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Tailoring effect of microsponge for targeted drug delivery

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Abstract

The fundamental appeal of the microsponge technology arises from the difficulty experienced with conventional formulations in releasing active ingredients over an extended period of time. It holds a promising future in various pharmaceutical applications in the coming years like enhanced product performance and elegancy, extended release, reduced irritation, improved thermal, physical, and chemical stability of product. A microsponge delivery system can entrap wide range of drugs and then release them onto the skin over a time and also in response to other stimuli including rubbing, moisture, pH, friction, or ambient skin temperature. It can also be used for controlled oral delivery of drugs using water soluble and bio erodible polymers. The present review describes microsponge technology including its preparation, characterization, programmable parameters and release mechanism of microsponge drug delivery system.

Keywords: Microsponges, Transdermal drug delivery, Programmable release, Topical formulation, Oral administration.

Introduction

Microsponge Delivery System (MDS) technology has been introduced in topical drug products to facilitate the controlled release of active drug into the skin in order to reduce the systemic exposure and minimize local cutaneous reactions to active drugs. 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.[1] A Microsponge delivery system 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.[2] Many of conventional delivery systems require high concentrations of active agents to be incorporated for effective therapy because of their low efficiency as delivery systems.[3] Thus, the need exists for delivery systems to maximize the period of time that an active ingredient is present, either on the skin surface or within the epidermis while minimizing its transdermal penetration into the body. The microsponge-based polymeric microspheres uniquely fulfill such requirements. The microsponge technology was developed by Won in 1987 and the original patents were assigned to advanced polymer system, Inc.[4] It is a unique technology for the controlled release of topical agents and consists of micro porous 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). The structure of microsponge is shown in the figure 1. Now days this delivery system can be incorporated into conventional

dosage forms such as creams, lotions, gels, ointments, and powder and share a broad package of benefits.

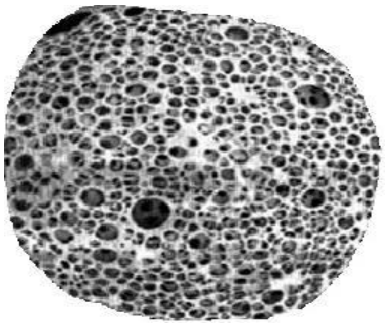

Figure 1: structure of microsponge

Characteristics of microsponges

- Microsponge formulations are stable over range of pH 1 to 11.
- Microsponge formulations are stable at the temperature up to 130^0C.
- Microsponge formulations are compatible with most vehicles and ingredients.
- Microsponge formulations are self sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.
- Microsponge formulations have higher payload (50 to 60%), still free flowing and can be cost effective.[5-9]

Characteristics of materials that is entrapped in microsponges

Most liquid or soluble ingredients can be entrapped in the particles. Actives ingredients that can be entrapped in microsponges must have 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.
- The solubility of active ingredients in the vehicle must be limited to avoid cosmetic problems.
- The spherical structure of microsponges should not collapse.
- Polymer design and payload of the microsponges for the active must be optimized for required release rate for given time period.
- It should be stable in contact with polymerization catalyst and conditions of polymerization.[7-15]

Preparation of microsponges

Drug loading in microsponges can take place in two ways, one-step process or by two-step process, as discussed in liquid-liquid suspension polymerization and quasi emulsion solvent diffusion techniques which based on physico-chemical properties of drug to be loaded.

1. 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.). The polymerization is then initiated by adding catalyst or by increasing temperature or irradiation rate for given time period. Monomer or combinations of monomers are selected and polymerization begins to form chain monomers as a result of cross linking ladders are formed between chains of monomer. Monomer ladder are folded to form spherical particles i.e. agglomeration of microspheres, which give rise to formation of bunches of microspheres. Binding of bunches to form microsponges, a reservoir type of system, which opens at the surface through pores. Some time 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, solvent may be used for faster and efficient incorporation of the drug substances.[16, 17] Reaction vessel for Microsponge preparation by liquid-liquid suspension Polymerization is shown in figure 2.

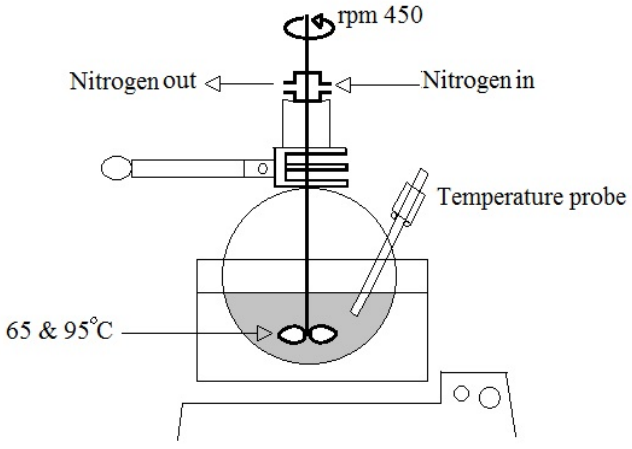

Figure 2: Reaction vessel for Microsponge preparation by liquid-liquid suspension Polymerization

2. Quasi-emulsion Solvent Diffusion

This is a two step process where the microsponges can be prepared by quasiemulsion solvent diffusion method using the different polymer amounts. To prepare the inner phase, Eudragit RS 100 was dissolved in ethyl alcohol. Then, drug can be then added to solution and dissolved under ultrasonication at 35°C. The inner phase was poured into the PVA solution in water (outer phase). Following 60 min of stirring, the mixture is filtered to separate the microsponges. The microsponges are dried in an air-heated oven at 40°C for 12 Hr and weighed to determine production yield (PY).[15, 18] Preparation of Microsponges by Quasi-emulsion solvent diffusion method is shown in figure 3.

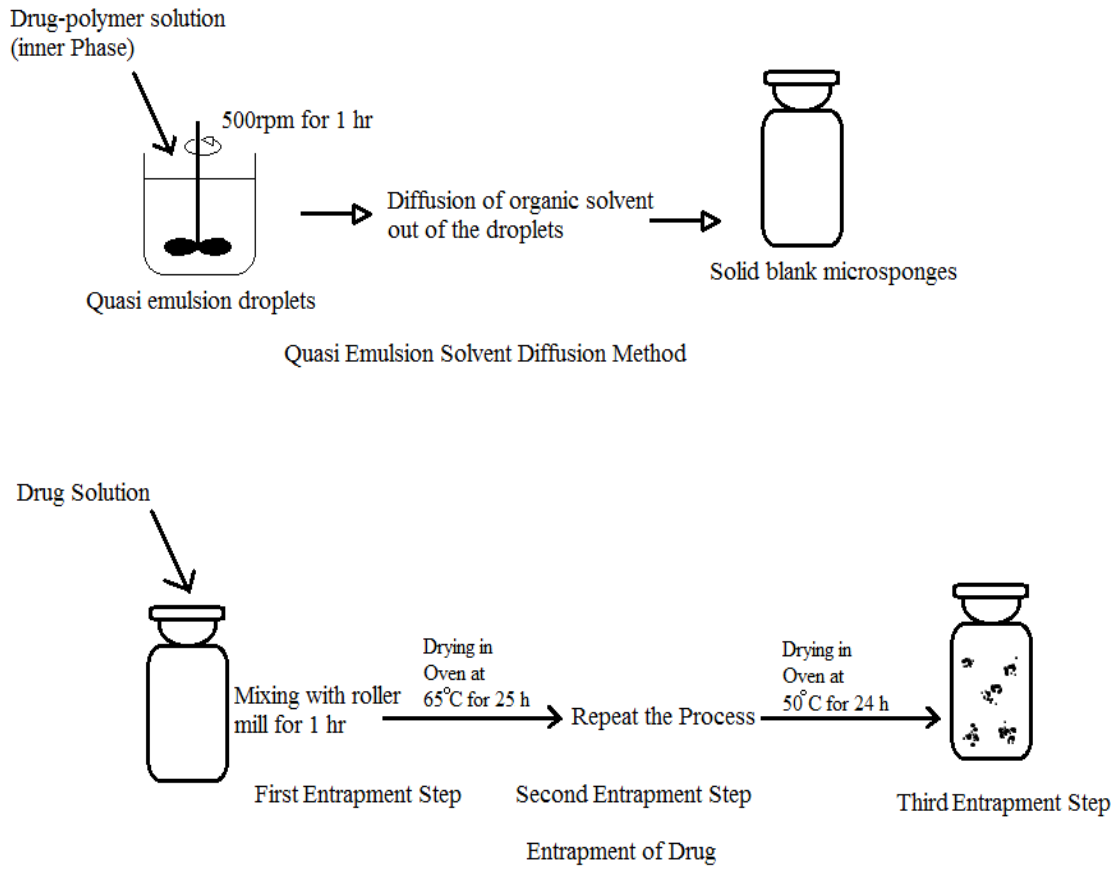

Figure 3: Preparation of Microsponges by Quasi-emulsion solvent diffusion method

Characterization of microsponges

Various methods are used for the evaluation of the MDS. These are following-

1. 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 size range.[19]

2. 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.[20]

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

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.

Production Yield= (Practical mass of microsponges / Theoritical mass (Polymer+drug)) X 100.[21]

4. 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.[18, 21]

5. 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.[23]

6. Polymer/monomer composition

Polymer composition of the MDS can affect partition coefficient of the entrapped drug between the vehicle and the microsponge system and hence have direct influence on the release rate of entrapped drug. Release of drug from Microsponge systems of different polymer compositions can be studied by plotting cumulative % drug release against time.[24]

7. 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.[25, 26]

8. Dissolution studies

Dissolution profile of microsponges can be studied by use of dissolution apparatus USP XXIII with a modified basket consist of 5µm stainless steel mesh. The 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.[27]

9. Drug release from the semi solid dosage forms and drug deposition studies

Drug release from the semi solid dosage forms are performed by the Franz- type static diffusion cells. In this epidermal side of the skin was exposed to ambient condition. While dermal side was kept facing the receptor solution. Receptor compartment containing 20 mL phosphate buffer pH 5.8 was thermo stated at 32±0.5°C and stirred at 600 rpm. Skin was saturated with diffusion medium for 1 h before the application of sample. A 200-mg of sample was applied on the donor compartment. For determination of drug deposited in the skin, the diffusion cell was dismantled after a period of 4, 8, 16, and 24 h. The skin was carefully removed, and drug present on the skin surface was cleaned with distilled water.[28]

10. 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).[29]

11. In-vitro diffusion studies

The in vitro diffusion studies of prepared microsponge gel were carried out in Keshary–Chien diffusion cell using through a cellophane membrane. 100 ml of phosphate buffer was used as receptor compartment, and then 500 mg of gel containing 10 mg of drug was spread uniformly on the membrane. The donor compartment was kept in contact with a receptor compartment and the temperature was maintained at 37 ± 0.5^{0}C. The solution on the receptor side were stirred by externally driven Teflon coated magnetic bars at predetermined time intervals, pipette out 5 ml of solution from the receptor compartment and immediately replaced with the fresh 5 ml phosphate buffer. The drug concentration on the receptor fluid was determined spectrophotometically against appropriate blank. The experiment was carried out in triplicate.[26]

Programmable release of drugs from microsponge system

In general, microsponges retard the release o 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 however; another study has shown that even the overall porosity (including the pore diameter and the number of pores) also affects the drug release.[30-34] Microsponges can be designed to release given amount of active ingredients over time in response to one or more external triggers:

1. 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.

2. pH triggered systems

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

3. 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 microsponge by modulation of temperature.

4. 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.[35-37]

Applications of microsponge systems

Microsponges are designed to deliver the pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects and modify drug release. Microsponge drug delivery systems offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, reduces systemic exposure and minimize local cutaneous reactions, increased elegance, and enhanced formulation flexibility.

Microsponge systems act by three primary ways:

1. As reservoirs releasing active ingredients over an extended period of time.

2. As receptacles for absorbing undesirable substances, such as excess skin oils.

3. As closed containers holding ingredients away from the skin for superficial action.

1. Topical Delivery

Microsponge delivery technology provides controlled release of the active ingredients onto the skin. Several microsphere-based topical agents have been evaluated for their safety and efficacy for cosmetic purposes and in the treatment of dermatological disorders, and are currently marketed in the US. These include formulations of benzoyl peroxide, retinoic acid, HQ plus retinol, and 5-FU. Amrutiya et al., developed microsponge based topical delivery system of mupirocin by using emulsion solvent diffusion method for sustained release and enhanced drug deposition in the skin.[38] Recently, a new formulation of HQ 4% with retinol 0.15% entrapped in microsponge reservoirs was developed for the treatment of melasmaand postinflammatory hyperpigmentation.[39] D'souza et al., developed topical anti-inflammatory gels of fluocinolone acetonide entrapped in eudragit based microsponge delivery system.[40] Carac contains 0.5% fluorouracil incorporated into a patented porous Microsponge System. The particles are dispersed in a cream and hold the active ingredient until applied to the skin.[41] An MDS system for retinoic acid was developed and tested for drug release and anti-acne efficacy.[42]

2. Oral Delivery

In oral drug delivery the microsponge system increase the rate of solubilization of poorly water soluble drugs by entrapping them in the microsponge system's pores. Chen et al used ketoprofen as a model drug for systemic drug delivery of microsponges. Ketoprofen microsponges were prepared by quasi-emulsion solvent diffusion method with Eudragit RS 100 and afterwards tablets of microsponges were prepared by direct compression method.[43] In another study, Paracetamol loaded eudragit based microsponges were prepared using quasiemulsion solvent diffusion method, then the colon specific tablets were prepared by compressing the microsponges followed by coating with pectin-hydroxypropylmethylcellulose (HPMC) mixture.[44] Dicyclomine loaded, Eudragit based microsponges were prepared using a quasiemulsion solvent diffusion method.[45] Dai et al prepared Microsponges containing flurbiprofen (FLB) and Eudragit RS 100 by quasi-emulsion solvent diffusion method. In vitro studies exhibited that formulation started to release the drug at the 8th hour.[46]

3. Bone substitutes

Bone-substitute compounds were obtained by mixing pre-polymerised powders of polymethylmethacrylate and liquid methylmethacrylate monomer with two aqueous dispersions of α-tricalcium phosphate (α-TCP) grains and calcium-deficient hydroxyapatite (CDHA) powders. The final composites appeared to be porous. Osteoconductivity and osteoinductivity of the final composites were tested in vivo by implantation in rabbits.[47]

4. Reconstruction of vascular wall using microsponge technology

The tissue-engineered patch was fabricated by compounding a collagen-microsponge with a biodegradable polymeric scaffold composed of polyglycolic acid knitted mesh, reinforced on the outside with woven polylactic acid. Tissue-engineered patches without precellularization were grafted into the porcine descending aorta (n = 5), the porcine pulmonary arterial trunk (n = 8), or the canine right ventricular outflow tract (as the large graft model; n = 4). Histological and biochemical assessments were performed 1, 2, and 6 months after the implantation. There was no thrombus formation in any animal. Two months after grafting, all the grafts showed good in situ cellularization by hematoxylin/eosin and immunostaining.[48]

The Application summery of microsponge is given in the table 1.

Table 1: Applications of microsponges

S. No.	Active agents	Applications
1	Sunscreens	Long lasting product efficacy, with improved protection against sunburns and sun related injuries even at elevated Concentration and with reduced irritancy and sensitization.
2	Anti-acne e.g. Benzoyl peroxide	Maintained efficacy with decreased skin irritation and sensitization.
3	Anti-inflammatory e.g. hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatoses.
4	Anti-fungals	Sustained release of actives.
5	Anti-dandruffs e.g. zinc pyrithione, selenium sulfide	Reduced unpleasant odour with lowered irritation with extended safety and efficacy.
6	Antipruritics	Extended and improved activity
7	Skin depigmenting agents e.g. hydroquinone	Improved stabilization against oxidation with improved efficacy and aesthetic appeal.
8	Rubefacients	Prolonged activity with reduced irritancy greasiness and odour.

Marketed formulations using the MDS

Marketed formulation using the MDS includes dermatological products which can absorb large amounts of excess of skin oil, while retaining an elegant feel on the skin's surface. Among these products (given in table 2) are skin cleansers, conditioners, oil control lotions, moisturizers, deodorants, razors, lipstick, makeup, powders, and eye shadows; which offers several advantages, including improved physical and chemical stability, greater available concentrations, controlled release of the active ingredients, reduced skin irritation and sensitization, and unique tactile qualities.

Table 2: List of marketed products using microsponge drug delivery system

S. No.	Product name	Advantages	Manufacturer	References
1	NeoBenz®Micro, Neo®MicroSD,NeoBenz®Microwash	Provide gradual release of active ingredient into skin and absorb natural skin oils.	Intendis Inc. Morristown NJ07962 USA	49
2	EpiQuin Micro	The Microsponge® system uses microscopic reservoirs that entrap hydroquinone and retinol. The MDS release these ingredients into the skin gradually throughout the day.	SkinMedica Inc	50
3	Lactrex™ 12% Moisturizing Cream	Lactrex™ 12% Moisturizing Cream contains 12% lactic acid and glycerin, a natural humectant, to soften and help moisturize dry, flaky, cracked skin.	SDR Pharmaceuticals Inc., Andover , NJ, U.S.A. 07821	51
4	Sportscream RS and XS	Topical analgesic, anti-inflammatory and counterirritant actives in a MDS for the management of musculoskeletal conditions	Embil Pharmaceutical Co. Ltd	52
5	Carac Cream, 0.5%	Carac is a once-a-day topical prescription product for the treatment of actinic keratoses (AK). It contains 0.5% fluorouracil, with 0.35% being incorporated into a patented porous microsphere composed of methyl methacrylate/glycol dimethacrylate cross-polymer and dimethicone.	Dermik Laboratories, Inc. Berwyn , PA 19312 USA	42
6	Oil free matte block spf20	Protect the skin from damaging UV rays and control oil production with this invisible sunscreen. Microsponge technology absorbs oil, maintaining an all day matte finish and preventing shine without any powdery residue.	Dermalogica	49
7	Oil Control Lotion	A feature-light lotion with technically advanced microsponges that absorb oil on the skin's surface during the day, for a matte finish.	Fountain Cosmetics	11
8	Retinol cream	Retinol is a topical vitamin A derivative which helps maintain healthy skin, hair and mucous membranes. For protect the potency of the vitamin A, retinol molecule is entrapped in the MDS.	Biomedic	53
9	Micro Peel Plus	The MicroPeel® Plus procedure stimulates cell turnover through the application of salicylic acid in the form of microcrystals using Microsponge® technology.	Biomedic	9

10	Salicylic Peel 20 and 30	Has excellent exfoliation and used for stimulation of the skin for more resistant skin types or for faster results.	Biophora.	49
11	Dermalogica Oil Control Lotion	A feather-light lotion containing microsponges to absorb oil on the skin's surface, helping to combat shine and maintain an all-day matte finish. Niacinamide, Zinc Gluconate, Yeast Extract, Caffeine and Biotin purify and inhibit overactive sebaceous gland activity while soothing irritation.	John and Ginger Dermalogica Skin Care Products	48
12	Aramis fragrances	24 Hour High Performance Antiperspirant Spray Sustained release of fragrance in the microsponge.	Aramis Inc.	54

Conclusions

The MDS which was originally developed for topical delivery of drugs can also be used for controlled oral delivery of drugs using bio-erodible polymers, especially for colon specific delivery. It provides a wide range of formulating advantages. Formulations can be developed with prolonged stability without use of preservatives. Safety of the irritating and sensitizing drugs can be increased and programmed release can control the amount of drug release to the targeted site. MDS holds a promising future in various pharmaceutical applications in the coming years as they have unique properties like enhanced product performance and elegancy. Thus microsponge has got a lot of potential and is a very emerging field which is needed to be explored.

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