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Microsponges: An Upcoming and Promising Drug Delivery System

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ABSTRACT

Over the past decade, numerous limitations of conventional dosage forms had attracted researchers to find a rational and appropriate drug delivery system. Microsponges were developed and studied as a novel programmable delivery system which is intended to deliver drug in controlled release pattern. It also aims epidermal localization of topical drug therapy to reduce their side effects by limiting systemic absorption through skin. Drug loaded microsponges are microporous beads, typically 10-25 µm in diameter which can entrap a wide variety of actives and can be formulated as creams, lotions, gels, ointments, powders, soaps. Microsponge formulations can increase product stability, enhance aesthetic qualities, and provide formulation flexibility and stability. Moreover, their non-antigenicity, non-toxicity, non-mutagenicity and non-biodegradability make them favourable candidates. Microsponge approach has also been applied in oral therapy, bone, tissue & cartilage engineering and showed remarkable results. This article provides description about the nature of microsponges, their characteristics, preparation, applications and commercial market status globally.

Keywords: Microsponges, topical delivery, controlled release, quasi-emulsification, programmable release

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INTRODUCTION

With the advent of 21st century, numerous technologies and advancements had been developed for delivery of drugs and medicaments using skin as a portal. Human skin is a large multilayered organ which serves as a barrier against physical and chemical attack, maintains body temperature and blood pressure, and prevents microbial invasion etc[1]. Several topical dosage forms have been developed for either local action or systemic effect such as creams, ointments, gels, lotions, transdermal patches etc[2]. But their efficacy is still under question.

Undesirable penetration of topical agents like corticosteroids or sunscreens, can lead to systemic side effects of adrenal suppression and irritancy or allergic reactions[3]. To overcome such problems, novel approaches have been studied and considerable emphasis have been laid on microsponges based drug delivery to facilitate epidermal localization and control drug release by incorporation into a carrier system so as to alter the therapeutic index and duration of the activity of drugs[4]. Microsponges are polymeric delivery systems composed of porous microspheres whose size may vary usually from 5-300 µm in diameter, depending upon the degree of smoothness or after-feel required for the end formula. A typical 25 µm sphere can have up to 250000 pores and an internal pore structure equivalent to 10 ft in length providing a total pore volume of about 1 ml/g. They are biologically inert particles that are made of synthetic polymers and protect the entrapped drug moiety from physical and environmental degradation. Their high degree of cross-linking make them insoluble, inert and have sufficient strength to withstand high shear commonly used in manufacturing of creams, lotions, and powders[5].

The microsponge systems can also prevent excessive accumulation of ingredients within the epidermis and the dermis. Potentially, the microsponge system can significantly reduce the irritation of effective drugs without reducing their efficacy. Thus, MDS proves a new generation of very well-tolerated and highly efficacious, novel products

Yet a safety concern is the potential bacterial contamination of the materials entrapped in the microsponges. As the size of the pore diameter is smaller, the bacteria ranging from 0.007 to 0.2 µm cannot penetrate into the tunnel like porous structure of the microsponges[6].

Characteristics of Microsponges[7]

- These are stable over range of pH 1 to 11;
- These are stable at temperature up to 130°C;
- These are compatible with most vehicles and ingredients;
- These are self sterilizing as their average pore size is 0.25µm where bacteria cannot

penetrate;

- These are non irritant, non mutagenic, non toxic and non greasy;
- These have higher payload (50 to 60%), still free flowing and can be cost effective.

Advantages[5, 8]:

- Oil control: it can absorb oil up to 6 times its weight without drying
- Continuous sustained release up to 12 hours
- Reduced irritancy and better tolerance improves patient compliance
- Superior formulation flexibility and high payload
- Improved thermal, physical and chemical stability
- Allow incorporation of immiscible products
- Improvement of product aesthetics and elegance
- Flexibility to develop novel product forms
- Improves material processing e.g. liquids can be converted into powders
- Improves efficacy and enhanced bioavailability

Characteristics of active ingredients[4]

Mostly liquid or soluble ingredients can be entrapped but immiscible compounds have also been studied. Active ingredients 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

Preparation of Microsponges

Based on the physico-chemical properties of the drug to be loaded, microsponges can be prepared by two methods: one step process or two steps process with respective in liquid-liquid suspension polymerization and quasi emulsion solvent diffusion techniques. If the drug is typically an inert non-polar material, it will create the porous structure called porogen. Porogen drug is that which neither hinders the polymerization nor become activated by it and stable to free radicals if entrapped with one step process.

Liquid- liquid suspension polymerisation:

The porous microspheres are prepared by various steps of suspension polymerization technique

in liquid-liquid systems as shown in figure 1. Immiscible monomers are first dissolved along with active ingredients in a suitable solvent containing monomer and are then dispersed in the aqueous phase having additives like surfactants, suspending agents etc. to facilitate formation of suspension. The polymerization is then activated by increasing temperature or irradiation or by addition of catalyst[9].

The polymerization process continues until the formation of a reservoir type of system with spherical structure (figure 2). After the polymerization process the solvent is removed leaving the spherical structured porous microspheres, i.e., microsponges. Microsponges are then washed and processed to make them ready for use. Particle formation and incorporation of active drug results in a single step[10]. The microsponge product can be made using styrene and divinyl benzene or methyl methacrylate and ethylene glycol dimethacrylate as starting materials.

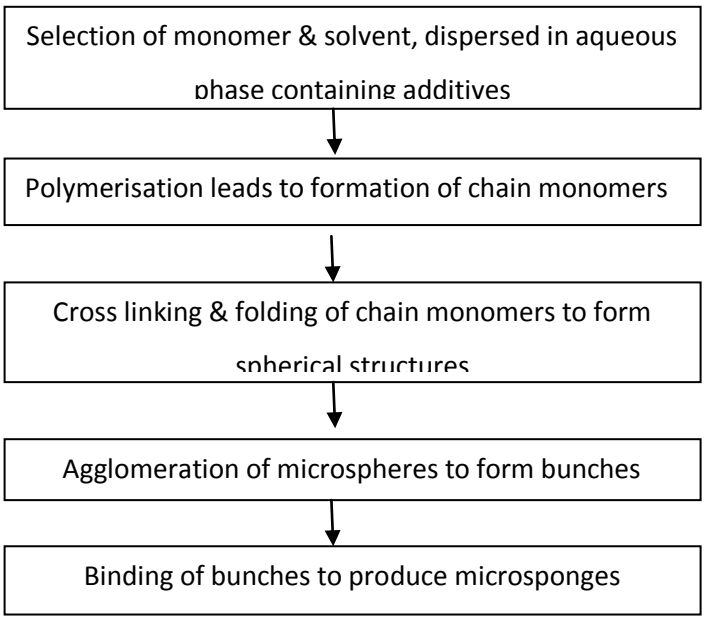

Figure 1. Steps in preparation of Microsponges

Quasi-Emulsion Solvent Diffusion:

he microsponges prepared by quasi-emulsion solvent diffusion method is a two step process (Top-down approach) using an external phase of distilled water and polyvinyl alcohol (PVA) 72 000. The internal phase consists of drug, ethyl alcohol, polymer and tri-ethylcitrate (TEC), which is added at an amount of 20% of the polymer in order to facilitate the plasticity. Initially, internal phase is prepared at 60°C and then added to the external phase at room temperature. After emulsification, the mixture is continuously stirred for 2 hours and filtered to separate the microsponges (figure 3). The product iss washed and dried by vacuum oven at 40°C for 24 hours[11].

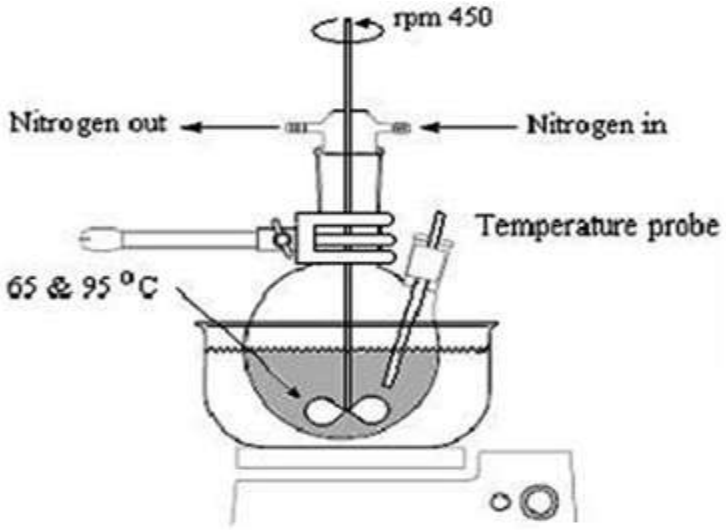

Figure 2. Microsponge preparation by liquid-liquid suspension polymerisation

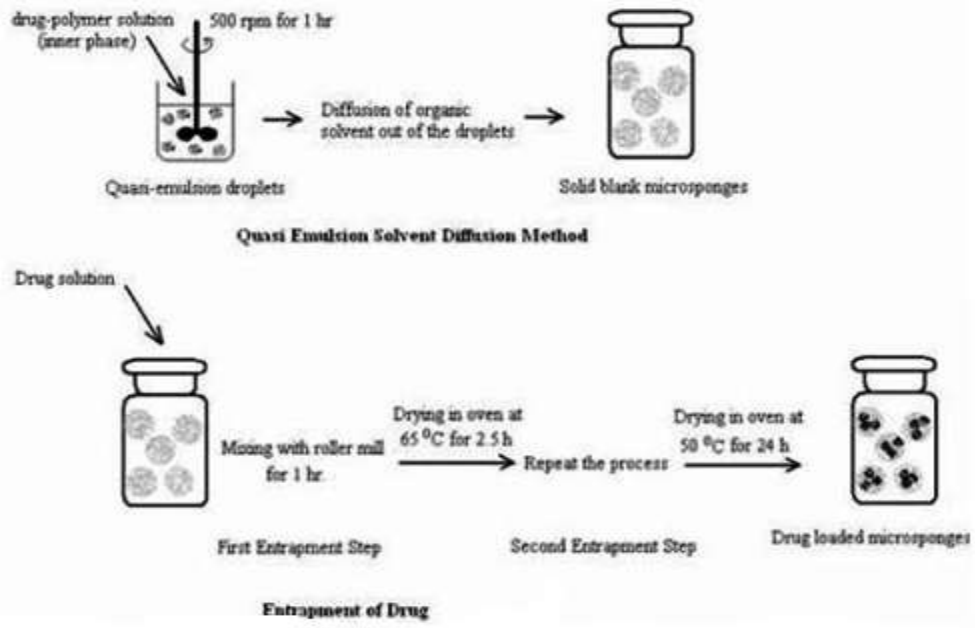

Figure 3. Microsponge preparation by Quasi-emulsion solvent diffusion method

Release Mechanism

Release of drug from microsponges is affected by altering the active drug/polymer ratio, polymer wall thickness, porosity etc. Microsponges are open, porous structures where drug can move in and out of the particles and into the vehicle to reach equilibrium[12, 13]. On applying the final product on skin, the active drug present in the vehicle is absorbed making the vehicle unsaturated, thus disturbing the equilibrium. This will initiate movement of drug from particles to the vehicle and eventually to the skin until the vehicle is absorbed. However, prolonged release of drug is maintained by gradual release from retained microsponges on stratum corneum of skin. This proposed release mechanism emphasizes the importance of selection of formulating

vehicles in microsponge preparations. If the active drug is too soluble in the vehicle, it will not provide the advantage of gradual prolonged release but rather act as if added in free form. Solvent should have minimal solubilizing power for the active drug which is not the case of conventional topical preparations.

Another way to avoid unwanted leaching of the drug from the microsponge polymer is to formulate the product with some free and some entrapped drug, so the vehicle is pre saturated. In this case there will not be any leaching of the drug of polymer during compounding. The rate of drug release will ultimately depend not only on the partition coefficient between the polymer and the vehicle (or the skin), but also on characteristic parameters of the beads like surface area and mean pore diameter[14]. Release can also be controlled through diffusion or other triggers such as moisture, pH, friction or temperature.

PROGRAMMABLE RELEASE[15]

(i) Pressure triggered systems

Microsponges release the entrapped drug material when pressurized or rubbed on skin; however the amount of drug released depends upon various characteristics of the sponge. By varying the type of polymer and different process variables, microsponges can be optimized for best release. On comparison with mineral oil containing microcapsules, mineral oil containing microsponge showed much more softening effect and the duration of emolliency was also much more for the microsponge systems.

(ii) Temperature triggered systems

Some entrapped active ingredients are too viscous at room temperature to flow spontaneously from microsponges onto the skin. Flow rate and release of such systems can be modulated by increased in skin temperature. Hence it is possible to alter release of substances from the microsponge by modulation of temperature. For example, viscous sunscreens were found to show higher release rate from microsponges when exposed to higher temperatures; thus a sunscreen would be released from a microsponge only upon exposure to heat from the sun.

(iii) pH triggered systems

By modifying the coating of the microsponges, a pH-based release of the active can be triggered. This has numerous applications in drug delivery of medicaments.

(iv) Solubility triggered systems

Microsponges loaded with water-soluble ingredients like anti-perspirants and antiseptics will release the ingredient in the presence of water. So, release rate of active drug can be achieved in the presence of an aqueous medium such as perspiration. Thus release is based on the ability of

the external medium to dissolve the active ingredient, its concentration gradient or the ability of microspore to swell.

PHYSICAL CHARACTERIZATION OF MICROSPONGES

(i) Particle size determination

Particle size analysis of loaded and unloaded microsponges can be done by laser light diffractometry[16] or any other suitable method. The values are expressed as mean size ranges for all formulations. 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 grittiness. So particles of size range between 10 - 25µm are preferred to be used in topical formulations.

(ii) 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 can be studied by scanning electron microscopy[17] (SEM). SEM of a fractured microsponge particle can be studied to explain its micro & ultra structure.

(iii) Determination of loading efficiency and production yield[13]

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

Loading efficiency = (Actual Drug Content/ Theoretical Drug Content) X 100

The production yield of the microsponges 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/Theoretical mass(Polymer+drug)] X 100

(iv) Determination of true density

The true density of microsponges can be determined using an ultra-pycnometer under helium gas using displacement method[18] and is calculated from a mean of repeated determinations.

(v) Characterization of pore structure[19- 20]

Pore volume and diameter are important in controlling the intensity and duration of effectiveness of the active drug. Pore diameter affects the migration of active drug from microsponges into the vehicle in which the material is dispersed. Mercury intrusion porosimetry[21] can be used to study the 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.

(vi) Compatibility studies

Compatibility of drug with reaction adjuncts & excipients can be studied by thin layer chromatography (TLC) and Fourier Transform Infra-red spectroscopy (FT-IR). Effect of polymerization on drug crystallinity can be studied by powder X-ray diffraction (XRD) and Differential Scanning Colorimetry[22-24] (DSC). For DSC, 5 mg sample is accurately weighed into aluminum pans, sealed and run at a heating rate of 15°C/min over a temperature range of 25–430°C in inert atmosphere of nitrogen.

(vii) Polymer/monomer composition

Microsphere size, drug loading and polymer composition are key factors in governing the drug release from microspheres[25]. Polymer composition can affect partition coefficient of the entrapped drug between the vehicle and microsponge 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.

(viii) Resiliency (viscoelastic properties)

Resiliency (viscoelastic properties) of microsponges can be modified to produce beadlets that are softer or firmer according to the need of the final formulation. It can be studied and optimized by considering release as a function of cross-linking with time[19]. Increased cross-linking tends to slow down the rate of release.

(ix) Dissolution studies

Drug dissolution profile of microsponges can be studied by use of dissolution apparatus USP XXIII with a modified basket consisting of 5µm stainless steel mesh. The speed of the rotation is set as 150 rpm. The dissolution medium is selected by considering solubility of active drug to ensure sink conditions[26]. Samples from the dissolution medium can be analyzed by suitable analytical method like UV spectrophotometer at various intervals.

(x) Drug release from semi solid dosage forms: Drug release studies from the semi solid dosage forms are performed by the Franz- type static diffusion cells. In this epidermal side of the skin is exposed to ambient conditions. While dermal side is kept facing the receptor solution. Receptor compartment contains 20mL phosphate buffer pH 5.8 which is thermo stated at 32±0.5°C and stirred at 600 rpm. Skin is saturated with diffusion medium for 1 h before the application of sample. A 200-mg of sample is applied on the donor compartment. For determination of drug deposited in the skin, the diffusion cell is dismantled after a period of 4, 8, 16, and 24 h. The skin is carefully removed, and drug present on the skin surface is cleaned with distilled water[27].

(xi) Kinetics of release

To determine the drug release mechanism and to compare differences in release profile among microsponges, the drug released amount versus time was used. The release data were analyzed with the following mathematical models:

$$\mathbf{Q = k_1 t^n \text{ or } \log Q = \log k_1 + n \log t}$$

Where **Q** is the amount of the released at time (h), **n** is a diffusion exponent which indicates release mechanism, and $\mathbf{k_1}$ is a constant characteristic of the drug– polymer interaction. From the slope and intercept of the plot of log Q versus log t, kinetic parameters **n** and $\mathbf{k_1}$ were calculated. For comparison purposes, the data was also subjected to a simple, Higuchi type equation:

$$\mathbf{Q = k_2\, t^{0.5} + C}$$

For release data dependent on the square root of time, it would give a straight line release profile, with k_2 presented as a root time dissolution rate constant and C as a constant.

(xii) Safety data

Micropsonges should be made of polymers which are non-irritating, non-mutagenic, non-allergenic, non-toxic and non-biodegradable[28]. In order to check their safety and non-antigenicity for human use, they are tested for skin irritation in rabbits & humans, eye irritation in rabbits, oral toxicity in rats, mutagenicity in bacteria and allergenicity in guinea pigs[29].

Applications of Microsponge Systems

Microsponge delivery systems are used to potentiate the safety, efficacy and aesthetic quality of topical preparations, over-the-counter and personal care products. Several products under development or in the market place utilize the Topical Microsponges 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 only.

Release of active ingredients from conventional topical formulations over an extended period of time is quite difficult to achieve. Cosmetics and skin care preparations are intended to work only on the outer skin layers. The active ingredient in conventional products is present in a relatively high concentration and is intended to be absorbed when applied to the skin. The common result is overmedication, followed by a period of under medication until the next application. Rashes and other side effects can occur when the active ingredients penetrate rapidly below the skin's surface. Microsponge technology is designed to allow a prolonged rate of release of the active ingredients, thereby offering possible reduction in the side effects while maintaining the therapeutic efficacy[30]. Microsponges are porous, polymeric microspheres that are commonly

used for topical and recently for oral administration also.

Microsponges are designed to deliver a pharmaceutical active ingredient efficiently at a minimum dose and also to enhance stability, reduce side effects and modify drug release (table 1).

Table 1. Applications of Microsponges

Active Agents	Applications
Sunscreens	Long lasting product efficacy, with improved protection against sunburns and sun related injuries even at elevated concentration and with reduced irritancy and sensitization.
Anti-acne e.g. Benzoyl peroxide	Maintained efficacy with decreased skin irritation and sensitization.
Anti-inflammatory e.g. hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatoses.
Antifungals	Sustained release of actives.
Antidandruff e.g. zinc pyrithione, selenium sulphide	Reduced unpleasant odour with lowered irritation with extended safety and efficacy.
Antipruritics	Extended and improved activity.
Skin depigmenting agents e.g. Hydroquinone	Improved stabilization against oxidation with improved efficacy and aesthetic appeal.
Rubefacients	Prolonged activity with reduced irritancy greasiness and odour.

(i) Micropsonges in Topical Drug Delivery

Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne and athletes foot causing skin irritation, a common side effect[31]. By reducing the percutaneous absorption of BPO by formulation into a controlled release delivery system, this side effect can be minimised[32-34]. Benzoyl peroxide microparticles were prepared using 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. Disorders of hyperpigmentation such as melasma and postinflammatory hyperpigmentation (PIH) are common, particularly in people with darker skin types. Hydroquinone (HQ) bleaching creams are gold standards for treating hyperpigmentation[35]. For the treatment of melasma and PIH, a new formulation containing HQ 4% with retinol 0.15% entrapped in microsponge reservoirs was developed release HQ gradually to prolong duration of treatment and to minimize skin irritation[36].

Mupirocin microsponges were prepared and optimized by an emulsion solvent diffusion method and incorporated into an emulgel base[37]. Drug release through cellulose dialysis membrane showed diffusion controlled release pattern and drug deposition studies using rat abdominal skin exhibited significant retention of active drug in skin from microsponge based formulations in 24

h. Draize patch test showed the optimized formulation to be stable and non-irritant. Microsponges-based emulgels 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 efficacy for treatment of primary and secondary skin infections such as impetigo, eczema and atopic dermatitis.

Fluconazole is an active topical agent against yeasts, yeast-like fungi and dimorphic fungi, causing skin irritation. Microsponge based delivery system using fluconazole with an appropriate drug release pattern to remarkably decrease irritation. Microsponges were prepared by liquid-liquid suspension polymerization of styrene and methyl methacrylate and dispersed in gel containing carbopol 940 and evaluated for drug release using Franz diffusion cell. The average drug release from the gel containing microspongic fluconazole was found to be 67.81 % in 12 h. Drug release from the gels containing microsponge loaded fluconazole and marketed formulations has followed zero order kinetics (r = 0.973, 0.988 respectively)[38]. Drug diffusion study reveals extended drug release from microsponges on comparison with marketed formulations containing un-entrapped fluconazole.

An MDS system for retinoic acid was also developed and tested for drug release and anti-acne action. Entrapped tretinoin demonstrated statistically significant reductions in inflammatory and non-inflammatory lesions[39].

(ii) Microsponges in Oral Drug Delivery

Microsponges increase the rate of solubilization of poorly water soluble drugs orally by entrapping them in the microsponge pores. For incorporation in microscopic pores, drug is reduced in size which significantly increased the surface area and thus enhances the rate of solubilization.

Controlled oral delivery of ibuprofen microsponges is achieved with an acrylic polymer, eudragit RS, by changing their intraparticle density. The release of ketoprofen from modified release microsponge 200 mg tablets and Profenid Retard 200 mg was studied in vitro and in vivo. The formulation containing ketoprofen microsponges offered good modified release. An in vivo study was designed to evaluate the pharmacokinetic parameters and to compare them with the commercially available ketoprofen retard tablets. Commercial ketoprofen retard tablets showed a more rapid absorption rate than modified release tablets and C_{max} was reached within 3.6 h after administration. However, the new modified release tablets showed a slower absorption rate and peak levels were reached 8 h after administration[11].

A Microsponge system also servesl to hold active drug protected from the environment and provide controlled delivery of oral medication to the lower gastrointestinal (GI) tract, where release will be triggered by action of specific enzymes in the colon. This approach opens up entirely new opportunities for use of MDS in colon specific targeting of drugs. Paracetamol loaded eudragit based microsponges were prepared using quasi-emulsion solvent diffusion method and compressed as tablets for colon targeting followed by coating with pectin: hydroxypropylmethylcellulose (HPMC) mixture. In vitro release studies exhibited that compression coated colon specific tablet formulations started releasing the drug at 6th hour corresponding to the arrival time at proximal colon[40].

Dicyclomine loaded, Eudragit based microsponges were prepared using a quasi-emulsion solvent diffusion method[41]. Kinetic analysis showed drug release pattern to follow Higuchi matrix controlled diffusion model. Drug release was biphasic with an initial burst/loading effect releasing 16 – 30 % of the drug in the first hour[40, 42]. Cumulative release for the microsponges over 8 hours ranged from 59 - 86 %.

Microsponges containing flurbiprofen (FLB) and Eudragit RS 100 were prepared by quasi-emulsion solvent diffusion method. Additionally, FLB was entrapped into a commercial Microsponge® 5640 system using entrapment method. The colon specific formulations were prepared by compression coating and also pore plugging of microsponges with pectin:HPMC mixture followed by tableting. Mechanically strong tablets prepared for colon specific drug delivery were obtained owing to the plastic deformation of sponge-like structure of microsponges. In vitro studies exhibited that compression coated colon specific tablet formulations started to release the drug at the 8th hour corresponding to the proximal colon arrival time due to the addition of 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 8th hour which was the time point that the enzyme acts[43].

(iii) Microsponges in Bone Tissue Engineering

3D biodegradable porous scaffolds play a vital role in articular cartilage tissue engineering. The hybrid structure of 3D scaffolds was developed that combined the advantages of natural type I collagen and synthetic PLGA knitted mesh[44]. The mechanically strong PLGA mesh served as a skeleton while the collagen microsponges facilitated cell seeding and tissue formation. The scaffolds were divided into 3 groups:

(1) THIN: collagen microsponge formed in interstices of PLGA mesh;

(2) SEMI: collagen microsponge formed on one side of PLGA mesh;

(3) SANDWICH: collagen sponge formed on both sides of PLGA mesh.

Bovine chondrocytes were cultured in these scaffolds and transplanted subcutaneously into nude mice for 2, 4 and 8 weeks. All three groups of transplants showed homogeneous cell distribution, natural chondrocyte morphology 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. When compared to native articular cartilage, the mechanical strength of the engineered cartilage reached 54.8%, 49.3% in Young's modulus and 68.8%, 62.7% in stiffness, respectively, in SEMI and SANDWICH. These scaffolds could be used for the tissue engineering of articular

cartilage with adjustable thickness. The design of the hybrid structures provides an approach for the preparation of 3D porous scaffolds.

A novel 3-D porous scaffold has been developed for bone tissue engineering by hybridizing synthetic poly (DL-lactic-co-glycolic acid) (PLGA), naturally derived collagen, and inorganic apatite[45]. First, a porous PLGA sponge was prepared. Then, collagen microsponges were formed in the pores of the PLGA sponge. Finally, apatite particulates were deposited on the surfaces of the collagen microsponges in the pores of PLGA sponge. The PLGA-collagen sponge served as a template for apatite deposition and the deposition was accomplished by alternate immersion of PLGA–collagen sponge in $CaCl_2$ and Na_2 HPO_4 aqueous solutions and centrifugation. The deposited particulates were small and scarce after one cycle of alternate immersion. Their number and size increased with the number of alternate immersion cycles. The surfaces of collagen microsponges were completely covered with apatite after three cycles of alternate immersion. The porosity of the hybrid sponge decreased gradually as the number of alternate immersion increased. Energy dispersive spectroscopy analysis and X-ray diffraction spectra showed that the calcium to phosphorus molar ratio of the deposited particulates and the level of crystallinity increased with the number of alternate immersion cycles and became almost the same as that of hydroxyapatite after four cycles of alternate immersion. The deposition process was controllable. Use of the PLGA sponge as a mechanical skeleton facilitated formation of the PLGA–collagen– apatite hybrid sponge into desired shapes and collagen microsponges facilitated the uniform deposition of apatite particulates throughout the sponge. The PLGA–collagen–apatite hybrid sponge would serve as a useful three-dimensional porous scaffold for bone tissue engineering.

(iv) Microsponges in Cardiovascular Engineering

Biodegradable material with autologous cell seeding requires a complicated and invasive

procedure that carries the risk of infection. To avoid such problems, a biodegradable graft material containing collagen microsponge that permits the regeneration of autologous vessel tissue has been developed. The ability of this material to accelerate in situ cellularization with autologous endothelial and smooth muscle cells was tested with and without precellularization.

Poly (lactic-co-glycolic acid) as a biodegradable scaffold was compounded with collagen microsponge to form a vascular patch material[46]. These poly (lacticco- glycolic acid)-collagen patches with (n = 10) or without (n = 10) autologous vessel cellularization were used to patch the canine pulmonary artery trunk. Histologic and biochemical assessments were performed 2 and 6 months after the implantation. There was no thrombus formation in either group and the poly (lactic-co-glycolic acid) scaffold was almost 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 fibres. The cellular and extracellular components in the patch had increased to levels similar to those in native tissues 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.

(v) Microsponges in Reconstruction of vascular wall

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[47]. 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). Histologic 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 immuno staining. The quantification of the cell population by polymerase chain reaction showed a large number of endothelial and smooth muscle cells 2 months after implantation. In the large graft model, the architecture of the patch was similar to that of native tissue 6 months after implantation and this patch can be used as a novel surgical material for the repair of the cardiovascular system.

MARKETED FORMULATIONS

Microsponge delivery system is ideal for skin and personal care products. They can absorb large amounts of excess skin oil, while retaining an elegant feel on the skin's surface. This technology is currently used in numerous products majorly covering cosmetic and toiletry companies globally[48]. These products include skin cleansers, conditioners, oil control lotions, moisturizers,

deodorants, razors, lipstick, makeup, powder and eye shadows; which offer added advantages of improved physical and chemical stability, higher drug concentrations, controlled release of active ingredients, decreased skin irritation and sensitization, and unique tactile qualities.

Marketed formulation using the MDS includes Ethical Dermatological products **(**APS defined ethical dermatology products as prescription and non-prescription drugs that are promoted primarily through the medical profession for the prevention and treatment of skin problems or diseases). Several ethical dermatological products approved by USFDA, OTC and personal care products are sold in the United States (listed in Table 2). Results from various human clinical studies proved that the technology offers the potential to reduce the drug side effects, maintain the therapeutic efficacy and potentially increase patient compliance with the treatment regimen.

Table 2. List of Marketed products formulated using microsponge delivery systems

NeoBenz®Micro, Neo®MicroSD NeoBenz®Microwash	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 crosspolymer. This polymeric 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.	Intendis Inc. Morristown NJ07962 USA
Retin-A-Micro	0.1% and 0.04% tretinoin entrapped in MDS for topical treatment of acne vulgaris. This formulation uses patented methyl methacrylate/ glycol dimethacrylate cross-polymer porous microspheres to enable inclusion of the active ingredient, tretinoin, in an aqueous gel.	Ortho-McNeil Pharmaceutical , Inc.
Retinol cream, Retinol 15 Night cream	A night time treatment cream with Microsponge technology using a stabilized formula of pure retinol, Vitamin A. Continued use of Retinol 15 will result in the visible diminishment of fine lines and wrinkles, a noticeable improvement in the skin discolorations due to aging, and enhanced skin smoothness.	Biomedic, Sothys
Carac Cream	Carac Cream contains 0.5% fluorouracil, with 0.35% being incorporated into a patented porous microsphere (Microsponge) composed of methyl methacrylate / glycol dimethacrylate cross-polymer and dimethicone. Carac is a once-a-day topical prescription product for the treatment of actinic keratosis (AK), a common pre-cancerous skin condition caused by over-exposure to the sun.	Dermik Laboratories, Inc. Berwyn , PA 19312 USA
Line Eliminator Dual Retinol Facial Treatment	Lightweight cream with a retinol (Vitamin A) in MDS, dual-system delivers both immediate and time released wrinkle-fighting action. Visibly diminishes appearance of	Avon

	fine lines, wrinkles & skin discolorations associated with aging.	
Salicylic Peel 20	Deep BHA peeling agent for (professional use only): Salicylic acid 20%, Microsponge Technology, Excellent exfoliation and stimulation of the skin for more resistant skin types or for faster results. Will dramatically improve fine lines, pigmentation, and acne concerns.	Biophora
Salicylic peel 30	Deeper BHA peeling agent for (professional use only): Salicylic acid 30%, Microsponge Technology, Most powerful exfoliation and stimulation of the skin. For more resistant skin types or for faster results. Will dramatically improve fine lines, pigmentation and acne concerns.	Biophora
Micro Peel Plus/ Acne Peel	The MicroPeel® Plus procedure stimulates cell turnover through the application of salicylic acid in the form of microcrystals using Microsponge® technology. These microcrystals target the exact areas on 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.	Biomedic
EpiQuin Micro	The Microsponge® system uses microscopic reservoirs that entrap hydroquinone and retinol. The microsponges 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. EpiQuin Micro is a prescription moisturizing fading cream that reduces the impact of these conditions known as melasma, post inflammatory hyper pigmentation or solar lentigines. Also help in Age spots, Sun spots, Facial discoloration	Skinmedica Inc
Sportscream RS and XS	Topical analgesic-anti-inflammatory and counter irritant actives in a Microsponge® Delivery System (MDS) for the management of musculoskeletal conditions	Embil Pharmaceutical Co.Ltd.
Oil free matte block spf20	This invisible oil-free sunscreen shields the skin from damaging UV sun rays while controlling oil production, giving you a healthy matte finish. Formulated with microsponge technology, Oil Free Matte Block absorbs oil, preventing shine without any powdery residue.	Dermalogica
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. Eliminate shine for hours with this feature-weight lotion, formulated with oil-absorbing Microsponge technology. The naturally- antibiotic Skin Response Complex soothes inflammation and tightness to promote healing. Acne-Prone, oily skin conditions.	Fountain Cosmetics
Lactrex™ 12% Moisturizing Cream	Lactrex™ 12% Moisturizing Cream contains 12% lactic acid as the neutral ammonium salt, ammonium lactate. Microsponge® technology has been included for comfortable application and long lasting moisturization.	SDR Pharmaceuticals,Inc., Andover, NJ,

	Lactrex™ also contains water and glycerin, a natural humectant, to soften and help moisturize dry, flaky, cracked skin.	U.S.A. 07821
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. Salicylic Acid clears congested follicles to minimize future breakout activity, while Enantia Chlorantha Bark Extract controls over-active oil glands, helping to reduce oily shine on skin's surface.	John and Ginger Dermalogica Skin Care Products
Aramis fragrances	24 Hour High Performance Antiperspirant Spray Sustained release of fragrance in the microsponge. The microsponge comes in the form of an ultra light powder, and because it is micro in size, it can absorb fragrance oil easily while maintaining a free-flowing powder characteristic where release is controlled due to moisture and temperature.	Aramis Inc.
Ultra Guard	Microsponge system that contains dimethicone to help protect a baby's skin from diaper rash. The new wipe contains a skin protectant that helps keep wetness and irritants from the baby's skin. The solution is alcohol-free, hypoallergenic and contains dimethicone, an ingredient found in baby creams, lotions and skin protectants.	Scott Paper Company

PATENTS OF MICROSPONGE PRODUCTS

(i) In September 1, 1987, Won; Richard (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[49] (United States Patent 4, 690, 825).

(ii) September 8, 1992, won; Richard (Palo Alto, CA) of Advanced Polymer Systems, Inc. (Redwood City, CA) received US patent for developing Two-step method for preparation of controlled release formulations[50] (United States Patent 5, 145, 675).

(iii) 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[51].

(iv) Advanced Polymer Systems Inc. has been granted a patent for the use of its Microsponge technology in tretinoin formulations. The patent will provide coverage through September 21,

2016[52].

(v) EpiQuin® Micro Hydroquinone USP 4%, under license from Amcol Intl. Corp. U.S. Patent Numbers 5, 851, 538 and 6, 896, 890[53].

CONCLUSION

Microsponges offer distinct advantages over conventional dosage forms by entrapping wide variety of drugs in its porous structure. In spite of its wide application in topical, oral, bone & tissue engineering, they also offer controlled release of medicaments triggered by stimulus of temperature, pressure & solubility. Formulations can be developed with 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. Future perspectives include nanosponges, microsponges in oral care cosmetic, long lasting coloured cosmetics & natural actives. MDS holds a promising future in various pharmaceutical applications in the coming years as they have unique properties like extended release, reduced irritancy, small size, self sterility and compatiblility with most vehicles and ingredients provide flexiblility to develop novel product forms.

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