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Microsponge Drug Delivery System: A Novel Dosage Form

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ABSTRACT

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 bioerodible 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. 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. Topical preparations have some disadvantages like unpleasant odour, greasiness and skin irritation and fail to reach the systemic circulation this problem is overcome by microsponge delivery system. Microsponge formulations are stable over range of PH 1 to 11; Microsponge formulations are stable at the temperature up to 130^0C; compatible with most vehicles and ingredients. The present review introduces Microsponge technology along with its synthesis, characterization, programmable parameters and release mechanism of MDS.

Keywords: Microsponge, microporous beads, Controlled release, Topical drug delivery, Solvent Diffusion Method, Quasi-Emulsion.

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INTRODUCTION

The microsponge technology was developed by Won in 1987 and the original patents were assigned to advanced polymer system, Inc [1]. This company developed a large number of variations of the technique and applied to the cosmetic as well as over the counter (OTC) and prescription pharmaceutical products. At present, this technology has been licensed to Cardinal Health, Inc., for use in topical products.

Microsponge Delivery System MDS is a unique technology for controlled delivery of drug. 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. 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]. To control the delivery rate of active agents to a predetermined site in human body has been one of the biggest challenges faced by drug industry. 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 [3]. 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. Further, these porous microspheres with active ingredients can be incorporated in to formulations such as creams, lotions and powders. Release of drug into the skin is initiated by a variety of triggers, including rubbing and higher than ambient skin temperature [4].

Conventional formulations of topical drugs are intended to work on the outer layers of the skin. Typically, such products release their active ingredients upon application, producing a highly concentrated layer of active ingredient that is rapidly absorbed [5]. Moreover, the application of topical drugs has many problems like greasiness, stickiness associated with the ointments and so on, that often result in lack of patient compliance. The fundamental appeal of the Microsponge technology overcomes these difficulties experienced with conventional formulations in releasing active ingredients over an extended period of time. Microsponge can be used to deliver active agents to the skin, with improved localization and prolonged residence of the drug at site of action.

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 [6]. 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 [1.] Microsponge Delivery System is being used currently in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products. 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.

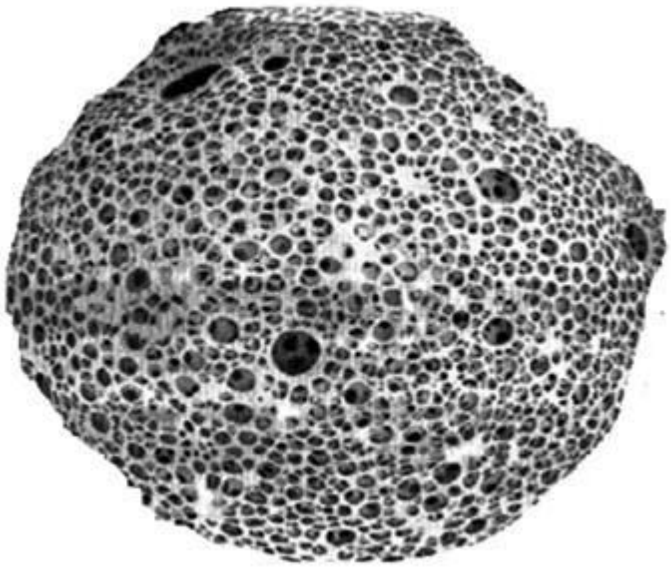

Figure. 1: Highly porous nature of a Microsponge

Characteristics of microsponges [5]

1) Microsponge formulations are stable over range of PH 1 to 11; [6]

2) Microsponge formulations are stable at the temperature up to 130^0C; [7, 8]

3) Microsponge formulations are compatible with most vehicles and ingredients; [5, 7, 8]

4) Microsponge formulations are self sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate; [8, 9]

5) Microsponge formulations have higher payload (50 to 60%), still free flowing and can be cost effective [9].

Advantages [12, 14]

- Advanced oil control, absorb up to 6 times its weight without drying
- Improved product elegancy.
- MDS allows the incorporation of immiscible products.
- Extended release
- Reduced irritation formulas
- Allows novel product form
- These are non-irritating, non-mutagenic, non-allergenic and non-toxic.
- 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
- Improves efficacy in treatment.
- Cure or control confirm more promptly.
- Improve control of condition
- Improve bioavailability of same drugs

Advantages over conventional formulation [8, 9]

Conventional formulations of topical drugs are intended to work on the outer layers of the skin. Such products release their active ingredients upon application, producing a highly concentrated layer of active ingredient that is rapidly absorbed. When compared to the Microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Potentially, the Microsponge system can reduce significantly the irritation of effective drugs without reducing their efficacy. For example, by delivering the active ingredient gradually to the skin like MDS Benzoyl peroxide formulations have excellent efficacy with minimal irritation.

Advantages over microencapsulation and liposomes [8, 14]

The MDS has advantages over other technologies like microencapsulation and liposomes. Microcapsules cannot usually control the release rate of actives. Once the wall is ruptured the actives contained within microcapsules will be released. Liposomes suffer from lower payload, difficult formulation, limited chemical stability and microbial instability. While microsponge system in contrast to the above systems are stable over range of pH 1 to 11, temperature up to

130^0C; 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.

Advantages over ointments [14, 15]

Ointments 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 odor and potential incompatibility of drugs with the vehicles, when microsponge system maximize amount of time that an active ingredient is present either on skin surface or within the epidermis, while minimizing its transdermal penetration into the body.

Characteristics of materials that are entrapped in Microsponges [16]:

The active ingredients used in microsponge must meet the 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.
- Polymer design and payload of the microsponges for the active must be optimized for required release rate for given time period.

RELEASE MECHANISMS [17, 18]

Microsponges can be designed to release given amount of active ingredients over time in response to one or more external triggers.

1) Temperature change [19]

Some entrapped actives 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 [8]. 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.

2) Pressure

Microsponge system releases the entrapped material rubbing/ pressure applied can release active ingredient from microsponges onto skin. 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.

3) 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.

4) Solubility [20]

Microsponges loaded with water-soluble ingredients like anti-prespirants and antiseptics will release the ingredient in the presence of water. The release can also be activated by diffusion taking into consideration the partition coefficient of the ingredient between the microsponges and the outside system. Sustained release microsponges can also be developed. Various factors that are to be considered during development of such formulations includes, Physical and chemical properties of entrapped actives. Physical properties of microsponge system like pore diameter, pore volume, resiliency etc. Properties of vehicle in which the microsponges are finally dispersed. Particle size, pore characteristics, resiliency and monomer compositions can be considered as programmable parameters and microsponges can be designed to release given amount of actives in response to one or more external triggers like; pressure, temperature and solubility of actives .

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. If the drug is typically an inert non-polar material, will create the porous structure it is called porogen. Porogen drug, which neither hinders the polymerization nor become activated by it and stable to free radicals is entrapped with one-step process.

(i) Polymerization

Porous microsphere prepared by the polymerization method i.e. Liquid-liquid suspension polymerization. They are conveniently prepared by this method. In this method of polymerisation the monomer is dissolved along with the active ingredient in suitable solvent and

then added in aqueous phase containing additives i.e. surfactant, suspending agents etc. The polymerization is then initiated by adding catalyst or by increasing temperature or irradiation. Polymerization of styrene or methyl methacrylate is carried out in round bottom flask. A solution of non-polar drug is made in the monomer, to which aqueous phase, usually containing surfactant and dispersant to promote suspension is added. Polymerization is effected, once suspension with the discrete droplets of the desired size is established, by activating the monomers either by catalysis or increased temperature. (Reaction vessel are shown in fig. 1)When the drug is sensitive to the polymerization conditions, two-step process is used. [20]

The polymerization is performed using substitute porogen and is replaced by the functional substance under mild experimental conditions.

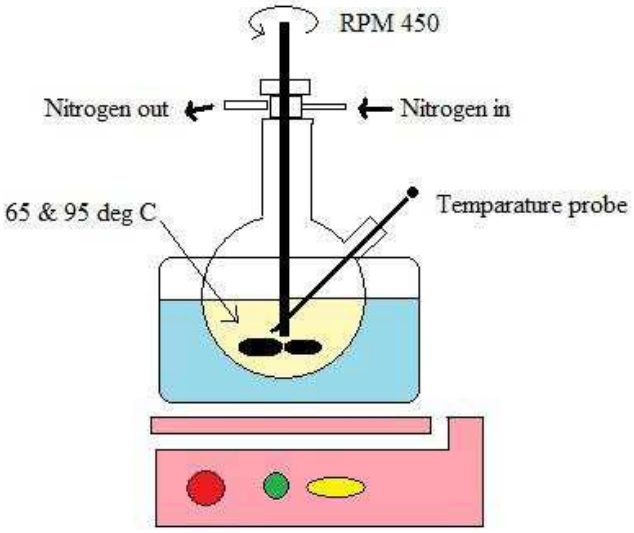

Figure. 2: Reaction vessel for Microsponge

The various steps in the preparation of microsponges are summarized as follows [21, 22]

- Selection of monomer or combination of the monomer
- Formation of chain monomer as polymerization begins
- Formation of monomer ladder as result of cross linkage between chain monomer
- Folding of monomer ladder to form spherical particles
- Agglomeration of microsphere lead to formation of bunches of microsphere Binding of bunches lead to formation of microsponge.

2) Quasi-emulsion Solvent Diffusion:

This is a two step process where the microsponges can be prepared by quasiemulsion solvent diffusion method (Figure 3) 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).[20, 22]

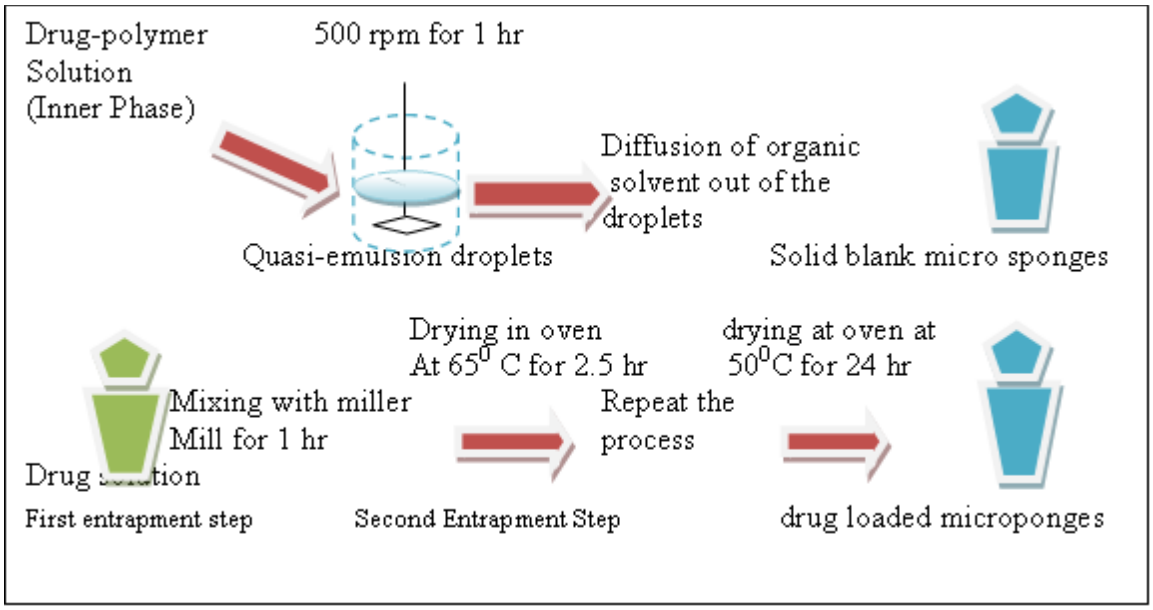

Figure. 3 Preparation of Microsponge by Quasi-emulsion solvent diffusion method

METHOD EVALUATION PARAMETERS OF MICROSPONGES:

Various method are used for the evaluation of the MDS they are following

- Particle size (Microscopy)
- Morphology and Surface topography
- Characterization of pore structure
- Loading efficiency and production yield
- Determination of true density
- Compatibility studies
- Polymer/monomer composition
- Resiliency
- Drug release study
- Kinetics of release
- Other In-vitro studies

1) Particle size determination:

Particle size analysis is performed by laser light diffractometry or any other suitable method. Free-flowing powders with fine aesthetic attributes are possible to obtain by controlling the size

of particles during polymerization. The values (*d*50) can be expressed for all formulations as mean 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 30 µm can impart gritty feeling and hence particles of sizes between 10 and 25 µm are preferred to use in final topical formulation. [23]

2) Scanning Electron Microscope (SEM) study:

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 [24]

3) Loading efficiency and production yield

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

Loading efficiency =

$$\frac{\text{Actual Drug Content in Microsponge}}{\text{Therotical Drug Content}} \quad \text{Eqn no.(1)}$$

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 [13].

Production Yeild(PY) =

$$\frac{\text{Practical Mass of Microsponges} \times 100}{\text{Therotical Mass}} \quad \text{Eqn no.(2)}$$

4) Characterization of pore structure [23, 24]

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.

The pore diameter of microsponges can be calculated by using Washburn equation. [18]

$$D = \frac{-4\gamma\cos\theta}{P} \quad \text{Eqn no. (3)}$$

Where D is the pore diameter (μm); γ the surface tension of mercury (485 dyn cm^{-1}); θ the contact angle (130^{o}); and P is the pressure (psia).

Total pore area (A_{tot}) was calculated by using equation,

$$A_{tot} = \frac{1}{\gamma \cos\theta} \int_{0}^{V_{tot}} P.dV \quad -- \textit{Eqn no. (4)}$$

Where P is the pressure (psia); V the intrusion volume (mL g^{-1}); V_{tot} is the total specific intrusion volume (mL g−1).

The average pore diameter (Dm) was calculated by using equation,

$$D_m = \frac{4\,V_{tot}}{A_{tot}} \quad -- \textit{Eqn no. (5)}$$

Envelope (bulk) density (ρ_{se}) of the microsponges was calculated by using equation,

$$\rho_{se} = \frac{W_s}{V_p - V_{Hg}} \quad -- \textit{Eqn no. (6)}$$

Where Ws is the weight of the microsponge sample (g); V_p the empty penetrometer (mL); V_{Hg} is the volume of mercury (mL).

Absolute (skeletal) density (ρ_{sa}) of microsponges was calculated by using equation,

$$\rho_{sa} = \frac{W_s}{V_{se} - V_{tot}} \quad -- \textit{Eqn no. (7)}$$

Where V_{se} is the volume of the penetrometer minus the volume of the mercury (mL).

Finally, the percent porosity of the sample was found from equation,

$$\text{Porosity (\%)} = \left(1 - \frac{\rho_{se}}{\rho_{sa}}\right) X\ 100 \quad -- \textit{Eqn no. (8)}$$

Pore morphology can be characterized from the intrusion–extrusion profiles of mercury in the microsponges as described by Orr. [25]

5) Determination of true density [24]

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

6) 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) [26, 27, 28.] For DSC approximately 5mg samples can be accurately weighed into aluminium pans and sealed and can be run at a heating rate of l5^{o}c/min over a temperature range 25–430^{0}C in atmosphere of nitrogen.

7) Polymer/monomer composition [29]

Factors such as microsphere size, drug loading, and polymer composition govern the drug release from microspheres. 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.

8) Resiliency (viscoelastic properties) [30, 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 slow down the rate of release.

9) Dissolution studies [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. 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.

10) Drug release from the semi solid dosage forms and drug deposition studies [33, 34]

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 thermostated 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.

11) *In-vitro* diffusion studies [33]

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±0.50. 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 spectrophotometrically against appropriate blank. The experiment was carried out in triplicate.

12) Other *In-vitro* studies are

Fourier transforms infrared (FTIR) analysis [34]

FTIR spectra of the drug, physical mixture of drug and Eudragit RS-100, formulations FPRS1nFPRS4 were recorded in potassium bromide disc using a Shimadzu Model 8400 FTIR spectrometer to ascertain compatibility.

Differential scanning calorimetric (DSC) analysis [34]

Thermal analysis using DSC was carried out on drug, physical mixture of the drug and Eudragit RS-100; accurately weighed samples were loaded into aluminium pans and sealed. All samples were run at a heating rate of 20ºC/min. over a temperature range 40-430ºC.

Statistical analysis [34]

The data obtained from each experiment were subjected to statistical analysis by Student t-test and one-way analysis of variance (ANOVA) using Graph Pad stat software. $P < 0.05$ was considered to be indicative of significance.

Stability studies [34, 35]

In pharmaceutical sense, stability is technically defined as the capacity of particular formulation in a specific container or closure system, to remain within its physical, chemical, microbiological, therapeutic and toxicological specification. Durability of a product may be defined as the capability of a particular formulation in a specific container to remain with the physical, chemical, microbiological, therapeutic and toxicological specification. Stability of Microsponge gel formulation on storage is of a great concern as it is the major resistance in the development of marketed preparations. The prepared formulation was tested for stability on storing them at 4 ± 1ºC, 25 ± 2ºC and 37 ± 5ºC & RH (Relative Humidity) 75 %. After one month and the three months they were evaluated for the following parameters-Appearance, pH, Drug content analysis, Drug release profiles, Rheological properties etc

SAFETY CONSIDERATION

1) Skin irritation studies in rabbits [36, 37]

The scores for erythema totalled for intact and abraded skin for all rabbits at 24 and 72 hr. The primary irritation index was calculated based on the sum of the scored reactions divided by 24 (two scoring intervals multiplied by two test parameters multiplied by six rabbits).

2) Anti-inflammatory activity by ear edema measurement [35]

Experiments reported in this study were performed after approval by the Animal Ethics Committee of our College and were carried out in accordance with the CPCSA guidelines Anti inflammatory activity was done by Male Swiss mice (25–35 g) housed at 22±2 ºC under a 12 hr light/12-hr dark cycle and with access to food and water, which were performed during the light phase of the cycle. The animals were allowed to acclimate to the laboratory for at least 2 hr before testing and were used only once. Edema was induced in the right ear by topical application of 0.1mg/ear of croton oil dissolved in 20µL of acetone. In house gels of FA containing free, entrapped drug and marketed gel were applied topically simultaneously with the croton oil. Ear thickness was measured before and 6 hr after the induction of inflammation using a digital vernier caliper and reported

3) Primary Eye Irritation Study (Unwashed Eyes) [3]

Test substance is instilled into one eye of each of 6 rabbits (unwashed eyes), The cornea, iris, and conjunctiva tissue of the treated eyes are graded for irritation effects at 1, 24, 48 and 72 hr after instillation. Observation period may be extended for up to 21 days to evaluate the reversibility of the effects observed.

4) Other evaluation studies are

Oral toxicity studies in rats, Mutagenicity in bacteria, allergenicity in guinea pigs, Compatibility studies by (TLC) thin layer chromatography.

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.

Table 1: Applications of microsponges [9, 39, 40]

Sr. no.	Active agents	Application
1	Anti-acne e.g. Benzoyl peroxide	Maintained efficacy with decreased skin irritation and sensitization. [41, 42]
2	Anti-inflammatory e.g. hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatomes. [39, 42]
3	Antifungal	Sustained release of actives. [9]
4	Antidandruffs e.g. zinc pyrithione, selenium sulfide	Reduced unpleasant odor with lowered irritation with extended safety and Efficacy. [7, 8]
5	Antipruritics	Extended and improved activity. [39, 9]
6	Skin depigmenting agents e.g. hydroquinone	Improved stabilization against oxidation with improved efficacy and aesthetic Appeal. [10, 25]
7	Rubefacients	Prolonged activity with reduced irritancy greasiness and odor. [37, 38]
8	Sunscreens	Long lasting product efficacy, with improved protection against sunburns and sun related injuries even at elevated concentration and with reduced irritancy and sensitization. [7, 8, 9]

Microsponge systems in 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, or

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

Releasing of active ingredients from conventional topical formulations over an extended period of time is quite difficult. Cosmetics and skin care preparations are intended to work only on the outer layers of the skin. The typical active ingredient in conventional products is present in a relatively high concentration and, when applied to the skin, may be rapidly absorbed. The common result is overmedication, followed by a period of under medication until the next application. Rashes and more serious side effects can occur when the active ingredients rapidly penetrate below the skin's surface. Microsponge technology is designed to allow a prolonged rate of release of the active ingredients, thereby offering potential reduction in the side effects while maintaining the therapeutic efficacy.

Topical Delivery:

Topical agents are a mainstay in cosmetics and the treatment of dermatological disorders. However, they are associated with substantial skin irritancy, especially in sensitive patients. The rapid release and subsequent accumulation of the active ingredients of the topical agents have been associated with this irritancy. 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, tretinoic acid, HQ plus retinol, and 5-FU. Formulations of topical agents utilizing the MDS technology have shown little or no irritancy in patients with acne, photo damaged skin, hyperpigmentation, or AK, without sacrificing the efficacy of the agents.

Topical agents are a mainstay in both cosmetics and the treatment of dermatological disorders. For dermatological disorders such as acne (a common skin complaint in the US), hyperpigmentation, and actinic keratoses (AK), topical retinoids-particularly tretinoin (retinoic acid) are widely used. Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne and athletes foot. Skin irritation is a common side effect, and 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. Benzoyl peroxide microparticles were prepared 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. [21]

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. In-vitro drug release, ex-vivo drug deposition, and in-vivo antibacterial activity of mupirocin loaded formulations were studied. Microsponges were spherical and porous, and there was no interaction between drug and polymer molecules. Emulgels containing microsponges showed desired physical properties. Drug release through cellulose dialysis membrane showed diffusion controlled release pattern and drug deposition studies using rat abdominal skin exhibited significant retention of active in skin from microsponge based formulations by 24 h. [44]

Disorders of hyperpigmentation such asmelasma and postinflammatory hyperpigmentation (PIH) are common, particularly among people with darker skin types. Hydroquinone (HQ) bleaching creams are considered the gold standard for treating hyperpigmentation. Recently, a new formulation of HQ 4% with retinol 0.15% entrapped in microsponge reservoirs was developed for the treatment of melasmaand PIH. Microsponges were used to release HQ gradually to prolong exposure to treatment to skin. Microsponges containing mupirocin were prepared by an emulsion solvent diffusion method. The optimized microsponges were incorporated into anemulgel base. Drug release through cellulose dialysis membrane showed diffusion controlled release pattern and drug deposition studies using rat abdominal skin exhibited significant retention of active in skin from microsponge based formulations by 24 h. The optimized

formulations were stable and non-irritant to skin as demonstrated by Draize patch test. Microsponges-based emulgel formulations showed prolonged efficacy in mouse surgical wound model infected with S.aureus. Mupirocin was stable in topical emulgel formulations and showed enhanced retention in the skin indicating better potential of the delivery system for treatment of primary and secondary skin infections, such as impetigo, eczema, and atopic dermatitis. [45]

D'souza *et al*., developed topical anti-inflammatory gels of fluocinolone acetonide entrapped in eudragit based microsponge delivery system. Fluocinolone acetonide (FA) is a corticosteroid chiefly used in dermatology to lessen skin inflammation and relieve itching. The percutaneous absorption increases risk related with systemic absorption of topically applied formulation. [46]

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. 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 increase the rate of solubilization.

A Microsponge system offers the potential for active ingredients to remain within a protected environment and provide controlled delivery of oral medication to the lower gastrointestinal (GI) tract, where it will be released upon exposure to specific enzymes in the colon. If this approach is successful then it should open up entirely new opportunities for MDS. It has been shown that microsponge system enhances the solubilization of drugs which are poorly soluble by entrapping these drugs in their pores.

In oral applications, the Microsponge system has been shown to increase the rate of solubilization of poorly water-soluble drugs by entrapping such drugs in the microsponge system's pores. An ketoprofen was used as a model drug for systemic drug delivery of microsponges in the study. 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. Different pressure values were applied to the tablet powder mass in order to determine the optimum pressure value for compression of the tablets. Results indicated that compressibility was much improved over the physical mixture of the drug and polymer; due to the plastic deformation of sponge-like structure microsponges produce mechanically strong tablets. [47]

Bone substitutes

Bone-substitute compounds were obtained by mixing pre-polymerised powders of polymethylmethacrylate and liquid methylmethacrylate monomer with two aqueous dispersions

of a-tricalcium phosphate (a-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. Formation of new trabecular bone was observed inside the pores where the inorganic powders had been placed. The material produced shows a good level of biocompatibility, good osteointegration rate and osteogenetic properties. [48]

Cardiovascular engineering using microsponge technology

Biodegradable materials with autologous cell seeding, requires a complicated and invasive procedure that carries the risk of infection. To avoid these problems, a biodegradable graft material containing collagen microsponge that would permit the regeneration of autologous vessel tissue has developed. The ability of this material to accelerate in-situ cellularization with autologous endothelial and smooth muscle cells was tested with and without pre-cellularization. Poly (lactic-co-glycolic acid) as a biodegradable scaffold was compounded with collagen microsponge to form a vascular patch material. Histological results showed the formation of an endothelial cell monolayer, a parallel alignment of smooth muscle cells, and reconstructed vessel wall with elastin and collagen fibers. The cellular and extracellular components in the patch had increased to levels similar to those in native tissue at 6 months. This patch shows promise as a bioengineered material for promoting in situ cellularization and the regeneration of autologous tissue in cardiovascular surgery. [49]

Microsponges for Biopharmaceuticals Delivery:

The microsponge delivery system (MDS) is employed for both in the delivery of biopharmaceuticals as well as in tissue engineering. Dai 2010 *et al*., developed 3D scaffolds hybrid structures that have advantages of natural type I collagen and synthetic PLGA knitted mesh. The collagen microsponges facilitated cell seeding and tissue formation and mechanically strong PLGA mesh served as a skeleton. The scaffolds were divided into three groups:

a) *Thin*: collagen microsponge formed in interstices of PLGA mesh;

b) *Semi*: collagen microsponge formed on one side of PLGA mesh;

c) *Sandwich*: collagen sponge formed on both sides of PLGA mesh.

In the scaffolds Bovine chondrocytes were cultured and transplanted subcutaneously into nude mice for 2, 4, and 8 weeks. All transplants showed natural chondrocyte morphology, homogeneous cell distribution, and abundant cartilaginous ECM deposition. Production of GAGs per DNA and the expression of type II collagen and aggrecan mRNA were much higher in the *Semi* and *Sandwich* groups than in the *Thin* group. Young's modulus showed 54.8 49.3%

mechanical strength of the engineered cartilage and in stiffness 68.8 62.7%, respectively, in *Semi* and *Sandwich* when compared to native articular cartilage. These scaffolds could be used for the tissue engineering of articular cartilage with adjustable thickness 43. Iwai *et al*., developed a biodegradable graft material containing collagen microsponge that would allow the regeneration of autologous vessel tissue in order to avoid these problems. Poly (lactic-co-glycolic acid) has been used as a biodegradable scaffold which was compounded with collagen microsponge to form a vascular patch material. The poly (lactic-co-glycolic acid) collagen patches with or without autologous vessel cellularization were used to patch the canine pulmonary artery trunk. Biochemical and histologic assessments were performed 2nd and 6th months after the implantation. Resulting, there was no thrombus formation in either group but the poly (lactic-co-glycolic acid) scaffold was approximately completely absorbed in both groups. Histologic results showed the formation of an endothelial cell monolayer, a parallel alignment of smooth muscle cells, and reconstructed vessel wall with elastin and collagen fibers. The cellular and extra-cellular components in the patch had enlarged to levels analogous to those in native tissue at 6 months. This patch also shows promise as a bioengineered material for promoting *in-situ* cellularization and the regeneration of autologous tissue in cardiovascular surgery. [50]

Tateishi *et al*., has also been studied developed biodegradable porous scaffolds for tissue engineering. 3D biodegradable porous scaffolds play a vital role in tissue engineering. A novel method were used for preparing porous scaffolds which consists of synthetic biodegradable polymers and developed by combining porogen leaching and freeze-drying techniques utilizing pre-prepared ice particulates as the porogen material. Biodegradable hybrid porous sponges of synthetic polymer and collagen have been prepared by hybridizing synthetic polymer sponges with collagen microsponges. The collagen microsponges were produced in the pores of synthetic polymer sponges. Hybrid sponges of synthetic polymer, collagen and inorganic hydroxyapatite were prepared by depositing hydroxyapatite particulates on the surfaces of the collagen microsponges in the synthetic polymer-collagen sponges. The synthetic polymer sponge were used as a mechanical skeleton to aid the formation of these hybrid sponges into desired shapes and contributed good mechanical strength and handling whereas the collagen and hydroxyapatite are used to promote cell interaction and facilitate cell seeding. [51]

MARKETED FORMULATIONS USING THE MDS

Microsponge delivery systems are used to enhance the safety, effectiveness and aesthetic quality of topical prescription, over-the-counter ("OTC") and personal care products. Products under

development or in the marketplace utilize the Topical Microsponge systems in three primary ways;

• As reservoirs releasing active ingredients over an extended period of time,

• As receptacles for absorbing undesirable substances, such as excess skin oils, or

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

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

Product	Manufacturer	Advantages
Carac Cream, 0.5%	Dermik Laboratories, Inc. Berwyn , PA 19312 USA	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. The product has a number of advantages over existing topical therapies, including reduced dosage frequency and less irritation with shorter duration of therapy. [40]
Oil Control Lotion	Fountain Cosmetics	A feature-light lotion with technically advanced microsponges that absorb oil on the skin's surface during the day, for a matte finish. Eliminate shine for hours with this feature-weight lotion, formulated with oil-absorbing Microsponge technology and hydrating botanicals. The naturally antibiotic Skin Response Complexes soothes inflammation and tightness to promote healing. Acne-Prone, oily skin conditions. [12]
Oil free matte block spf20	Dermalogica	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. Cornstarch and Vinyl Dimethicone/Methicone Silsesquioxane Cross-polymer act as microsponges to absorb excess surface oils on skin. [52]
Retinol cream	Biomedic	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. This helps to maximize retinol dosage while reducing the possibility of irritation. [9, 51]
Salicylic Peel 20 and 30	Biophora.	Salicylic acid 20% and 30%, microsponge technology has excellent exfoliation and used for stimulation of the skin for more resistant skin types or for faster results. It will considerably improve pigmentation, fine lines and acne concerns. Salicylic acid moves easily through the pores, clearing them

		out while reducing inflammation. This treatment effectively combats acne leaving an amazingly smooth and clear complexion. [48]
Sportscream RS and XS	Embil Pharmaceutical Co. Ltd.	Topical analgesic, anti-inflammatory and counterirritant actives in a MDS for the management of musculoskeletal conditions. [27, 9]
Micro Peel Plus	Biomedic	The MicroPeel® Plus procedure stimulates cell turnover through the application of salicylic acid in the form of microcrystals using Microsponge® technology. These microcrystals target on exact areas of the skin that need improvement. The MicroPeel® Plus aggressively outperforms other superficial chemical peels by freeing the skin of all dead cells while doing no damage to the skin. [9, 52]
EpiQuin Micro	SkinMedica Inc	The Microsponge® system uses microscopic reservoirs that entrap hydroquinone and retinol. The MDS release these ingredients into the skin gradually throughout the day. This provides the skin with continuous exposure to hydroquinone and retinol over time, which may minimize skin irritation. [49]
Lactrex™ 12% Moisturizing Cream	SDR Pharmaceuticals, Inc., Andover , NJ , U.S.A. 07821	It contains 12% lactic acid as the neutral ammonium salt, ammonium lactate. Microsponge® technology has been included for comfortable application and long lasting moisturization. Lactrex™ also contains water and glycerine, a natural humectant, to soften and help moisturize dry, flaky, cracked skin. [52]
NeoBenz®Micro, Neo®MicroSD NeoBenz®Microwash	Intendis Inc. Morristown NJ07962 USA	NeoBenz®Micro 5.5% cream, NeoBenz® Micro SD 5.5% single dose cream pre-filled sponge applicator and NeoBenz®Microwash 7% are topical preparations containing Benzoyl peroxide incorporated into patented porous Microsponge® composed of methyl methacrylate/glycol dimethacrylate cross polymer. This system has been shown to provide gradual release of active ingredient into skin and absorb natural skin oils. Benzoyl peroxide is an oxidizing agent that posses antibacterial properties and is classified as keratolytic. [52]

PATENT INFORMATION

In September 1, 1987, Won R (Palo Alto, CA) of Advanced Polymer Systems, Inc. (Redwood City, CA) received US patent for developing Method for delivering an active ingredient by controlled time release utilizing a novel delivery vehicle which can be prepared by a process utilizing the active ingredient as a porogen (United States Patent 4,690,825)[22]. September 8, 1992, Won R (Palo Alto, CA) of Advanced Polymer Systems, In (Redwood City, CA) received

US patent for developing Two-step method for preparation of controlled release formulations (United States Patent 5,145,675) [1].

Advanced Polymer Systems, Inc. and subsidiaries ("APS" or the "Company") is using its patented Microsponge(R) delivery systems and related proprietary technologies to enhance the safety, effectiveness and aesthetic quality of topical prescription, over-the-counter ("OTC") and personal care products like tretinoin, 5-fluorouracil and Vitamin-A etc. As on July 23, 2006, the Company has a total of 10 issued U.S. patents and an additional 92 issued foreign patents. 21 patent applications are pending worldwide. Dean, JR. et al received US patent no. 4863856 for the development of weighted collagen microsponges having a highly cross-linked collagen matrix are described suitable for use in culturing organisms in motive reactor systems. The microsponges have an open to the surface pore structure, pore sizes and volumes suitable for immobilizing a variety of bioactive materials (United States Patent 4863856) [39] Won R. United States Patent No. 4,690,825, Method for delivering an active ingredient by controlled time release utilizing a novel delivery vehicle, which can be prepared by a process utilizing the active ingredient as a porogen. Sep. 1987. 23. Dean J.R., Robert C., Frederick H., Richard A., Philip G., Runstadler J.R. United States Patent 4863856, Weighted collagen microsponge for immobilizing bioactive materials, 1989.

CONCLUSION

MDS has become highly competitive and rapidly evolving technology and more and more research are carrying out for cost-effective therapy. MDS holds a promising future in various pharmaceutical applications in the coming years as they have unique properties like enhanced product performance and elegancy. 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 bioerodible 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. It provides a wide range of formulating advantages. Liquids can be transformed into free flowing powders. Formulations can be developed with otherwise incompatible ingredients 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.

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