The prime aim of any drug delivery system is to provide therapeutic amount of drug to proper site in the body, to punctually achieve and maintain the desired drug concentration. Drugs which get easily absorbed from the gastrointestinal tract and having a short half-life gets eliminated rapidly from the blood circulation. The efficient oral drug delivery may depend upon several factors like gastric emptying, gastrointestinal transit time of the drug or dosage form, drug release from designed dosage form and site of absorption of drug. Controlled release of drugs onto the epidermis with assurance that the drug remains primarily localized and does not enter the systemic circulation in significant amounts is an area of research that is successively done by the microsponge delivery system.

Keywords: Microsponge, controlled release, Topical drug delivery

**INTRODUCTION**

Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge like spherical particles that consist of a myriad of interconnecting voids within a non-collapsible structure with a large porous surface (Fig. 1). Moreover, they may enhance stability, reduce side effect and modify drug release favourably [1, 2].

![Microsponge System](image1.png)

Figure 1

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. It can provide increased efficacy for topically active agents with enhanced safety, extended product stability and improved aesthetic properties in an efficient manner [3, 4]. When applied to the skin, the microsponge drug delivery system (MDS) releases its active ingredient on a time mode and also in response to other stimuli such as rubbing, temperature, and pH. Microsponges have the capacity to absorb or load a high degree of active materials into the particle or onto its surface [5]. By incorporation into a carrier system, it is possible to alter the therapeutic index and duration of the activity of drugs. Microsponges are microscopic spheres capable of absorbing skin secretions, therefore reducing oiliness and shine from the skin. Spherical particles composed of clusters of even tinier spheres are capable of holding four times their weight in skin secretions. Microsponge particles are extremely small, inert, indestructible spheres that do not pass through the skin. Rather, they collect in the tiny nooks and crannies of the skin and slowly release the entrapped drug, as the skin needs it. The microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Potentially, the microsponge system can significantly reduce the irritation of effective drugs without reducing their efficacy. 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. The microsponge particles themselves are too large to be absorbed into the skin and this adds a
measure of safety to these microsponge materials. Another safety concern is the potential bacterial contamination of the materials entrapped in the microsponge. As the size of the pore diameter is smaller, the bacteria ranging from 0.007 to 0.2 μm cannot penetrate into the tunnel structure of the microsponges.

The microsponge technology was developed by Won in 1987, and the original patents were assigned to Advanced Polymer Systems, Inc. Microsponges are porous microspheres having myriad of interconnected voids of particle size ranging between 5-300 μm. They are used as a carrier system since have capacity to entrap wide range of actives in their non-collapsible structures with porous surface; through which active ingredients are released in controlled manner [6]. Further these microsponges with actives can be incorporated into formulations such as tablets, capsules, creams, gel, lotions and powders and share a broad package of benefits [7-11]. Micro-sponge polymers possess the versatility to load a wide range of actives providing the benefits of enhanced product efficacy, mildness, tolerability, and extended wear to a wide range of skin therapies [12].

Advantages over other technologies:
The advantages include [13, 14]:

1. Microsponges offer better control of drug release than microcapsules. Microcapsules cannot usually control the release rate of the active pharmaceutical ingredients (API). Once the wall is ruptured, the API contained within the microcapsules will be released.
2. Microsponges show better chemical stability, higher payload and easier formulation compared with liposomes.
3. In contrast to ointments, microsponges have the ability to absorb skin secretions, therefore, reducing greasiness and shine from the skin. Ointments are often aesthetically unappealing, greasy and sticky, resulting in lack of patient compliance (Table 1).

### Table 1: Therapeutic application of microsponges [13]

<table>
<thead>
<tr>
<th>Active agents</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunscreens</td>
<td>Long lasting product efficacy, with improved protection against sunburns and sun related injuries even at elevated concentration and with reduced irritancy and sensitization</td>
</tr>
<tr>
<td>Anti-acne e.g. Benzoyl peroxide</td>
<td>Maintained efficacy with decreased skin irritation and sensitization</td>
</tr>
<tr>
<td>Antifungals</td>
<td>Sustained release of actives</td>
</tr>
<tr>
<td>Anti-inflammatory e.g. hydrocortisone</td>
<td>Long lasting activity with reduction of skin allergic response and dermatoses</td>
</tr>
<tr>
<td>Anti-dandruffs e.g. zinc pyrithione, selenium sulfide</td>
<td>Reduces unpleasant odor with lowered irritation and with extended safety and efficacy</td>
</tr>
<tr>
<td>Antipruritics</td>
<td>Extended and improved activity</td>
</tr>
<tr>
<td>Skin depigmenting agents e.g. hydroquinone</td>
<td>Improved stabilization against oxidation with improved efficacy and aesthetic appeal</td>
</tr>
<tr>
<td>Rubefacients</td>
<td>Prolonged activity with reduced irritancy greasiness and odor</td>
</tr>
</tbody>
</table>

Salient features of drugs entrapped:
There are certain requirements that should be fulfilled (or considered) when active ingredients are entrapped into microsponge [11, 14]:

1) It should exhibit complete miscibility in monomer or have the ability to be miscible using the least amount of a water immiscible solvent.
2) Must be inert to monomers and do not increase the viscosity of the preparation during formulation.
3) It should be water immiscible or almost slightly soluble.
4) The solubility of active ingredients in the vehicle should be minimum; otherwise the microsponge will be diminished by the vehicle before application.
5) It should maintain (preserve) the spherical structure of microsponge.
6) It should be stable in polymerization conditions.
7) Only 10 to 12 % w/w microsponge can be incorporated into the vehicle to eliminate cosmetic delinquent.
8) Payload and polymer design of the microsponges for the active must be adjusted to obtain the desired release rate of a given period of time.

METHOD OF PREPARATION

### 1. Liquid-liquid suspension polymerization [13, 14]
The porous microspheres are prepared by suspension polymerization method in liquid-liquid systems (Fig. 2). 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. 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. The various steps involved in the preparation of microsponges are summarized as follows:
Step 1: Selection of monomer as well as combination of monomers.
Step 2: Formation of chain monomers as polymerization starts.
Step 3: Formations of ladders as a result of cross-linking between chain monomers.
Step 4: Folding of monomer ladder to form spherical particles.
Step 5: Agglomeration of microspheres leads to the production of bunches of microspheres.
Step 6: Binding of bunches to produce microsponges.

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 RS 100 which is dissolved in ethyl alcohol. Then, the drug is slowly added to the polymer solution and dissolved under ultrasonication 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 (Fig. 3). 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 hrs.

Figure 3

Characteristics of microsponges
The potential characteristics are as listed [16, 17]:
1. Microsponges show acceptable stability over pH ranging from 1 to 11 and at high temperatures (up to 130°C).
2. Microsponges exhibit good compatibility with various vehicles and ingredients.
3. Microsponges have high entrapment efficiency up to 60%.
4. Microsponges are characterized by free flowing properties.
5. The average pore size of microsponges is small (0.25 µm) in a way to prevent the penetration of bacteria, thus they do not need sterilization or addition of preservatives.
6. Microsponges are non-allergenic, non-irritating, non-mutagenic and non-toxic.
7. Microsponges can absorb oil up to 6 times their weight without drying.

Drug enclosed in microsponge drug delivery system [18]
- Ketoprofen
- Benzyl peroxide
- Retinol
- Fluconazole
- Ibuprofen
- Tretinoin
- Trolamine

Advantages [19]
- Advanced oil control, absorb up to 6 times its weight without drying
- Extended release
- Reduced irritation formulas
- Allows novel product form
- Improved product aesthetics
- Extended release, continuous action up to 12 hours
- Reduced irritation, better tolerance means broader consumer acceptance
- Improved product aesthetics, gives product an elegant feel
- Improves stability, thermal, physical and chemical stability
- Allows incorporation of immiscible products.
- Improves material processing e.g. liquid can be converted to powders
- Allows for novel product forms.
- Improves efficacy in treatment.
- Cure or control confirm more promptly.
- Improve control of condition.
Efficiency

- Improve bioavailability of same drugs.

**Evaluation Parameters**

- Particle size (Microscopy)
- Morphology and Surface topography
- Loading efficiency and production yield
- Resiliency
- Compatibility studies
- Drug release study

**Particle size and shape**
The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine the shape and outer structure of microparticles. LM provides a control over coating parameters in case of double walled microparticles. The microparticles structures can be visualized before and after coating and the change can be measured microscopically. SEM provides higher resolution in contrast to the LM. SEM allows investigations of the microparticles surfaces and after particles are cross-sectioned, it can also be used for the investigation of double walled systems. Confocal fluorescence microscopy is used for the structure characterization of multiple walled microparticles. Laser light scattering and multi size coulter counter other than instrumental methods, which can be used for the characterization of size, shape and morphology of the microparticles (microsponges) [20].

**Morphology and surface topography of microsponges**
For morphology and surface topography, 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 microsponge particle can also be taken to illustrate its ultra structure [21].

**Determination of Loading Efficiency and Production Yield**
The loading efficiency (%) of the microsponges can be calculated according to the following equation [22]:

\[
\text{Loading Efficiency} = \left( \frac{\text{Actual drug content in microsponges}}{\text{Theoretical drug content}} \right) \times 100
\]

Eq.1

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 microsponge obtained.

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

**Determination of true density**
True density can be measured by an ultra-pycnometer using helium gas, and calculated as a mean of repeated determinations [23].

**Pore structure**
Porosity parameters of microsponges are essential in monitoring the intensity and the duration of active ingredient effect. Average pore diameters, shape and morphology of the pores can be determined by using mercury intrusion porosimetry technique. The effect of pore diameter and volume on the rate of drug release from microsponges can also be studied using the same technique [24].

**Compatibility studies**
Compatibility of drug with reaction adjuncts can be studied by thin layer chromatography (TLC) and Fourier Transform Infra-red spectroscopy (FT-IR). Effect of polymerization on crystallinity of the drug can be studied by powder X-ray diffraction (XRD) and Differential Scanning Colorimetry (DSC). For DSC approximately 5 mg samples can be accurately weighed into aluminum pans and sealed and can be run at a heating rate of 15 C/min over a temperature range 25–430 C in atmosphere of nitrogen [25].

**Resiliency (viscoelastic properties)**
Resiliency (viscoelastic properties) of microsponges can be modified to produce beadlets that is softer or firmer according to the needs of the final formulation. Increased cross-linking tends to slow down the rate of release [26].

**Drug release kinetics**
The dissolution profile of each formulation have been subjected to various models such as Zero order kinetics (percentage drug release against time), First order kinetics (log percentage drug unreleased against time), Higuchi (percentage drug released against square root of time) and Korsemeyer-Peppas (log percent drug released against log of time) were applied to assess the kinetics of drug release from prepared microsponges [27].

**Physicochemical characterization**

**Thermoanalytical methods:**
Thermal analysis using differential scanning calorimetry (DSC) is carried out for the pure drug, polymer and the drug-polymer physical mixture to confirm compatibility. DSC is also performed for the microsponge formulations to ensure that the formulation process does not change the nature of the drug. Samples (approximately 2 mg) are placed in aluminum pans, sealed and operated at a heating rate of 20°C/min over a temperature range 40 to 430°C. The thermograms obtained by DSC for the physical mixtures, as well as microsponges, should be observed for broadening, shifting and appearance of new peaks or disappearance of certain peaks. The peak corresponding to the melting of the drug should be preserved in all thermograms [28].

**Fourier transform infrared spectroscopy (FTIR):**
Fourier transform infrared spectroscopy (FTIR) is carried out for the pure drug, polymer and the drug-polymer physical mixture and microsponge formulations. The samples are incorporated in potassium bromide discs and evaluated using
FTIR spectrometer. The peaks corresponding to the characteristics bands of the drug should be preserved in the spectra of the microsponges to indicate that no chemical interaction or changes took place during the preparation of the formulations [29].

**Powder X-ray diffraction (XRD):**

Powder X-ray diffraction (XRD) can be performed for both pure drug, polymer and microsponge formulation to investigate the effect of polymerization on crystallinity of the drug. The disappearance of the characteristic peaks of the drug in the formulation could indicate that the drug is dispersed at a molecular level in the polymer matrix [30].

**In vitro release studies, release kinetics and mechanism**

In vitro release studies can be performed using United States Pharmacopeial (USP) dissolution apparatus equipped with a modified basket consisted of 5 µm stainless steel mesh at 37°C. The release medium is selected according to the type of formulation that is, topical or oral, while considering solubility of active ingredients to ensure sink conditions. Sample aliquots are withdrawn from the medium and analyzed by suitable analytical method at regular intervals of time. The drug release from topical preparations (for example, creams, lotions and emulgels) containing microsponges can be carried out using Franz diffusion cells. Dialysis membrane is fitted into place between the two chambers of the cell. A predetermined amount of formulation is mounted on the donor side of Franz cell. The receptor medium is continuously stirred at and thermostated with a circulating jacket. Samples are withdrawn at different time intervals and analyzed using suitable method of assay [31, 32]. To determine the drug release kinetics and investigate its mechanism from microsponges, the release data are fitted to different kinetic models. The kinetic models used are; first order, zero order, Higuchi and Korsmeyer-Peppas models [33-35]. The goodness of fit was evaluated using the determination coefficient (R²) values.

**Marketed formulations**

Table 2 gives the details of the marketed microsponge formulations.

### Table 2: Marketed products based on microsponge delivery system [24]

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retin-A-Micro 0.1 And 0.04% tretinoin entrapped in MDS, for topical treatment of acne vulgaris. This formulation uses patented methyl methacrylate/glycol dimethacrylate cross-polymer porous microspheres.</td>
<td>Ortho-McNeil Pharmaceutical,Inc.</td>
</tr>
<tr>
<td>Carac cream, 0.5% Carac cream contains 0.5% fluorouracil, with 0.35% being incorporated into a patented porous microsphere (Microponge) composed of methyl methacrylate / glycol dimethacrylate cross-polymer and dimethicone.</td>
<td>Dermik Laboratories, Inc.Berwyn,PA19312 USA</td>
</tr>
<tr>
<td>Line eliminator facial treatment Lightweight cream with a retinol (Vitamin A) in MDS, delivers both immediate and time-released wrinkle-fighting action.</td>
<td>Avon</td>
</tr>
<tr>
<td>Retinol cream The retinol molecule is kept in the microponge system to protect the potency of vitamin A. This helps to maximize the retinol dosage, while reducing the possibility of irritation. Retinol is a topical vitamin A derivative, which helps maintain healthy skin, hair, and mucous membranes.</td>
<td>Biomedic</td>
</tr>
<tr>
<td>Retinol 15 nightcream A night time treatment cream with Microponge system. The formula contain of pure reti nol. Continuous use of Retinol 15 will result in the visible diminishment of fine lines and wrinkles, and improve in skin discolorations.</td>
<td>Biomedic,sothys</td>
</tr>
<tr>
<td>EpiQuin micro The Microponge® system entraps hydroquinone and retinol. The microsponges release these ingredients into the skin gradually throughout the day, which may minimize skin irritation.</td>
<td>Skin Medica Inc</td>
</tr>
</tbody>
</table>

**REFERENCES**


Saroj KP, Microsponges as the versatile tool for drug delivery system, IJRPC, 1(2), 243-258 (2011).


