to the skin, providing prolonged release over time. This proposed mechanism of action highlights the importance of formulating vehicles for use with microsponge entrapments. If the active is too soluble in the desired vehicle during compounding of the finished products, the products will not provide the desired benefits of gradual release. Instead they will behave as if the active was added to the vehicle in a free form. Therefore, while formulating microsponge entrapments, it is important to design a vehicle that has minimal solubilizing power for the actives. This principle is contrary to the conventional formulation principles usually applied to topical products. For these conventional systems it is normally recommended to maximize the solubility of the active in the vehicle.[33,34]

**Marketed formulations of microsponges**

**Table 1. showing marketed topical formulations of microsponges**

<table>
<thead>
<tr>
<th>Microsponges drug delivery</th>
<th>Drugs</th>
<th>Disease treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gels</td>
<td>Benzyl peroxide</td>
<td>Anti acne treatment</td>
</tr>
<tr>
<td></td>
<td>fluconazole</td>
<td>Anti fungal</td>
</tr>
<tr>
<td></td>
<td>Diclofenac sodium</td>
<td>Anti-inflammatory</td>
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<tr>
<td></td>
<td>Terbinafine HCL</td>
<td>Antifungal</td>
</tr>
<tr>
<td>Lotions</td>
<td>Benzyl peroxide</td>
<td>Antiacne treatment</td>
</tr>
<tr>
<td>Creams</td>
<td>Hydroquinone and retinol</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Others</td>
<td>Ibuprofen</td>
<td>NSAID</td>
</tr>
</tbody>
</table>
APPLICATIONS OF MICROSPONGES Microsponges are used mostly for topical, oral administration as well as biopharmaceutical delivery. It offers the formulator a range of alternatives to develop drug and cosmetic products.[35] These are developed to deliver an active ingredient efficiently at the low dose and Microspponge drug delivery system unique, novel and versatile and extremely attractive in cosmetic world.[36] Recent applications of microsponge from sea weed were to detect the diseases and also microsponge drug delivery in RNA silencing. Some applications of MDS are described as follows:

Applications

**Sunscreens:** Long lasting product efficacy, with improved protection against sunburns and sun related injuries even at elevated concentration and with reduced irritancy and sensitization.

**Anti-acne:** E.g. Benzoyl peroxide Maintained efficacy with decreased skin irritation and sensitization.[37]

**Anti-inflammatory:** E.g. hydrocortisone Long lasting activity with reduction of skin allergic response and dermatoses. Anti-fungals: Sustained release of actives Ingredient.

**Anti-dandruffs:** E.g. zinc pyrithione, selenium sulfide. Reduced unpleasant odour with lowered irritation with extended safety and efficacy.

**Antipruritics:** Extended and improved activity. Skin depigmenting: E.g. hydroquinone.

**Rubefacients:** Prolonged activity with reduced irritancy greasiness and odour.[38]

**In Food Industry:** Nanosponges are useful for masking, reduction and elimination of bitter components from fruit juices and other dietary products by selective combination of polymer and crosslinker.[39]

**Chemotherapy:** Nanosponges have been studied as a potential delivery system for anticancer therapies in which enhancement of bioavailability and activity was seen in molecules such as Paclitaxel and Tamoxifen. Different cancer cells had been treated by nanosponges like breast cancer or fast acting glioma type with help of single dose of injections.[40]
CONCLUSION

A Microsponge Delivery System can entrap wide range of actives and then release them onto the skin over a time and in response to trigger. It is a unique technology for the controlled release of topical agents and consists of microporous beads loaded with active agent and also use for oral as well as biopharmaceutical drug delivery. Microsponge can be effectively incorporated into topical drug delivery system for retention of dosage form on skin, and also use for oral delivery of drugs using bio erodible polymers, especially for colon specific delivery and controlled release drug delivery system thus improving patient compliance by providing site specific drug delivery system and prolonging dosage intervals. Therefore, microsponge has got a lot of potential and is a very emerging field which is needed to be explored. Microsponges constitute a significant part by virtue of their small size and efficient carrier characteristics.

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