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Review Article

RECENT ADVANCES IN MICROSPONGES DRUG DELIVERY SYSTEM

MOHITE P.B.[1]*, KHANAGE S.G.[1], HARISHCHANDRE V.S.[1], SHIRSATH YOGITA[1]

[1]Department of Quality Assurance Techniques, Mula Education Society's College of Pharmacy Sonai, Savitribai Phule Pune University, Pune, Maharashtra
Email: mohitepb@gmail.com

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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. Microsponges consist of microporous 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 drug delivery system (MDDS) 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 nontoxic. The present review introduces Microsponge technology along with its synthesis, characterization, programmable parameters and release mechanism of MDDS.

Keywords: Controlled Drug Delivery System, Microsponge Technology, Programmable Release, Microsponge.

INTRODUCTION

In recent years it has become more and more evident that the development of new drugs alone is not sufficient to ensure progress is drug therapy. A promising strategy involves the development of suitable drug carrier system. The *in-vivo* fate of the drug is not only determined by the properties of the drug, but it is also by the carrier system, which permits a controlled and localized release of the active drug according to the specific need of the therapy. Microsponge are porous spherical microparticles having a particle size range of 5-300 µm with a capability to entrap a wide range of active ingredients and are used as a carrier for topical drug delivery. These microspheres act like microscopic sponges, storing the active drug until its release is triggered by application to the skin surface. The release of drug into the skin can be initiated by a various triggers like rubbing, concentration gradient, higher skin temperature, application of pressure etc. 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. The Microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Thus can significantly reduce the irritation of effective drugs without reducing their efficacy. Further these porous microspheres with active ingredients can be incorporated into formulations such as gels, creams, lotions and powders. Microsponge consists of non-collapsible structures with porous surface through which active ingredients are released in a controlled manner which would be highly advantageous for irritant drug like Benzoyl peroxide which would result in excellent efficacy with minimal irritation and to drugs which are to be released in a controlled manner so as to maintain the systemic concentration in a controlled manner [1].

Microsponge

Microsponges are porous, polymeric microspheres that are mostly used for prolonged topical administration. Microsponges are designed to deliver a pharmaceutically active ingredient efficiently at minimum dose and also to enhance stability, reduce side effects, and modify drug release profiles. These attributes have been successfully demonstrated in the FDA-approved Retin-A Micro® (0.1% or 0.04% tretinoin) and Carac (0.5% 5-flurouracil) products for acne treatment and actinic keratoses, respectively [2]. Many of conventional delivery systems require high concentrations of active agents to be incorporated for effective therapy because of their low

Efficiency as delivery systems Thus, the need exists for delivery systems to maximize the period of time that an active ingredient is present, either on the skin surface or within the epidermis while minimizing its transdermal penetration into the body. The microsponge based polymeric microspheres uniquely fulfill such requirements. Microsponges are prepared by several methods utilizing emulsion systems as well as by suspension polymerization in a liquid–liquid system. The most common emulsion system used is oil-in-water (o/w), with the microsponge being produced by the emulsion solvent diffusion (ESD) method [3].

History of microsponge

The microsponge technology was developed by Won in 1987 and the original patents were assigned to Advanced Polymer Systems, Inc. This Company developed a large number of variations of the technique and applied those to cosmetic as well as OTC and prescription pharmaceutical products. At the present time, this interesting technology has been licensed to Cardinal Health, Inc. for use in topical products.

Hypothetical mechanism of microsponge

The active ingredient is added to the vehicle in an entrapped form. As the microsponge particles have an open structure (i.e., they do not have a continuous membrane surrounding them), the active is free to move in and out from the particles and into the vehicle until equilibrium is reached, when the vehicle becomes saturated. 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 or absorbed. Even after that the microsponge particles retained on the surface of the 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 the 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. This principle is contrary to the conventional formulation principles usually applied to 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 is activated by the shift in equilibrium from the polymer into the carrier. 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 from the polymer during compounding. The rate of active release will ultimately depend not only on the partition coefficient of the active ingredient between the polymer and the vehicle (or the skin), but also on some of the parameters that characterize the beads. Examples of these include surface area and primarily, mean pore diameter. Release can also be controlled through diffusion or other triggers such as moisture, pH, friction or temperature [4].

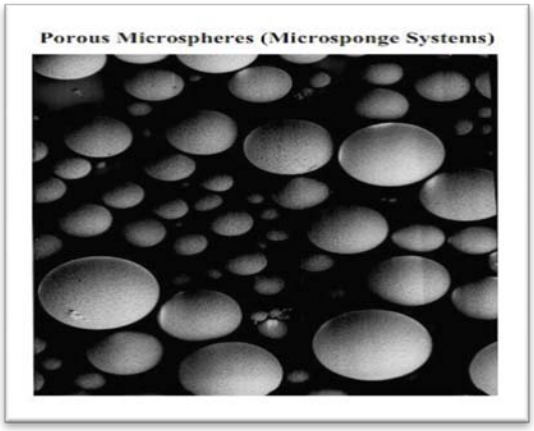

Fig. 1: Porous Microsponges [5]

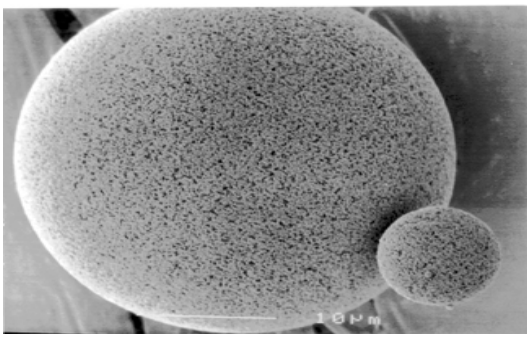

Fig. 2: Highly porous nature of a Microsponge [6]

Characteristics of microsponges

1. Microsponges formulations are stable over range of pH 1-11

2. Microsponge formulations are stable at temperature up to 130 °C

3. Microsponge formulations are self-sterilizing as their average pore size o.25 µm where bacteria cannot penetrate.

4. Microsponge formulations are compatible with most vehicles and ingredients

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

Characteristics of materials that is entrapped in Microsponges

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

1. It should be either fully miscible in monomer or capable of being made miscible by addition of small amount of a water immiscible solvent.

2. It should be water immiscible or at most only slightly soluble.

3. It should be inert to monomers.

4. 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.

5. The spherical structure of Microsponges should not collapse.

6. Polymer design and payload of the Microsponges for the active must be optimized for required release rate for given time period.

7. It should be stable in contact with polymerization catalyst and conditions of polymerization

Potential features of microsponge drug delivery systems

The potential features are as listed

1. Microsponges show acceptable stability over pH ranging from 1 to 11 and at high temperatures (up to 130 °C).

2. Microsponges exhibit good compatibility with various vehicles and ingredients.

3. Microsponges have high entrapment efficiency up to 50 to 60%.

4. Microsponges are characterized by free-flowing properties.

5. The average pore size of Microsponges is small (0.25 µm) in a way to prevent the penetration of bacteria; thus they do not need sterilization or addition of preservatives.

6. Microsponges are non-allergenic, non-irritating, non-mutagenic and non-toxic.

7. Microsponges can absorb oil up to 6 times their weight without drying.

8. Microsponges can enhance product performance.

9. Microsponges can reduced irritation and hence improve patient compliance.

10. Microsponges can improve product elegancy [7, 8].

Benefits of microsponge technology

1. Microsponge technology offers

2. Enhanced product performance.

3. Extended release.

4. Reduced irritation and hence improved patient compliance.

5. Improved product elegance.

6. Improved oil control as it can absorb oil up to 6 times its weight without drying.

7. Improved formulation flexibility.

8. Improved thermal, physical, and chemical stability.

9. Flexibility to develop novel product forms.

10. In contrast to other technologies like microencapsulation and liposome, MDS has a wide range of chemical stability, higher payload and are easy to formulate.

11. Microsponge systems are non-irritating, non-mutagenic, non-allergenic and non-toxic [9].

Table 1: Optimum values for microsponge formulation [10]

Specification	Optimum values
Drug: polymer ratio	3:1, 4:1 and 5:1
Amount of drug(g)	2
PVA (mg)	30-70
Inner phase solvent	Ethyl alcohol
Amount of inner phage solvent(ml)	10(ml)
Amount of water in outer phage (ml)	200(ml)
Temp in inner phage (^{o}c)	37
Stirrer type	Three blade
Stirring rate (rpm)	500
Stirring time (min)	60

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 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 [11].

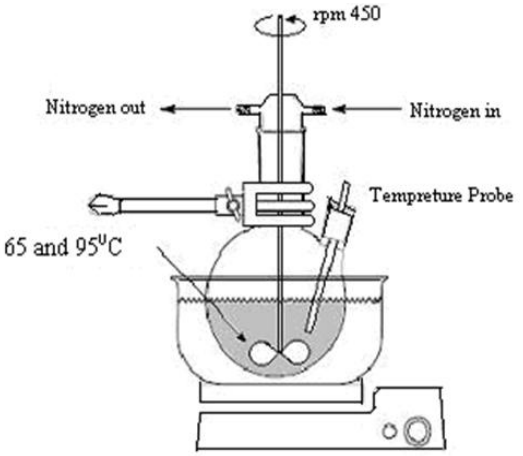

Fig. 3: Reaction vessel for Microsponge [12]

Liquid-liquid suspension polymerization

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

Preparation by liquid-liquid suspension method

The various steps in the preparation of Microsponges are summarized as

1. Selection of monomer or combination of monomers.
2. Formation of chain monomers as polymerization begins.
3. Formations of ladders as a result of cross-linking between chain
4. Monomers.

5. Folding of monomer ladder to forms spherical particles-Agglomeration of microspheres, which give rise to the formation of bunches of microspheres.

6. Binding of bunches to for 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 atypical carriers for variety of functional substances, e. g. Anti-acne, anti-inflammatory, antiquities, antifungal, rubefacients etc. When the drug is sensitive to the polymerization conditions, two-step processes used. The polymerization is performed using substitute Porogen and is replaced by the functional substance under mild experimental conditions [12].

Quasi-emulsion solvent diffusion

This is a two-step process where the microsponges can be prepared by quasi-emulsion solvent diffusion method using the different polymer amounts. To prepare the inner phase, Eudragit RS 100 was dissolved in ethyl alcohol. Then, drug can be then added to solution and dissolved under ultrasonicator at 35oC. 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 microsponge are dried in an air heated oven at 40^{o}C for 12Hr and weighed to determine production yield [13].

Release mechanism

Programmable release

Pressure triggered systems

Microsponges 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.

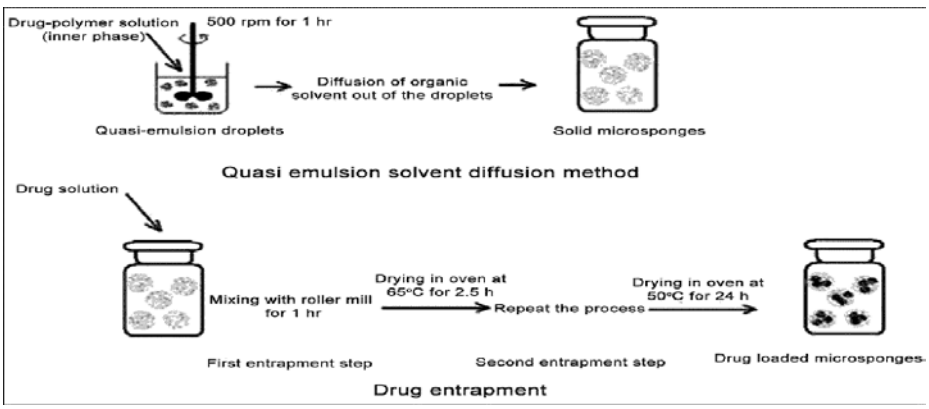

Fig. 4: Preparation of microsponges by Quasi-emulsion solvent diffusion method [13]

Temperature-triggered systems

Some entrapped active ingredients can be too viscous at room temperature to flow spontaneously from microsponge 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 microsponge when exposed to higher temperatures; thus a sunscreen would be released from a microsponge only upon exposure to the heat from the sun [14].

pH triggered systems

Triggering the pH-based release of the active can be achieved by modifying the coating on the 0microsponge. This has many applications in drug delivery.

Solubility triggered systems

Presence of an aqueous medium such as perspiration can trigger the release rate of active ingredients. Ingredients such as antiseptics, deodorants and antiperspirants may be formulated in such types of systems. 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 microsponge network

Characterization of microsponges

Physical characterization of Microsponges

Particle size determination

Particle size analysis of loaded and unloaded microsponge 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 microsponge of different particle size will be plotted against time to study effect of particle size on drug release. Particles larger than 30μm can impart gritty feeling and hence particles of sizes between 10 and 25μm are preferred to use in final topical formulation.

Morphology and surface topography of microsponges

For morphology and surface topography, prepared Microsponges can be coated with gold–palladium under an argon atmosphere at room temperature and then the surface morphology of the Microsponges can be studied by scanning electron microscopy (SEM). SEM of a fractured microsponge particle can also be taken to illustrate its ultrastructure.

Determination of loading efficiency and production yield

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

Loading efficiency = Actual Drug Content in Microsponges X 100……. (1)

Theoretical drug content

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

Production Yield= Practical mass of microsponges X 100…… (2)

Theoretical mass (Polymer+drug)

Determination of true density

The true density of microparticles is measured using an ultra-pycnometer under helium gas and is calculated from a means of repeated determinations [15].

Characterization of pore structure

Pore volume and diameter are vital in controlling the intensity and duration of effectiveness of the active ingredient. Pore diameter also affects the migration of active ingredients from microsponges into the vehicle in which the material is dispersed. Mercury intrusion porosimetry can be employed to study effect of pore diameter and volume with rate of drug release from microsponges. Porosity parameters of microsponges such as intrusion–extrusion isotherms, pore size distribution, total pore surface area, average pore diameters, interstitial void volume, percent porosity, percent porosity filled, shape and morphology of the pores, bulk and apparent density can be determined by using mercury intrusion porosimetry.

Compatibility studies

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

Polymer/monomer composition

Factors such as microsphere size, drug loading, and polymer composition govern the drug release from microspheres. The polymer composition of the MDS can affect partition coefficient of the entrapped drug between the vehicle and the microsponge system and hence have a direct influence on the release rate of entrapped drug. The release of drug from microsponge systems of different polymer compositions can be studied by plotting cumulative % drug release against time.

Resiliency (viscoelastic properties)

Resiliency (viscoelastic properties) of microsponges can be modified to produce bead etc that is softer or firmer according to the needs of the final formulation. Increased cross-linking tends to slow down the rate of release.

Dissolution studies

The 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 the suitable analytical method at various intervals.

Kinetics of release

The drug release mechanism and the release profile differences among microsponge can be determined by the drug released amount versus time. The release data can be 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 k1 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 [16].

Physicochemical characterization of microsponges

Scanning electron microscopy

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 ultrastructure.

Fourier transform infrared spectroscopy (FTIR):

Fourier transform infrared spectroscopy (FTIR) is carried out for the pure drug, polymer and the drug-polymer physical mixture and microsponge formulations. The samples are incorporated in potassium bromide discs and evaluated using FTIR spectrometer. The peaks corresponding to the characteristics bands of the drug should be preserved in the spectra of the microsponges to indicate that no chemical interaction or changes took place during the preparation of the formulations.

Powder X-ray diffraction (XRD)

Powder X-ray diffraction (XRD) can be performed for both pure drug, polymer and microsponge formulation to investigate the effect of polymerization on the crystallinity of the drug. The disappearance of the characteristic peaks of the drug in the formulation could indicate that the drug is dispersed at a molecular level in the polymer matrix [17].

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 marketplace 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.

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

Releasing of active ingredients from conventional topical formulations over an extended period of time is quite difficult. Cosmetics and skin care preparations are intended to work only on the outer layers of the skin. The typical active ingredient in conventional products is present in a relatively high concentration and, when applied to the skin, may be rapidly absorbed. The common result is overmedication, followed by a period of under medication until the next application. Rashes and more serious side effects can occur when the active ingredients rapidly penetrate below the skin's surface. Microsponge technology is designed to allow a prolonged rate of release of the active ingredients, thereby offering potential reduction in the side effects while maintaining the therapeutic efficacy. 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 [18, 19].

In topical drug delivery

Genetically engineered melanin is incorporated in microsponges (sunscreens), melanosponge-α to spread it evenly hence give protection against UV-A and UV-B radiation. Fluocinolone acetonide (FA) is a corticosteroid primarily used in dermatology to reduce skin inflammation and relieve itching 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. Disorders of hyper pigmentation such as melasma and post inflammatory hyper pigmentation (PIH) are common, particularly among people with darker skin types. Hydroquinone (HQ) bleaching creams are considered the gold standard for treating hyper pigmentation. 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. 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. 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. 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 w), once-a-day dosing, and more rapid recovery time from irritation. 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 [20, 21].

In oral drug delivery

A microsponge system offers several advantages for oral drug delivery such as

1. Preserve the active ingredients within a protected environment and offer oral controlled delivery to the lower part of the gastrointestinal tract (GIT).

2. Microsponge systems improve the solubility of poorly soluble drugs by entrapping these drugs in their porous structure.

3. As the porous structure of the microsponge is very small in size, the drugs entrapped will be reduced to microscopic particles with higher surface area, and consequently improved rate of solubilization.

4. Maximize the amount of drugs to be absorbed, as the time it takes the microsponge system to pass through the intestine is considerably increased.

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. The release of ketoprofen incorporated into modified release ketoprofenmicrosponge200 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 [49]. 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: hydroxyl propylmethylcellulose (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. Dicyclomine loaded, Eudragit based microsponges were prepared using a quasiemulsion 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 h 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 Microsponge5640 system using entrapment method. The colon specific formulations were prepared by compression coating and also pore plugging of microsponges with pectin: hydroxyl propylmethyl 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 [22].

In Bone tissue engineering

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 w. 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. 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 CaCl2 and Na2HPO4 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. Energydispersive spectroscopy analysis and X-ray diffraction spectra showed that the calciumto-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 [23].

In cardiovascular engineering

A biodegradable material 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 microsponges 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 (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 mo 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 mo. This patch shows promise as a bioengineered material for promoting in situ cellularization and the regeneration of autologous tissue in cardiovascular surgery [24].

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. 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 mo 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 mo after implantation. In the large graft model, the architecture of the patch was similar to that of native tissue 6 mo after implantation and this patch can be used as a novel surgical material for the repair of the cardiovascular system [25].

Table 2: Applications of microsponge systems

S. No.	Formulations	Active agents	Applications	References
1	Sunscreens	e. g: oxybtnzone	Long lasting product efficacy, with improved protection against sunburns and sun related injuries even at elevated concentration and with reduced irritancy and sensitization	Comoglu T *et al.* (2007)[26]
2	Anti-acne	e. g. Benzoyl peroxide	Maintain efficacy with decreased skin irritation and sensitization.	Jain V *et al.* (2010)[27]
3	Anti-inflammatory	e. g. Hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatoses.	Orlu M *et al.* (2006)[28]
4	Anti-fungal	e. g. Itraconazole, Econazole	Sustained release of actives.	Dai W *et al.* (2010)[29]
5	Antipruritics	e. g. hydroquinone	Extended and improved activity.	Chen G *et al.* (2001)[30]
6	Rubefacients	e. g. capsaicin	Prolonged activity with reduced irritancy greasiness and odour.	Iwai S *et al.* (2004)[31]

Table 3: List of marketed products using microsponge drug delivery system

Product name	Advantages	Company
Retin-A-Micro	0.1 And 0.04% tretinoin entrapped in MDS, for the topical treatment of acne vulgaris. This formulation uses patented methyl methacrylate/glycol+8 dimethacrylate cross-polymer porous microspheres.	Ortho-McNeil Pharmaceutical,Inc.
Carac cream, 0.5%	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.	Dermik Laboratories, Inc. Berwyn,PA19312 USA
EpiQuinmicro	The Microsponge system entrap hydroquinone and retinol. The microsponges release these ingredients into the skin gradually throughout the day, which may minimize skin irritation	Skin MedicaInc
Micro peel plus	The MicroPeelPlus stimulates cell turnover through the application of salicylic acid in the form of microcrystals using Microsponge technology. TheMicroPeel Plus aggressively outperforms other superficial chemical peels by freeing the skin of all dead cells, while doing no damage to the skin.	Biomedic
Ultra guard	Microsponge system that contains dimethicone to help protects a baby's skin from diaper rash	Scott Paper
Retinol cream	The retinol molecule is kept in the microsponge system to protect the potency of vitamin A. This helps to maximize the retinol dosage while reducing the possibility of irritation. Retinol is a topical vitamin A derivative, which helps maintain healthy skin, hair, and mucous membranes.	Biomedic

CONCLUSION

Microsponge Delivery System can entrap wide range of actives and then release them onto the skin at a time and in response to trigger. It is a unique technology for the controlled release of topical agents and consists of microporous beads loaded with active agent and also use for oral as well as biopharmaceutical drug delivery. A microsponge delivery system can release its active ingredient on a time mode and also in response to other stimuli. Thus microsponge has got a lot of potential and is a very emerging field which is needed to be explored.

CONFLICT OF INTERESTS

Declared none

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