INNOVATIVE AND NOVEL STRATEGY: MICROSPONGES FOR TOPICAL DRUG DELIVERY

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ABSTRACT

Microsponge type of drug delivery is the latest technology which has been introduced in topical skin care, drug products to facilitate the controlled release of the active medicament into the skin in order to reduce systemic exposure and control local cutaneous reactions to active drugs. Microsponge can be loaded into a topical route of drug delivery system for the residue of dosage form of skin and thus controlled release drug delivery system is achieved and in return improving the patient compliance by providing target drug delivery system and prolonging dosage intervals.

Microsponge is polymeric delivery systems composed of porous microspheres. They are tiny sponge-like spherical particles and posses large porous surface area. Furthermore, they may enhance stability, reduce side effects, improve patient compliance and modify drug release. Microsponges are the polymer-based microspheres system that has the capacity to entrap a wide variety of substances, and can then be incorporated into a different formulation.

Keywords: Microsponge Delivery System, Quasi-emulsion solvent diffusion.

INTRODUCTION

Microsponge is Neoteric technology, which provides extended release of pharmaceutical active ingredients and mostly used for topical administration. Now a day the major challenge to the pharmaceutical industry is to control the rate of delivery of active pharmaceutical ingredient to a pre-determined site. So to improve efficacy and patient compliance, researcher focused on designing of different controlled release drug delivery systems. In 1987, Won was developed the microsponge technology and the original patents were authorized by Advanced Polymer System, Inc. Microsponge having a myriad of interconnected size ranging voids of particle from 5-150 μm. The main purpose of this delivery system to achieved desired concentration of the drug in blood in the microsponge delivery systems which is therapeutically more effective and non-toxic for long periods in the recent study. Primarily microsponge is the use for transdermal drug delivery system. Various methods for preparation of microsponge drug delivery systems studied.

A typical 25 μm sphere can have up to 25000 pores and have an internal pore structure equivalent to 10 feet in length and this results in a large reservoir type system within each microsponge, which can be loaded with up to its own weight of the active agent. The microsponge particles are too large to be absorbed into the skin.

Properties of drug for loading into microsponge

1. It must be fully miscible in monomer otherwise, should be made miscible by addition of a small amount of a water immiscible solvent.
2. It should be watered immiscible or at most only slightly soluble.
3. With respect to monomers it should be inert.
4. The solubility of active ingredients in the vehicle must be checked to avoid cosmetic problems; otherwise the vehicle will evacuate the microsponge before the application.
5. The spherical structure of microsponge should not faint.
6. Design of Polymer for the active must be optimized for a given time period for required release rate. It must be stable in contact with polymerization catalysts and states of polymerization.

Advantages of microsponge drug delivery system

1. Microsponge is act as a controlled drug delivery system.
2. Drug directly applied to target organs.
3. It increases stability of drugs.
4. These are capable of absorbing skin secretions and lessen the oiliness.
6. Reduced irritation and hence improved patient compliance.
7. Improved product elegance.
8. It can improve efficacy in the treatment.
9. It can also improve bioavailability of the drugs.
10. Flexibility to develop novel product forms.
11. MDS has a wide range of chemical stability and are easy to formulate.
12. Microsponge systems are non-irritating, non-mutagenic, non-allergenic and non-toxic.
13. Microsponge system can reduce significantly the irritation of effective drugs.
14. Without reducing their efficacy, it can prevent excessive accumulation of ingredients within the skin surface.

Potential feature of microsponge drug delivery system

- Improved oil control as it can absorb oil up to 6 times its weight.
- Microsponge system compatible with vehicles and active ingredients.
- Self sterilizing as average pore size is 0.25µm where bacteria cannot penetrate.
- These are non-irritating, non-mutagenic, non-allergenic and not-toxic.
- Release is extended up to 12 hours.
- Microsponge system stable in the range of pH 1 to 11, temperature up to 130 °C.
- Liquids can be converted into powders by improving material processing.

Figure 1: Programmable release from microspones

Pressure triggered systems

Microsponge system releases the entrapped material when pressurized/rubbed; the amount released depends upon special characteristics of the sponge. The microsponge best suited for a given application may be optimized by varying the type of material and different process variables.

Temperature triggered systems

Some active ingredients loaded in microsponge can be too viscous at room temperature to flow spontaneously into the skin. The flow rate can be increased by increasing the skin temperature and hence release. So it is possible to regulate the release of substances from the microspore by modulation of temperature.

pH triggered systems

Triggering the pH-based release of the active can be achieved by modifying the coating on the microspore. This has many applications in drug delivery.

Solubility triggered system

Microsponge loaded with water-soluble ingredients will release the ingredient in the presence of water. The release rate of active ingredients can be triggered in the presence of aqueous medium. This release may be achieved based on the ability of the external medium to dissolve the active, the concentration gradient or the capability to swell the microspore network.

Drugs explored in the microsponge delivery system

- Paracetamol
- Benzoyl peroxide
- Ketoprofen
- Fluconazole
- Acyclovir sodium
- Retinol
- Erythromycin
- Mupirocin
- Indomethacin
- Miconazole
- Curcumin
- Tretinoin
- Hydroquinone
- Ibuprofen
- Prednisolone
- Carboplatin
- Eudragit RS 100 and RL 100
- Ethylcellulose
- Polystyrene
- Acrylic polymer
- PHEMA
- Carbopol 934

Polymers used for the preparation of microspones

<table>
<thead>
<tr>
<th>Polymers</th>
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</thead>
<tbody>
<tr>
<td>Eudragit RS 100 and RL 100</td>
</tr>
<tr>
<td>Ethylcellulose</td>
</tr>
<tr>
<td>Polystyrene</td>
</tr>
<tr>
<td>Acrylic polymer</td>
</tr>
<tr>
<td>PHEMA</td>
</tr>
<tr>
<td>Carbopol 934</td>
</tr>
</tbody>
</table>
PREPARATION OF MICROSPONGES DRUG DELIVERY SYSTEM\textsuperscript{23-27}

1. **Liquid-liquid suspension polymerization**\textsuperscript{28,29,30}

   The porous microsphere based microsponges are prepared by the suspension polymerization method. In this polymerization technique the immiscible monomers are first dissolved with active ingredients in a suitable solvent and are then dispersed in the aqueous phases which consist of surfactant or suspending agents that are used for the formation of suspension. The polymerization is then activated by increasing temperature or irradiation or by addition of catalyst. The polymerization process continues until the reservoir type of system with spherical structure is formed. After the polymerization process the solvent is removed, leaving the microsponges.

2. **Quasi-emulsion solvent diffusion**\textsuperscript{31,32,33}

   Quasi-emulsion solvent diffusion technique (two-step process) is used for the preparation of Porous microsphere (microsponges). In this method an inner phase containing polymer such as eudragit dissolved in solvent like ethyl alcohol. The drug is slowly added to the polymer solution, then dissolved under ultrasonication at the temperature 35°C and plasticizer such as triethylcitrate (TEC) is added in order to assist the plasticity. The inner phase is then poured into external phase containing polyvinyl alcohol and distilled water with continuous stirring for 2 to 3 hours. Then, the mixture is filter to separate the microsponges. The microsponges is then washed and dried in an oven at 40°C for 10 to 12 h.

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**Figure 2:** One step and two step preparation of microsponges

**Figure 3:** Formation of Suspension for Preparation of Liquid-Liquid Suspension Polymerization.

**Figure 4:** Quasi-emulsion solvent diffusion method.
MECHANISM OF ACTION

The active ingredients are added to the vehicle in an entrapped form.

The active is free to move in and out from particles and into the vehicle as they have an open structure and the vehicle becomes saturated at equilibrium state.

Once the product is applied to the skin, the active will be absorbed into the skin, depleting the vehicle, which become unsaturated, thus disturbing the equilibrium.

A flow of microsponge particle to vehicle and from vehicle to skin, until the vehicle is either absorbed or dried.

Figure 5: Release mechanism of microsponge drug delivery

Table 1: Optimum values for microsponges formulation

<table>
<thead>
<tr>
<th>Sr.no</th>
<th>Specification</th>
<th>Optimum value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Drug and polymer ratio</td>
<td>1:1, 1:2, 1:3, 2:1 &amp; 3:1</td>
</tr>
<tr>
<td>2</td>
<td>Amount of drug (mg)</td>
<td>100-300</td>
</tr>
<tr>
<td>3</td>
<td>Polyvinylalcohol (mg)</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>Inner phase solvent (ml)</td>
<td>Ethyl alcohol</td>
</tr>
<tr>
<td>5</td>
<td>Amount of inner phase solvent</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>Amount of water in outer phase (ml)</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>Temperature of inner phase</td>
<td>25ºC</td>
</tr>
<tr>
<td>8</td>
<td>Type of process</td>
<td>Magnetic stirrer and bath sonicator</td>
</tr>
<tr>
<td>9</td>
<td>magnetic stirrer speed</td>
<td>1000 rpm</td>
</tr>
</tbody>
</table>

EVALUATION METHODOLOGY OF MICROSPONGE

Particle size evaluation - The particle size distribution is evaluated using optical microscope or electron microscope. Particle size determination of Microsponge can be performed by laser light diffractometry or other suitable method. The values (d₅₀) can be expressed for all formulations as mean size ranges. Particle size greater than 30 µm can give gritty feeling and hence particles sizes between 10 and 25 µm are used in the final formulation.

Morphology and surface topography - In the morphological study of microsponge topography various techniques are used such as the photon correlation spectroscopy (Pcs), Transmission electron spectroscopy (TEM), scanning electron microscopy (SEM).

Determination of loading efficiency: The loading efficiency (%) of the microsponges can be calculated as follows:

\[
\text{Loading efficiency} = \left( \frac{\text{Actual Drug Content in microsponges}}{\text{Theoretical Drug Content}} \right) \times 100
\]

Determination of production yield: The production yield of the microsponges can be determined by:

\[
\text{Production Yield} = \left( \frac{\text{Practical Mass of Microsponges}}{\text{Theoretical Mass (Polymer} + \text{Drug)}} \right) \times 100
\]

Determination of true density - The true density of the microsponge can be measured using an ultrapycnometer in the presence of helium gas and is calculated from a mean of repeated determinations.

Compatibility study - It can be studied by thin layer chromatography (TLC) and Fourier Transform Infra-red spectroscopy (FT-IR). Effect of polymerization on the crystallinity of drug can be studied by powder X-ray diffraction (XRD) and differential scanning calorimetric.

Release evaluation: Release of microsponges can be controlled through diffusion or other triggering mechanism such as moisture, pH, friction, temperature. This release mechanism used to enhance product aesthetics.

Resiliency: For the production of bullets a particle that is softer or firmer according to the needs of the final formulation viscoelastic properties of the microsponge
can be modified. Increased cross-linking tends to decrease the rate of release.

**Stability study:** Gel formulation is subject to stability testing as per ICH norms. Gel fill in clean, lacquered, collapsible aluminum tubes, and various replicates kept at 40 ± 2°C and 75 ± 5% relative humidity in a humidity Chamber. Gel assessed for change in appearance, pH and in vitro release profile at an interval of 30, 60 and 90 days.

**APPLICATION OF MICROSPONGE**

It offers the formulator range of alternative to develop the drug and cosmetic products. Over-the-counter products that incorporate microsponge drug delivery system include numerous moisturizers, specialized rejuvenated products, and sunscreens.38-42

**Topical drug delivery using microsponge technology**43 - (A) Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne and athlete’s foot. Controlled release of BPO of the microsphere delivery system to the skin could reduce the side effect.

(B) A Microsphere based topical formulation of mupirocin, used as antibiotic for skin infection, to achieve sustained drug release. The increased absorption of mupirocin in the skin from microsphere delivery system suggests the delivery system to be an efficient system for treatment of primary and secondary skin infections as compared to conventional mupirocin emulgel and marketed mupirocin ointment.

**Oral drug delivery using microsphere technology** - The Microsphere system provides the controlled delivery of oral medications to the lower gastrointestinal tract, where upon exposure to specific enzymes it will be released in the colon. It has been shown that microsphere systems enhances the solubilization of poorly soluble drugs by entrapping these drugs in their pores. Controlled oral delivery of ketoprofen prepared with Eudragit RS100 by quasi emulsion solvent diffusion method and subsequently tablet of microsphere was prepared by the direct compression method results show that compressibility was much improved in the physical mixture of the drug and the polymer due to the plastic deformation of sponge like microsphere structure.

**Microsphere used for bone and tissue engineering** - Bone like compounds were obtained by the mixing prepolymerized powder of polymethyl methacrylate monomer with two aqueous dispersion of tricalcium phosphate grains and calcium deficient hydroxyapatite powders. The final compound appeared to be porous and developed as microsphere.

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**Table 2: List of marketed products based on microsponges**51, 52, 53

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Pharmaceutical Uses</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycolic Acid Moisturizer w/SPF 15</td>
<td>Anti-Wrinkles, soothing</td>
<td>AMCOL Health &amp; Beauty Solution</td>
</tr>
<tr>
<td>Retin A Micro</td>
<td>Acne vulgaris</td>
<td>Ortho-McNeil Pharmaceutical, Inc</td>
</tr>
<tr>
<td>Line Eliminator Dual Retinol Facial Treatment</td>
<td>Anti-wrinkle</td>
<td>Avon</td>
</tr>
<tr>
<td>Retinol 15 Night cream</td>
<td>Anti-wrinkles</td>
<td>Sothys</td>
</tr>
<tr>
<td>Retinol cream</td>
<td>Helps maintain healthy skin</td>
<td>Biomedic</td>
</tr>
<tr>
<td>EpiQuin Micro</td>
<td>Hyper pigmentation</td>
<td>SkinMedica Inc</td>
</tr>
<tr>
<td>Sports cream RS and XS</td>
<td>Anti-inflammatory</td>
<td>Embil Pharmaceutical Co. Ltd.</td>
</tr>
<tr>
<td>Salicylic Peel 20</td>
<td>Excellent exfoliation</td>
<td>Biophora</td>
</tr>
<tr>
<td>Oil free matte block SPF 20</td>
<td>Sunscreen</td>
<td>Dermalogica</td>
</tr>
<tr>
<td>Lactrex™12%</td>
<td>Moisturizing Cream</td>
<td>SDR Pharmaceuticals, Inc</td>
</tr>
<tr>
<td>Ultra Guard</td>
<td>Protects baby’s skin</td>
<td>Scott Paper Company</td>
</tr>
</tbody>
</table>

**Table 3: Patents filed on microsponges**57

<table>
<thead>
<tr>
<th>Patent Number</th>
<th>Patent Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>S100783</td>
<td>Weighted microsphere for immobilizing bioactive material</td>
</tr>
<tr>
<td>1288370</td>
<td>Weighted collagen microsphere</td>
</tr>
<tr>
<td>4997753</td>
<td>Weighted collagen microsphere for immobilizing bioactive material</td>
</tr>
<tr>
<td>1275955</td>
<td>Weighted microsphere</td>
</tr>
<tr>
<td>4863856</td>
<td>Weighted collagen microsphere for immobilizing bioactive materials</td>
</tr>
<tr>
<td>4861714</td>
<td>Weighted collagen microsphere for immobilizing bioactive material</td>
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<td>0217917</td>
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<td>1986056694</td>
<td>Weighted microsphere for immobilizing bioactive material</td>
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<tr>
<td>WO/1986/005811</td>
<td>Weighted microsphere for immobilizing bioactive material</td>
</tr>
<tr>
<td>4092381</td>
<td>Methods of fabricating microsphere deuterated hydrocarbon polymer targets which emit neutrons when irradiated by high energy beams</td>
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</table>
FUTURE EXPECTANCY

Microsponge is the present day novel technology, which is the mostly developed for the topical delivery system and recently for oral administration. It provides various kinds of advantages. Microsponges are carefully designed pharmaceutical active ingredient that deliver the drug effectively at the target site with the minimum dose and also to enhance stability, reduce side effects and control drug release. The real face off in the future is the development of the delivery system for the oral peptide delivery by altering the ratio of polymers. Microsponges will be an excellent drug delivery system. Microsponges drug delivery system that can accurately control the release rates to the specific sites of the body will be sought in great detail in the years to come that have an immense on the health care system and. Some microsponge related products are already approved; several products are currently under development and clinical assessment.

CONCLUSION

The microsponge delivery system is a novel technology for the controlled release of macroporous beads, loaded with an active agent, offering a potential reduction in side effects and maintaining their therapeutic efficacy. The microsponge drug delivery system is believed to reduce side effects, improved stability, increased elegance, enhanced formulation flexibility and also offers entrapment of its ingredients. Microsponge systems are non-irritating, non-mutagenic, non-allergenic, and nontoxic. This technology is being used currently in cosmetics, over-the-counter skin care, sunscreens, and prescription products. This kind of drug delivery technology may lead to a better understanding of the healing of several diseases.

REFERENCES

Jyoti et al.


