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Review Article

MICROSPONGES AS THE VERSATILE TOOL FOR DRUG DELIVERY SYSTEM

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ABSTRACT

Microsponge technology has been introduced in topical drug products to facilitate the controlled release of active drug into the skin in order to reduce systemic exposure and minimize local cutaneous reactions to active drugs. Microsponge consists of macroporous beads, typically 10-25 microns in diameter, loaded with active agent. When applied to the skin, the microsponge releases its active ingredient on a time mode and also in response to other stimuli (rubbing, temperature, pH, etc) that are used mostly for topical and recently for oral administration. Microsponge technology has many favorable characteristics which make it a versatile drug delivery vehicle. Microsponge Systems can suspend or entrap a wide variety of substances, and then be incorporated into a formulated product such as a gel, cream, liquid or powder. The outer surface is typically porous, allowing the sustained flow of substances out of the sphere. Microsponge delivery system (MDS) can provide increased efficacy for topically active agents with enhanced safety, extended product stability, enhanced formulation flexibility, reduced side effects and improved aesthetic properties in an efficient and novel manner. In addition these are non-irritating, non-mutagenic, non-allergenic, and non toxic. The present review introduces Microsponge technology along with its synthesis, characterization, programmable parameters and release mechanism of MDS.

Keywords: Microsponge, Controlled release, Topical drug delivery, Oral drug delivery.

INTRODUCTION

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. 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[1]. No efficient vehicles have been developed for controlled and localized delivery of drugs into the stratum corneum and underlying skin layers and not beyond the epidermis[2]. 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[3] . 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. These vehicles require a high concentration of active agents for effective therapy because of their low efficiency of delivery system, resulting in irritation and allergic reactions in significant users. Other drawbacks of topical formulations are uncontrolled evaporation of active ingredient, unpleasant odor. The fundamental appeal of the Microsponge technology stems from these difficulties experienced with conventional formulations in releasing active ingredients over an extended period of time. Conventional dermatological products typically provide

active ingredients in relatively high concentrations but with a short duration of action. This may lead to a cycle of short-term overmedication followed by long-term under medication. Rashes or more serious side effects can occur when active ingredients penetrate the skin. In contrast, Microsponge technology allows an even and sustained rate of release, reducing irritation while maintaining efficacy. Microsponge delivery systems are uniform, spherical, porous polymeric microspheres having myriad of interconnected voids of particle size range 5-300μm (Figure 1). These microsponges have the capacity to entrap a wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens and anti-infective, etc. are used as a topical carrier system[4] . Microspheres, averaging 25 μm in diameter[5] and embedded in the vehicle, act like microscopic sponges, storing the active drug until its release is triggered by application to the skin surface. Micropores within the spheres comprise a total pore density of approximately 1ml/g, and pore length 10ft for extensive drug retention. Further these porous microspheres with active ingredients can be incorporated in to formulations such as creams, lotions and powders. Microsponges consisting of non-collapsible structures with porous surface through active ingredients are released in a controlled manner[3]. Release of drug into the skin is initiated by a variety of triggers, including rubbing and higher than ambient skin temperature.

Their high degree of cross-linking results in particles that are insoluble, inert and of sufficient strength to stand up to the high shear commonly used in manufacturing of creams, lotions, and powders. Their characteristic feature is the capacity to adsorb or "load" a high degree of active materials into the particle and on to its surface. Its large capacity for entrapment of actives, up to three times its weight, differentiates microsponge products from other types of dermatological delivery systems. The active payload is protected in the formulation by the microsponge particle; it is delivered to skin via controlled diffusion. This sustained release of actives to skin over time is an extremely valuable tool to extend the efficacy and lessen the irritation commonly associated with powerful therapeutic agents like α-hydroxy acids which may produce burning, stinging or redness in individuals with sensitive skin. Microsponge polymers possess the versatility to load a wide range of actives providing the benefits of enhanced product efficacy, mildness, tolerability, and extended wear to a wide range of skin therapies[6]. When microsponge delivery system applied to the skin, the release of drug can be controlled through diffusion or other variety of triggers, including rubbing, moisture, pH, friction, or ambient skin temperature.

The microsponge technology was developed by Won in 1987, and the original patents were assigned to Advanced Polymer Systems, Inc[7]. 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.

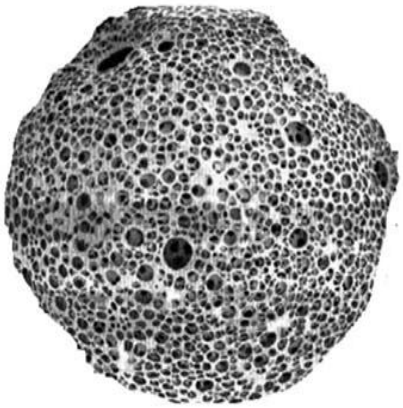

Fig. 1: Highly porous nature of a Microsponge

CHARACTERISTICS OF MICROSPONGES[8]

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

free flowing and can be cost effective.

CHARACTERISTICS OF MATERIALS THAT IS ENTRAPPED IN MICROSPONGES[9]

Most liquid or soluble ingredients can be entrapped in the particles. Actives that can be entrapped in microsponges must meet following requirements,

- It should be either fully miscible in monomer or capable of being made miscible by addition of small amount of a water immiscible solvent.
- It should be water immiscible or at most only slightly soluble.
- It should be inert to monomers.
- The solubility of actives in the vehicle must be limited to avoid cosmetic problems; not more than 10 to 12% w/w microsponges must be incorporated into the vehicle. Otherwise the vehicle will deplete the microsponges before the application.
- The spherical structure of microsponges should not collapse.
- Polymer design and payload of the microsponges for the active must be optimized for required release rate for given time period.
- It should be stable in contact with polymerization catalyst and conditions of polymerization[8].

DRUGS EXPLORED IN MDS[9-12]

- Kotoprofen
- Benzyl peroxide
- Retinol
- Fluconazole
- Ibuprofen
- Tretinoin
- Trolamine

FORMULATION AIDS

Various polymers can form a microsponge 'cage'. These include Ethyl Cellulose, Eudragit RS100, Polystyrene and PHEMA[13-16]. In addition to actives; some microsponges contain plasticizers that help stabilize their structure.

ADVANTAGES OVER CONVENTIONAL FORMULATIONS

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

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°C; compatible with most vehicles and ingredients; self sterilizing as average pore size is 0.25µm where bacteria cannot penetrate; higher payload (50 to 60%), still free flowing and can be cost effective.

ADVANTAGES OVER OINTMENTS

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.

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 are based on physicochemical 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) Liquid-liquid suspension polymerization

The porous microspheres are prepared by suspension polymerization method in liquid-liquid systems[10]. In their preparation, the monomers are first dissolved along with active ingredients in a suitable solvent solution of monomer and are then dispersed in the aqueous phase, which consist of additives (surfactant, suspending agents, etc.). The polymerization is then initiated by adding catalyst or by increasing temperature or irradiation (Shown in Figure 2)

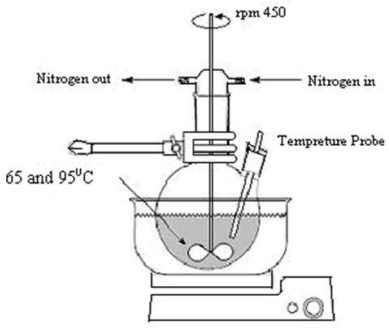

Fig. 2: Reaction vessel for Microsponge Preparation by Liquid liquid suspension method

The various steps in the preparation of microsponges are summarized as14

- Selection of monomer or combination of monomers.
- Formation of chain monomers as polymerization begins.
- Formations of ladders as a result of cross linking between chain monomers.
- Folding of monomer ladder to form spherical particles- Agglomeration of microspheres, which give rise to formation of bunches of microspheres.
- Binding of bunches to form microsponges.

The polymerization process leads to the formation of a reservoir type of system, which opens at the surface through pores. In some cases an inert liquid immiscible with water but completely miscible with monomer is used during the polymerization to form the pore network. After the polymerization the liquid is removed leaving the porous microspheres, i.e., microsponges. Impregnating them within preformed microsponges then incorporates the functional substances.

Sometimes solvent may be used for faster and efficient incorporation of the active substances. The microsponges act as a topical carriers for variety of functional substances, e.g. Anti-acne, anti-inflammatory, anti purities, anti fungal, rubefacients, etc[4]. When the drug is sensitive to the polymerization conditions, two-step process is used. The polymerization is performed using substitute porogen and is replaced by the functional substance under mild experimental conditions[17].

(ii) Quasi-emulsion solvent diffusion

This is a two step process where the microsponges can be prepared by quasi-emulsion 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) [18].

RELEASE MODULATION

In general, microsponges retard the release of the drug. Various groups have studied the release of actives from such systems[19- 24]. Some studies have shown an improved rate of release by increasing the active / polymer ratio and lowering the polymer wall thickness; however these results are not supported by another set of studies. Thus, there seem to be many other factors affecting the release of the drug from the microsponges. Another important

parameter that governs the release seems to be the pore diameter[5] however; another study [13] has shown that even the overall porosity (including the pore diameter and the number of pores) also affects the drug release.

The microsponge particles have an open structure and the active is free to move in and out from the particles and into the vehicle until equilibrium is reached. Once the finished product is applied to the skin, the active that is already in the vehicle will be absorbed into the skin, depleting the vehicle, which will become unsaturated, therefore disturbing the equilibrium. This will start a flow of the active from the microsponge particle into the vehicle and from it to the skin until the vehicle is either dried absorbed. Even after that the microsponge particles retained on the surface of stratum corneum will continue to gradually release the active to the skin, providing prolonged release over time. This proposed mechanism of action highlights the importance of formulating vehicles for use with microsponge entrapments. If the active is too soluble in the desired vehicle during compounding of finished products, the products will not provide the desired benefits of gradual release. Instead they will behave as if the active was added to the vehicle in a free form. Therefore, while formulating microsponge entrapments, it is important to design a vehicle that has minimal solubilizing power for the actives. The principle is contrary to the conventional formulation principles usually applied to the topical products. For these conventional systems it is normally recommended to maximize the solubility of the active in the vehicle. When using microsponge entrapments some solubility of the active in the vehicle is acceptable because the vehicle can provide the initial loading dose of the active until release from the microsponge. Another way to avoid undesirable premature leaching of the active from the microsponge polymer is to formulate the product with some free and some entrapped active, so the vehicle is pre saturated. In this case there will not be any leaching of the active form of polymer during compounding. The rate of active release will ultimately depend not only on the partition coefficient of the active ingredient between the polymer and the vehicle (or the skin), but also on some of the parameters that characterize the beads. Examples of these include surface area and primarily, mean pore diameter[5]. Release can also be controlled through diffusion or other triggers such as moisture, pH, friction or temperature.

PROGRAMMABLE RELEASE[25]

(i)Pressure triggered systems

Microsponge system releases the entrapped material when pressurized/rubbed; the amount released depends upon various characteristics of the sponge. By varying the type of material and different process variables, the microsponge best suited for a given application may be optimized. When compared with mineral oil containing microcapsules, mineral oil containing microsponge showed much more softening effect. The duration of emolliency was also much more for the microsponge systems.

(ii)Temperature triggered systems

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

(iii)pH triggered systems

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

(iv)Solubility triggered system

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

PHYSICAL CHARACTERIZATION OF MICROSPONGES

(i) Particle size determination[26]

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

(ii) Morphology and surface topography of microsponges[27]

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.

(iii) Determination of loading efficiency and production yield[20]

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

$$\text{Loading efficiency} = \frac{\text{Actual Drug Content in Microsponges}}{\text{Theoretical Drug Content}} \times 100 \quad \ldots\ldots\ldots (1)$$

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

$$\text{Production Yield} = \frac{\text{Practical mass of microsponges}}{\text{Theoritical mass (Polymer+drug)}} \times 100 \quad \ldots\ldots\ldots (2)$$

(iv) Determination of true density[28]

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

(v) Characterization of pore structure [29, 30]

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.

(vi) Compatibility studies[31-33]

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

(vii) Polymer/monomer composition[34]

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.

(viii) Resiliency (viscoelastic properties)[29]

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.

(ix) Dissolution studies

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.

(x) Kinetics of release

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

$$Q = k_1 t^n \text{ or } \log Q = \log k_1 + n \log t \ldots . (3)$$

Where Q is the amount of the released at time (h),

n is a diffusion exponent which indicates the release mechanism, and

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 k_1 were calculated.

For comparison purposes, the data was also subjected to Eq. (4), which may be considered a simple, Higuchi type equation.

$$Q = k_2 t^{0.5} + C \ldots \ldots . (4)$$

Eq. (4), for release data dependent on the square root of time, would give a straight line release profile, with k_2 presented as a root time dissolution rate constant and C as a constant.

APPLICATIONS OF MICROSPONGE SYSTEMS

Microsponge delivery systems are used to enhance the safety, effectiveness and aesthetic quality of topical prescription, over-the-counter and personal care products. Products under development or in the market place utilize the Topical 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 over-medication, 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.

Microsponges are porous, polymeric microspheres that are used mostly for topical and recently for oral administration. Microsponges are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects and modify drug release. (Shown in Table 1)[35]

(i)Topical drug delivery using microsponge technology

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[13].

Disorders of hyperpigmentation such as melasma 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 melasma and PIH. Microsponges were used to release HQ gradually to prolong exposure to treatment and to minimize skin irritation[36]. Microsponges containing mupirocin were prepared by an emulsion solvent diffusion method. The optimized microsponges were incorporated into an emulgel 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 nonirritant 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[37].

Fluconazole is an active agent against yeasts, yeast-like fungi and dimorphic fungi, with possible drawback of itching in topical therapy. Microspongic drug delivery system using fluconazole with an appropriate drug release profile and to bring remarkable decrease in frequently appearing irritation. Microsponges were prepared by liquid-liquid suspension polymerization of styrene and methyl methacrylate. Microsponges were dispersed in gel prepared by using carbopol 940 and evaluated for drug release using Franz diffusion cell. The average drug release from the gels containing microspongic fluconazole was 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). Drug diffusion study reveals extended drug release, in comparison with marketed formulations containing un-entrapped fluconazole. Microspongic system for topical delivery of fluconazole was observed potential in extending the release[38]. Carac contains 0.5% fluorouracil incorporated into a patented porous Microsponge System. The particles are dispersed in a cream and hold the active ingredient until applied to the skin. Carac cream is the newest topical treatment for multiple actinic or solar keratoses. Carac provides sufferers with options for shorter duration of therapy (1, 2 or 4 weeks), once-a-day dosing, and more rapid recovery time from irritation[39].

An MDS system for retinoic acid was developed and tested for drug release and anti-acne efficacy. Statistically significant greater reductions in inflammatory and non-inflammatory lesions were obtained with entrapped tretinoin in the MDS[40].

(ii)Oral drug delivery using microsponge technology

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.

Controlled oral delivery of ibuprofen microsponges is achieved with an acrylic polymer, eudragit RS, by changing their intraparticle density[9].

The release of ketoprofen incorporated into modified release ketoprofen microsponge 200 mg tablets and Profenid Retard 200 mg was studied in vitro and in vivo. The formulation containing ketoprofen microsponges yielded good modified release tablets. An in vivo study was designed to evaluate the pharmacokinetic parameters and to compare them with the commercially available ketoprofen retard tablets containing the same amount of the active drug. Commercial ketoprofen retard tablets showed a more rapid absorption rate than modified release tablets and peak levels were reached within almost 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[41].

A Microsponge system offers the potential to hold active ingredients in 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. This approach opens up entirely new opportunities for MDS by colon specific targeting of drugs.

Paracetamol loaded eudragit based microsponges were prepared using quasi-emulsion solvent diffusion method, then the colon specific tablets were prepared by compressing the microsponges 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[42]. Dicyclomine loaded, Eudragit based microsponges were prepared using a quasi-emulsion solvent diffusion method. Kinetic analysis showed that the main mechanism of drug release was by Higuchi matrix controlled diffusion. Drug release was biphasic with an initial burst effect with 16 – 30 % of the drug was released in the first hour. Cumulative release for the microsponges over 8 hours ranged from 59 - 86 %[43].

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: hydroxypropylmethyl cellulose (HPMC) mixture followed by tabletting. 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 addition made[44].

(iii)Bone tissue engineering using microsponge technology

3D biodegradable porous scaffold plays a very important 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. 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 a strategy for the preparation of 3D porous scaffolds [45].

A novel three-dimensional 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. 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_2HPO_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[46].

(iv)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 precellularization.

Poly (lactic-co-glycolic acid) as a biodegradable scaffold was compounded with collagen microsponge to form a vascular patch material. These poly (lactic-co-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 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[47].

(v)Reconstruction of vascular wall using microsponge technology

The tissue-engineered patch was fabricated by compounding a collagen-microsponge with a biodegradable polymeric scaffold composed of polyglycolic acid knitted mesh, reinforced on the outside with woven polylactic acid. Tissue-engineered patches without precellularization were grafted into the porcine descending aorta (n = 5), the porcine pulmonary arterial trunk (n = 8), or the canine right ventricular outflow tract (as the large graft model; n = 4). 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 immunostaining. 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[48].

MARKETED FORMULATIONS OF MICROSPONGE49-51

Marketed formulation using the MDS includes Dermatological products which can absorb large amounts of excess of skin oil, while retaining an elegant feel on the skin's surface. Among these products (given in table 2) are skin cleansers, conditioners, oil control lotions, moisturizers, deodorants, razors, lipstick, makeup, powders, and eye

shadows; which offers several advantages, including improved physical and chemical stability, greater available concentrations, controlled release of the active ingredients, reduced skin irritation and sensitization, and unique tactile qualities.

CONCLUSION

Ease manufacturing, simple ingredients and wide range actives can be entrapped along with a programmable release make microsponges extremely attractive. MDS is originally developed for topical delivery of drugs like anti-acne, anti-inflammatory, anti-fungal, anti-dandruffs, antipruritics, rubefacients etc. Now days it can also be used for tissue engineering and controlled oral delivery of drugs using bio erodible polymers, especially for colon specific delivery. Microsponge delivery systems that can precisely control the release rates or target drugs to a specific body site have an enormous impact on the health care system. MDS holds a promising future in various pharmaceutical applications in the coming years by virtue of their unique properties like small size, efficient carrier characteristics enhanced product performance and elegancy, extended release, reduced irritation, improved thermal, physical, and chemical stability so flexible to develop novel product forms. New classes of pharmaceuticals, biopharmaceuticals (peptides, proteins and DNA-based therapeutics) are fueling the rapid evolution of drug delivery technology. Thus MDS is a very emerging field which is needed to be explored.

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.
Antidandruffs e.g. zinc pyrithione, selenium sulfide	Reduced unpleasant odor 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 odor.

Table 2: List of Marketed Products using MDS

Product name	Advantages	Manufacturer
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 fine lines, wrinkles & skin discolorations associated with aging.	Avon	
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 counterirritant 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. Lactrex™ also contains water and glycerin, a natural humectant, to soften and help moisturize dry, flaky, cracked skin.	SDR Pharmaceuticals, Inc., Andover, NJ, 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

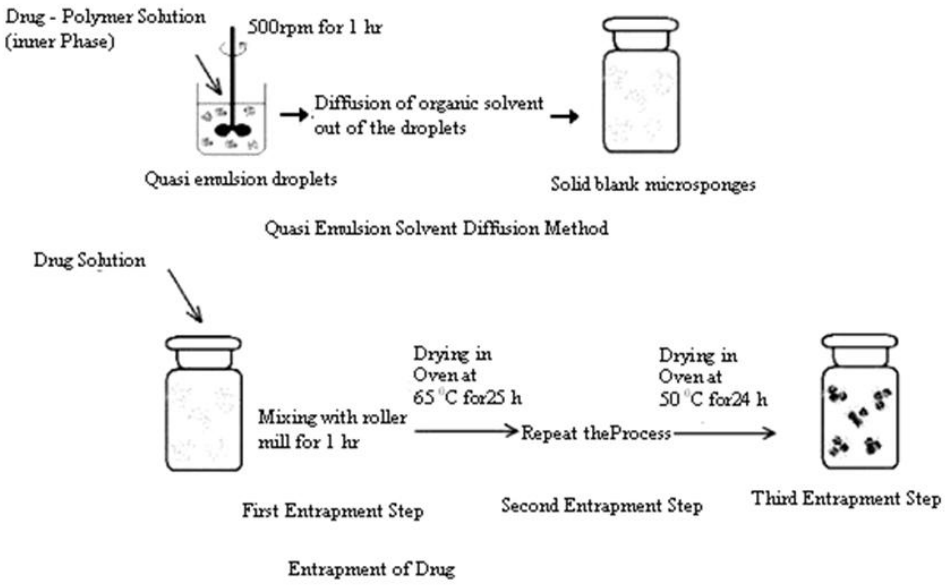

Fig. 3: Preparation of Microsponges by Quasi-emulsion solvent diffusion method

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