MICROSPONGES: A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Microsponges are porous, polymeric microspheres that are mostly used for prolonged topical administration. Microsponges are designed to deliver a pharmaceutically active ingredient efficiently at minimum dose and also to enhance stability, reduce side effects, and modify drug release profiles. The Microsponge Delivery System (MDS) is a unique technology for the controlled release of topical agents and consist of macro porous beads, typically 10-25 microns in a diameter, loaded with active agent. When applied to the skin, the Microsponge releases its active ingredient on a time mode and also in response to other stimuli (rubbing, pH, etc.). MDS technology is being used currently in cosmetics, over the counter (OTC) skin care, sunscreens and prescription products. Conventional preparations have some disadvantages like unpleasant odour, greasiness and skin irritation. These problems are overcome by microsponge delivery system. Microsponge based drug delivery system produces controlled released action. It also produces site specific and target organ action produced. Microsponge (MDS) mainly developed in topical drug delivery as well as oral controlled delivery system. It also used in cosmetic formulations.

Key words- Microsponges, drug delivery, preparation, characterization, topical, oral.

INTRODUCTION

The drug delivery technology landscape has become highly competitive and rapidly evolving. More and more developments in delivery systems are being integrated to optimize the efficacy and cost effectiveness of the therapy.1 Several predictable and reliable systems were developed for systemic drugs under the heading of transdermal delivery system (TDS) using the skin as portal of entry.2 It has improved the efficacy and safety of many drugs that may be better administered through skin. But TDS is not practical for delivery of materials whose
final target is skin itself. 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 has only recently been addressed with success. No efficient vehicles have been developed for controlled and localized delivery of drugs into the stratum corneum and underlying skin layers and not beyond the epidermis. Application of topical drugs suffers many problems such as ointments, which are often aesthetically unappealing, greasiness, stickiness etc. that often results into lack of patient compliance. These vehicles require high concentrations of active agents for effective therapy because of their low efficiency of delivery system, resulting into irritation and allergic reactions in significant users. Other drawbacks of topical formulations are uncontrolled evaporation of active ingredient, unpleasant odour and potential incompatibility of drugs with the vehicles. Thus the need exists for system to maximize amount of time that an active ingredient is present either on skin surface or with in the epidermis, while minimizing its transdermal penetration into the body. The microspponge delivery system fulfills these requirements.

A Microsponge Delivery System (MDS) is patented, highly cross-linked, porous, polymeric microspheres polymeric system consisting of porous microspheres that can entrap wide range of actives and then release them onto the skin over a time and in response to trigger. \(^3\) It is a unique technology for the controlled release of topical agents and consists of microporous beads, typically 10-25 microns in diameter, loaded with active agent. When applied to the skin, the MDS releases its active ingredient on a time mode and also in response to other stimuli (rubbing, temperature, pH, etc). MDS technology is being used in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products. Delivery system comprised of a polymeric bead having network of pores with an active ingredient held within was developed to provide controlled release of the active ingredients whose final target is skin itself.\(^4\) The system was employed for the improvement of performance of topically applied drugs.\(^5, 6\) The common methods of formulation remains same; the incorporation of the active substance at its maximum thermodynamic activity in an optimized vehicle and the reduction of the resistance to the diffusion of the stratum corneum. and liposomes. Microcapsules cannot usually control the release rate of actives. Once the wall is ruptured the actives contained with in microcapsules will be released. Liposomes suffer from lower payload, difficult formulation, limited chemical stability and microbial instability. While microspponge system in contrast to the above systems are stable over range of pH 1 to 11, temperature up to 130°C; compatible with most vehicles and ingredients; self sterilizing as
average pore size is 0.25µm where bacteria cannot penetrate; higher payload (50 to 60%), still free flowing and can be cost effective. Most liquid or soluble ingredients can be entrapped in the particles. Actives that can be entrapped in microsponges must meet following requirements,

- It should be either fully miscible in monomer or capable of being made miscible by addition of small amount of a water immiscible solvent.
- It should be water immiscible or at most only slightly soluble.
- It should be inert to monomers.
- It should be stable in contact with polymerization catalyst and conditions of polymerization.

Release can be controlled through diffusion or other triggers such as moisture, pH, friction, or temperature. This release technology is available for absorbent materials or to enhance product aesthetics. Microspone delivery system can be incorporated into conventional dosage forms such as creams, lotions, gels, ointments, and powder and share a broad package of benefits. Systems can and improve its formulation flexibility.

**Characteristics of Microsponges**

- Microspone formulations are stable over range of pH 1 to 11;
- Microspone formulations are stable at the temperature up to 130°C;
- Microspone formulations are compatible with most vehicles and ingredients;
- Microspone formulations are self sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate;
- Microspone formulations have higher payload (50 to 60%), still free flowing and can be cost effective.

**Advantages of MDS**

- Microsponges can absorb oil up to 6 times its weight without drying.
- It provides continuous action up to 12 hours i.e. extended release.
- Improved product elegancy.
- Lessen the irritation and better tolerance leads to improved patient compliance.
- They have better thermal, physical and chemical stability.
- These are non-irritating, non-mutagenic, nonallergenic and non-toxic.
- MDS allows the incorporation of immiscible products.
- They have superior formulation flexibility.
• In contrast to other technologies like microencapsulation and liposomes, MDS has wide range of chemical stability, higher payload and are easy to formulate.
• Liquids can be converted into powders improving material processing.
• It has flexibility to develop novel product forms.
• MDS can improve bioavailability of same drugs.

**PREPARATION OF MICROSPONGES**

Microsponges 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 physico-chemical properties of drug to be loaded.

**• Quasi-Emulsion Solvent Diffusion**\(^{(10)}\).

To prepare the inner organic phase, Eudragit RS 100 is dissolved in ethyl alcohol. The drug is added to solution and dissolved under ultrasonication at 35° C the inner phase is poured into the polyvinyl alcohol solution in water. Following stirring for 60 min, then mixture is filtered to separate the microsponge. The Microsponges are dried in an air-heated oven at 40° C for 12 hr. ingredients can be entrapped in microsponge polymers at the time of synthesis. They can be post-loaded after the microsphere structure has been pre-formed. The letter process is the preferred mode since many pharmaceuticals and cosmetic ingredients, would decompose at the temperatures used for polymerization.

![Figure 1: Preparation of Microsponges by Quasi Emulsion Solvent Diffusion](image)

Figure 1: Preparation of Microsponges by Quasi Emulsion Solvent Diffusion
Method

Liquid-liquid Suspension Polymerization\(^{11-13}\)

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 phase, 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.

![Reaction vessel for microsponge preparation by liquid-liquid suspension polymerization](image)

**Figure 2: Reaction vessel for microsponge preparation by liquid-liquid suspension polymerization**

**RELEASE MODULATION\(^{14-20}\)**

In general, microsponges retard the release of the drug. Various groups have studied the release of actives from such systems. Some studies have shown an improved rate of release by increasing the active/polymer ratio and lowering the polymer wall thickness; however these results are not supported by another set of studies. Thus, there seem to be many other factors affecting the release of the drug from the microsponges. Another important parameter that governs the release seems to be the pore diameter\(^5\) however; another study 13 has shown that even the overall porosity (including the pore diameter and the number of pores) also affects the drug release. The microsponge particles have an open structure and the active is free to move in and out from the particles and into the vehicle until equilibrium is reached.
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 absorbed. Even after that the microsponge particles retained on the surface of 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 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. The principle is contrary to the conventional formulation principles usually applied to the topical products. For these conventional systems it is normally recommended to maximize the solubility of the active in the vehicle. When using microsponge entrapments some solubility of the active in the vehicle is acceptable because the vehicle can provide the initial loading dose of the active until release from the microsponge. Another way to avoid undesirable premature leaching of the active from the microsponge polymer is to formulate the product with some free and some entrapped active, so the vehicle is presaturated. In this case there will not be any leaching of the active form of polymer during compounding. The rate of active release will ultimately depend not only on the partition coefficient of the active ingredient between the polymer and the vehicle (or the skin), but also on some of the parameters that characterize the beads. Examples of these include surface area and primarily, mean pore diameter. Release can also be controlled through diffusion or other triggers such as moisture, pH, friction or temperature.

**PROGRAMMABLE RELEASE**

(i) Pressure triggered systems

Microsponge system releases the entrapped material when pressurized/rubbed; the amount released depends upon various characteristics of the sponge. By varying the type of material and different process variables, the microsponge best suited for a given application may be optimized. When compared with mineral oil containing microcapsules, mineral oil containing microsponge showed much more softening effect. The duration of emolliency was also much more for the microsponge systems.
(ii) Temperature triggered systems
Some entrapped active ingredients can be too viscous at room temperature to flow spontaneously from microsponges onto the skin. Increased in skin temperature can result in an increased flow rate and hence release. So it is possible to modulate the release of substances from the microspponge by modulation of temperature. For example, viscous sunscreens were found to show a higher release from microsponges when exposed to higher temperatures; thus a sunscreen would be released from a microsponge only upon exposure to the heat from the sun.

(iii) pH triggered systems
Triggering the pH-based release of the active can be achieved by modifying the coating on the microspponge. This has many applications in drug delivery.

(iv) Solubility triggered system
Microsponges loaded with water-soluble ingredients like anti-prespirants and antiseptics will release the ingredient in the presence of water. Presence of an aqueous medium such as perspiration can trigger the release rate of active ingredients. Thus release may be achieved based on the ability of the external medium to dissolve the active, the concentration gradient or the ability to swell the microspore network.

Evaluation Parameters of Microsponges
• Particle size (Microscopy)
• Morphology and Surface topography
• Characterization of pore structure
• Loading efficiency and production yield
• Characterization of pore structure
• Compatibility studies
• Resiliency
• Drug release study

Physical Characterization of Microsponges
Particle Size Determination
Particle size analysis of loaded and unloaded microsponges can be performed by laser light diffractometry or any other suitable method. The values can be expressed for all formulations as mean particle size range. Cumulative percentage drug release from microsponges of
different particle size will be plotted against time to study effect of particle size on drug release. Particles larger than 30µm can impart gritty feeling and hence particles of sizes between 10 and 25µm are preferred to use in final topical formulation.

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.

Determination of Loading Efficiency and Production Yield

The loading efficiency (%) of the Microsponges can be calculated according to the following equation:

\[
\text{Loading Efficiency} = \frac{\text{Actual Drug Content in microsponges}}{\text{Theoretical Drug Content}} \times 100
\]

The production yield of the microparticles can be determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponge obtained.

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

Determination of True Density

The true density of microparticles is measured using an ultra-pycnometer under helium gas and is calculated from a mean of repeated determinations.

Characterization of Pore Structure

Pore volume and diameter are vital in controlling the intensity and duration of effectiveness of the active ingredient. Pore diameter also affects the migration of active ingredients from microsponges into the vehicle in which the material is dispersed. Mercury intrusion porosimetry can be employed to study effect of pore diameter and volume with rate of drug release from microsponges. Porosity parameters of microsponges such as intrusion–extrusion isotherms, pore size distribution, total pore surface area, average pore diameters, interstitial void volume, percent porosity, percent porosity filled, shape and morphology of the pores, bulk and apparent density can be determined by using mercury intrusion porosimetry.
Compatibility Studies\textsuperscript{(26-29)}
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 5mg samples can be accurately weighed into aluminium pans and sealed and can be run at a heating rate of 15oC/min over a temperature range 25–430oC in atmosphere of nitrogen.

Polymer/Monomer Composition\textsuperscript{(30)}
Factors such as microspponge size, drug loading, and polymer composition govern the drug release from microsponges. Polymer composition of the MDS can affect partition coefficient of the entrapped drug between the vehicle and the microspponge system and hence have direct influence on the release rate of entrapped drug. Release of drug from microspponge systems of different polymer compositions can be studied by plotting cumulative % drug release against time. Release rate and total amount of drug released from the system composed of methyl methacrylate/ethylene glycol dimethacrylate is slower than styrene/divinyl benzene system.

Resiliency\textsuperscript{(31)}
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 slowdown the rate of release. Hence resiliency of microsponges will be studied and optimized as per the requirement by considering release as a function of cross-linking with time.

Dissolution Studies\textsuperscript{(32)}
Dissolution profile of microsponges can be studied by use of dissolution apparatus (USP XXIII) with a modified basket consisted of 5µm stainless steel mesh. Speed of the rotation is 150 rpm. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. Samples from the dissolution medium can be analyzed by suitable analytical method at various intervals.

APPLICATIONS OF MICROSPONGES\textsuperscript{(33)}
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. These are developed to deliver an active ingredient efficiently at the low dose and
also to enhance stability, reduce side effects and modify drug release. Microsponge drug delivery system unique, novel and versatile and extremely attractive in cosmetic world. 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 describe in

Table 1:

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<tr>
<th>Applications</th>
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<tr>
<td><strong>Sunscreens:</strong></td>
<td>Long lasting product efficacy, with improved protection against</td>
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<td>sun burns and sun related injuries even at elevated concentration</td>
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<tr>
<td></td>
<td>and with reduced irritancy and sensitization.</td>
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<tr>
<td><strong>Anti-acne:</strong></td>
<td>E.g. Benzoyl peroxide Maintained efficacy with decreased skin</td>
</tr>
<tr>
<td></td>
<td>irritation and sensitization.</td>
</tr>
<tr>
<td><strong>Anti-inflammatory:</strong></td>
<td>E.g. hydrocortisone Long lasting activity with reduction of skin</td>
</tr>
<tr>
<td></td>
<td>allergic response and dermatoses.</td>
</tr>
<tr>
<td><strong>Anti-fungals:</strong></td>
<td>Sustained release of actives Ingredient.</td>
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<tr>
<td><strong>Anti-dandruffs:</strong></td>
<td>E.g. zinc pyrithione, selenium sulfide. Reduced unpleasant odour</td>
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<tr>
<td></td>
<td>with lowered irritation with extended safety and efficacy</td>
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<tr>
<td><strong>Antipruritics:</strong></td>
<td>Extended and improved activity.</td>
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<tr>
<td><strong>Skin depigmenting:</strong></td>
<td>E.g. hydroquinone. Improved stabilization against oxidation with</td>
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<tr>
<td></td>
<td>improved efficacy and aesthetic agents appeal.</td>
</tr>
<tr>
<td><strong>Rubefacients:</strong></td>
<td>Prolonged activity with reduced irritancy greasiness and odour.</td>
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1. Microsponge for topical delivery\(^{(34-37)}\)

The Microsponge systems are based on microscopic, polymer-based microspheres that can bind, suspend or entrap a wide variety of substances and then be incorporated into a formulated product, such as a gel, cream, liquid or powder. A single Microsponge is as tiny as a particle of talcum powder, measuring less than one-thousandth of an inch in diameter. Like a true sponge, each microsphere consists of a myriad of interconnecting voids within a non-collapsible structure that can accept a wide variety of substances. The outer surface is typically porous, allowing the controlled flow of substances into and out of the sphere.

Several primary characteristics, or parameters, of the Microsponge system can be defined during the production phase to obtain spheres that are tailored to specific product applications and vehicle compatibility. Microsponge systems are made of biologically inert polymers. Extensive safety studies have demonstrated that the polymers are non-irritating, nonmutagenic, non-allergenic, non-toxic and non-biodegradable. As a result, the human body
cannot convert them into other substances or break them down. Although they are microscopic in size, these systems are too large to pass through the stratum corneum when incorporated into topical products.

Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne, with skin irritation as a common side effect. It has been shown that controlled release of BPO from a delivery system to the skin could reduce the side effect while reducing percutaneous absorption. Therefore, microspponge delivery of Benzoyl peroxide was developed using an emulsion solvent diffusion method by adding an organic internal phase containing benzoyl peroxide, ethyl cellulose and dichloromethane into a stirred aqueous phase containing polyvinyl alcohol and by suspension polymerization of styrene and divinyl benzene. The prepared microsponges were dispersed in gel base and microspponge gels are evaluated for anti-bacterial and skin irritancy. The entrapped system released the drug at slower rate than the system containing free BPO. Topical delivery system with reduced irritancy was successfully developed

2. Microspponge for oral delivery

In oral applications, the microspponge system has been shown to increase the rate of solubilization of poorly water-soluble drugs by entrapping such drugs in the microspponge system's pores. As these pores are very small, the drug is in effect reduced to microscopic particles and the significant increase in the surface area thus greatly increases the rate of solubilization. Controlled oral delivery of ibuprofen microsponges is achieved with an acrylic polymer, Eudragit RS, by changing their intraparticle density. Sustained release formulation of chlorpheniramine maleate, using powder-coated microsponges, is prepared by the dry impact blending method, for oral drug delivery. Controlled oral delivery of Ketoprofen prepared by quasi-emulsion solvent diffusion method with Eudragit RS 100 and afterwards tablets of microsponges were prepared by the direct compression method. Results indicated that compressibility was much improved in the physical mixture of the drug and polymer; due to the plastic deformation of the sponge-like microspponge structure, producing mechanically strong tablets. Colon-specific, controlled delivery of flurbiprofen was conducted by using a commercial Microsponge 5640 system. In vitro studies exhibited that compression-coated colon-specific tablet formulations started to release the drug at the eighth hour, corresponding to the proximal colon arrival time, due to addition of the enzyme, following a modified release pattern, while the drug release from the colon-specific formulations prepared by pore
plugging the microsponges showed an increase at the eighth hour, which was the point of time when the enzyme addition was made.

3. Microsponge for Bone and Tissue Engineering\(^{(40,41)}\)

Bone-substitute compounds were obtained by mixing pre polymerized powders of polymethylmethacrylate and liquid methylmethacrylate monomer with two aqueous dispersions of tricalcium phosphate grains and calcium deficient hydroxyl apatite powders. The final composites appeared to be porous and acted as microsponges. Basic fibroblast growth factor (bFGF) incorporated in a collagen sponge sheet was sustained released in the mouse sub-cutis according to the biodegradation of the sponge matrix, and exhibited local angiogenic activity in a dose-dependent manner. The injection of collagen microsponges incorporating bFGF induced a significant increase in the blood flow, in the murine ischemic hind limb, which could never have been attained by the bolus injection of bFGF. These results suggest the significance and therapeutic utility of the type I collagen as a reservoir of bFGF.

MARKET FORMULATION USING A MDS

<table>
<thead>
<tr>
<th>Sr.NO.</th>
<th>PRODUCT</th>
<th>MANUFACTURE</th>
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<tbody>
<tr>
<td>1</td>
<td>Carac Cream, 0.5%</td>
<td>Dermik Laboratories, Inc. Berwyn, PA 19312 USA</td>
</tr>
<tr>
<td>2</td>
<td>Oil Control Lotion</td>
<td>Fountain Cosmetics</td>
</tr>
<tr>
<td>3</td>
<td>Retinol cream</td>
<td>Biomedic</td>
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<tr>
<td>4</td>
<td>EpiQuin Micro</td>
<td>SkinMedical Inc</td>
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<tr>
<td>5</td>
<td>Sportscream RS and XS</td>
<td>Embil Pharmaceutical Co. Ltd</td>
</tr>
<tr>
<td>6</td>
<td>Micro Peel Plus</td>
<td>Biomedic</td>
</tr>
<tr>
<td>7</td>
<td>Oil free matte block spf20</td>
<td>Dermalogica</td>
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CONCLUSION

The microsponge drug delivery technology is widely applicable to the dermatological drug delivery products. The microsponge delivery technology of controlled release system in which active pharmaceutical ingredients are loaded in the microporous beads and initiates reduction in side effects with improved therapeutic efficacy. The microsponge drug delivery system has properties like improved stability and enhanced flexibility in formulation. MDS is originally developed for topical delivery of drugs like anti-acne, anti-inflammatory, antifungal, anti-dandruffs, antipruritics, rubefacients etc. But MDS also expands its application in oral drug delivery, bone and tissue engineering, in detecting the diseases and inRNAi
silencing. Hence, the microsponge drug delivery system focuses as an important tool for future inventions in controlled drug delivery system

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