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A Review on Microsponge Delivery System

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ABSTRACT

Microsponge is recent novel technique for control release and target specific drug delivery system. Microsponge technology has been introduced in pharmaceutical industry to provide the controlled release of active drug ingredient for the application into the skin in order to decrease systemic exposure and reduce local cutaneous reactions to active drugs. Microsponges comprises of microporous beads, typically 10-25 microns in diameter, loaded with active agent. The microsponge releases its active ingredient on a time mode, when applied to the skin, and also in response to other stimuli that are used mostly for topical and recently for oral administration. Microsponge technology has many favourable characteristics which make It all around suitable as 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 mostly porous, allowing the sustained flow of substances out of the sphere. Microsponge drug delivery system causes increased efficacy for the topically active agents with enhanced safety and product stability for a longer period of time with reduction in side effects. In addition their non-allergenic, non-irritating, non-mutagenic and nontoxic behaviour makes them the suitable dosage form. The present review emphasis Microsponge drug delivery system along with its release mechanism.

Keywords: Novel drug delivery system, Microsponges, Microsponge drug delivery system, Quasi-emulsion solvent diffusion method.

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INTRODUCTION

One of the biggest challenges faced by pharmaceutical scientists is to control the rate of delivery of the active ingredients to a particular organ in the human body. Various reliable systems have been investigated for the transdermal delivery system using the skin as the entry for the several organ. It has improved the safety and efficacy of numerous drugs that may be better administered via skin. But transdermal delivery system is not provable for delivery of materials whose final target is skin itself[1]. It is a challenging area of research for the drugs which are applied on the epidermis for their controlled systemic circulation in predetermined amounts as well as their localization in the target organs. Topical delivery of drugs faces different types of problems. Ointments, which are used for aesthetic purposes offers various problems such as greasy and sticky appearance, thus leads to patient incompliance. There is need of high concentrations of active ingredients for such type of vehicles in order to achieve effective therapy, resulting in irritation and allergic reactions[2]. The other disadvantages of topical formulations include uncontrolled rate of evaporation of active agents with unpleasant odour, high chances of incompatibility of drugs with the vehicles. Thus, there exists the need for system to maximize the amount of time that an active agent is present either on skin surface or within the epidermis, meanwhile minimizing its transdermal penetration into the body. The microsponge delivery system fulfills these requirements. Microsponges are said to be a porous microspheres which consist of numerous of interconnected voids of particle size ranging from 5-300 µm. The microsponges are having capacity to entrap wide range of pharmaceutical active ingredients such as fragrances, essential oils, sunscreens, emollients and anti-infectives which serve to be a topical drug delivery system. Finally the use of the porous microsponges with addition to active ingredients can be formulated into various dosage forms such as creams, lotions and powders. The non-collapsible structures are found within the porous surface of microsponge through which active ingredients are released in controlled manner. The basic approach of the microsponge technology lies in the application of conventional formulations for releasing the active ingredients from prolonged period of time. Cosmetics and skin care preparations are made to work only on the

epidermal layer of the skin. The common result is over-medication, which results in the serious side effects[3,4]. Therefore Microsponge is a advance technology for delivering the drugs in a well released pattern with maximum therapeutic effect.

Benefits of Microsponge Technology[4]

Microsponge technology gives:

• Increased product performance.

• Extended release.

• Improved patient compliance and reduced irritation.

• Improved product elegancy.

• Improved formulation flexibility and Improved oil control as it can absorb oil up to 6 times its weight without drying

• Improved the thermal, physical, and chemical stability of the drug.

• It should have Flexibility to develop novel product forms.

• Microsponge systems are non-allergenic, non-irritating, non-mutagenic and non-toxic.

Characteristics of the Materials Entrapped in Microsponges

Majority of soluble ingredients and liquids may be entrapped in the microsponges. Actives that can be entrapped in microsponges must meet following requirements.

• It should be either properly miscible in monomer or eligible of being made miscible by adding of small amount of a water immiscible solvent.

• It should be slightly soluble or water immiscible.

• It should be inert to monomers.

• It should be constant in contact with polymerization catalyst and conditions of polymerization[5].

Potential features of microsponge drug delivery systems[6]

The potential features are as listed:-

1. Microsponges show acceptable stability over pH ranging from 1 to 11 and at high temperatures i.e 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 designated by free flowing properties.

5. The average pore size of microsponges is small (0.25 µm) in a way to inhibit the penetration of bacteria, Hereby they do not need sterilization or addition of preservatives.

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

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

Advantages of Microsponges

Microsponges have several advantages which are explained below:

High surface area

A 25 µ sphere can have a pore volume of about 1 ml/g with pore length of about 10 ft and can have up to 25,000 pores. This confer an vast surface area for high entrapment. Because of the entrapment and adsorption of actives upon the polymeric cage, the discharge of actives is sustained. This facilitates the formulation of skin irritants or actives with short time of action, which otherwise may require re-application every few hours[7].

Simple production methodology

The production of microsponges is comparatively simple in scaling up and that is why there is a higher potential for commercialization.

Drugs explored in the microsponge delivery system[8,9]

- Ketoprofen
- Mupirocin
- Tretinoin
- Fluconazole
- Hydroquinone
- Acyclovir Sodium
- Retinol
- Erythromycin
- Miconazole
- Curcumin
- Itraconazole
- Ibuprofen
- Prednisolone
- Paracetamol
- Indomethacin
- Benzoyl Peroxide

Release Mechanisms from Microsponges[10]

Pressure Triggered System

Microsponge system releases the entrapped material when pressurized; the amount released depends upon various characteristics of the sponge. By change 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 then mineral oil containing microsponge showed much more softening effect. The period of emolliency was also much more for the microsponge systems.

Temperature Triggered System

It is believable to modulate the release of substances from the microsponge by penetration of temperature. The much viscous sunscreens were found to exhibit at peak release from microsponges when they exposed to high rate temperatures, Hereby a sunscreen would be released from a microsponge only onto exposure to the heat from the sun.

pH triggered systems

Triggering the pH-based release of the active can be achieved by re-producting the coating on the microsponge. Even though this has several applications in drug delivery, only a few applications are possible for cosmetic delivery.

Solubility triggered systems

At the present of an aqueous medium such as perspiration can trigger the discharge rate of active agents. Ingredients like antiseptics, deodorants and antiperspirants may be formulated in such type of systems. Release may be obtained based on the strength of the external medium to dissolve the active agent, the concentration gradient or the capacity to swell the microsponge network.

Safety of microsponges

Many polymers used in the formulation are inert and the incapability of microsponges to pass through the stratum corneum increases their safety. Furthermore, it reduces the irritation of various actives, and thereby demonstrates its harmlessness.

Advantages of Microsponges over other Formulations[11]

Advantages over conventional formulations

Conventional formulations of topical drugs are studied to work on the outer layers of the skin. Such type of products release their active agents onto application, originate a highly concentrated layer of active ingredient that is rapidly absorbed. When compared to the conventional system, microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Potentially, the Microsponge drug delivery system can decrease significantly the disturbance of effective drugs without reducing their efficacy.

Advantages over microencapsulation and liposomes

The Microsponge drug delivery system has advantages over other technologies like microencapsulation and liposomes. Microcapsules cannot commonly control the release rate of active ingredients. Once the wall is ruptured the actives contained within microcapsules will be released. Liposomes undergo from limited chemical stability, lower payload, difficult formulation and microbial instability. Meanwhile, microsponge system in contrast to the above systems has various merits such as:

- It has stability over the pH range of 1 to 11 and temperature up to 130°C.
- It is compatible with most vehicles and ingredients.
- It has the property of self-sterilizing as their average pore size is 0.25 µm where bacteria cannot penetrate.
- It has higher payload and is still free flowing.
- It has advantage of cost effectiveness over the other formulations.

Advantages over ointments

Ointments are often aesthetically unappealing, greasy and sticky that often results in lack of patient compliance. These vehicles have high concentrations of active agents for effective therapy therefore it has low capacity of delivering the active drug. As the result, into irritation and allergic reactions in valuable users. Other demerits of topical formulations are uncontrolled evaporation of active agents, unpleasant odour and potential incompatibility of drugs with vehicles[12].

Preparation of Microsponges

Drug loading in microsponges can take place in two ways, by one-step or two-step process; based on physicochemical properties of drug to be loaded. If the drug is typically an inert non-polar material, it will create the porous structure which is called as porogen. Porogen drug, which neither prevent the polymerization nor get activated by it and stable to free radicals, that is entrapped with one-step process[13].

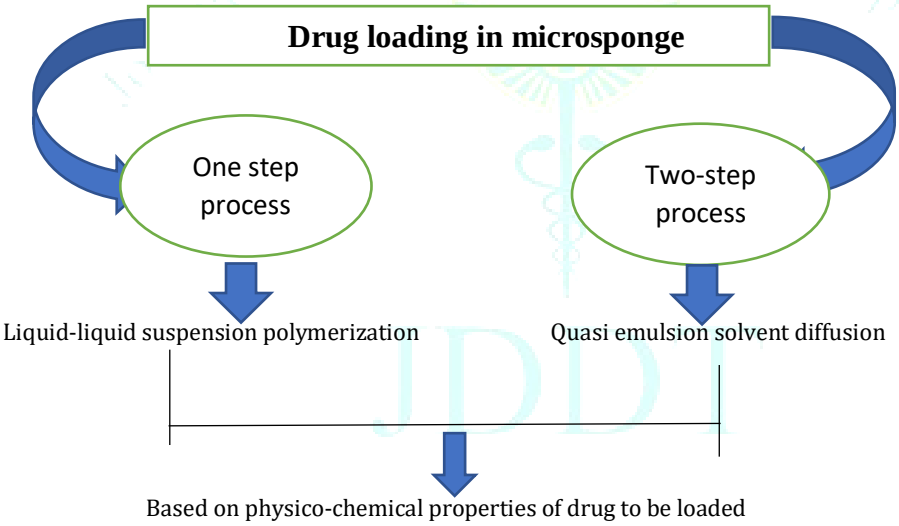

Fig. 1 Methods of preparation of microsponges[13]

Liquid-Liquid Suspension Polymerization

Microsponges are easily prepared by liquid-liquid suspension polymerization method. Polymerization of styrene or methyl methacrylate is carry out in round bottom flask. In their preparation, monomers are firstly dissolved along with non-polar active agents in appropriate solvent solution of monomer and then dispersed in the aqueous phase, which consists of additives like surfactant, and suspending agents, they are help in the formation of suspension. Once suspension with discrete droplets of the desired size is established, polymerization is achieved by activating monomers either by catalysis or by increased temperature as well as irradiation. The various steps in preparation of microsponges are summarized as:

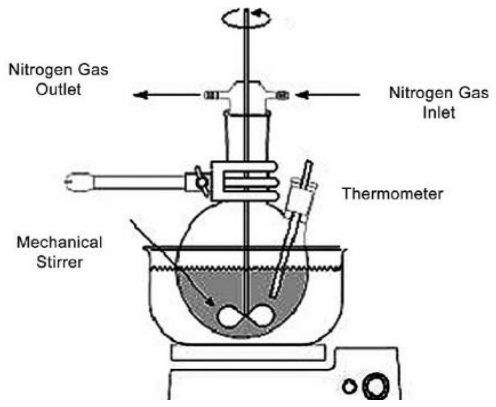

Fig. 2 Preparation of microsponges by liquid-liquid suspension polymerization method[13]

- Polymerization leads to the formation of ladders as a result of cross-linking between chain monomers.
- Folding of monomer ladder lead to the formation of spherical particles and their agglomeration resulted in formation of bunches of microspheres.
- Binding of these bunches formed microsponge.
- After polymerization the liquid is diffused out leaving microsponges. Though a convenient method, major disadvantage of this process is probable entrapment of unreacted monomeric residues.

Quasi-Emulsion Solvent Diffusion

When the drug is sensitive to the polymerization situations, two-step process is used for preparation of microsponges. Microsponges are prepared by a quasi-emulsion solvent diffusion method by using the different polymer quantities. In the emulsion solvent diffusion the relation between the drug and the good solvent is stronger than that of the suitable solvent and the poor solvent. The drug is dissolved in the good solvent, and the solution is dispersed into the poor solvent, producing emulsion (quasi) droplets, even though the pure solvents are miscible. The suitable solvent diffuses gradually out of the emulsion droplets in the surrounding cheap solvent phase, and the poor solvent expand into the droplets by which the drug crystallizes within the droplets. This is a two-step process where into the polymer along with the active agents, plasticizer and diffusible substance i.e Porogen is poured into an outer aqueous phase, which bassically consists of a stabilizer namely polyvinyl alcohol. After emulsification, the system is continuously stirred for 2 hours and maintained at a high temperature if required. Diffusion of the porogen within the outer medium results in a large porous microparticle called 'Microsponge'. Then the mixture is filtered and separate the microsponges. The product is washed and dried in vacuum oven at 50°C for 24 hours.

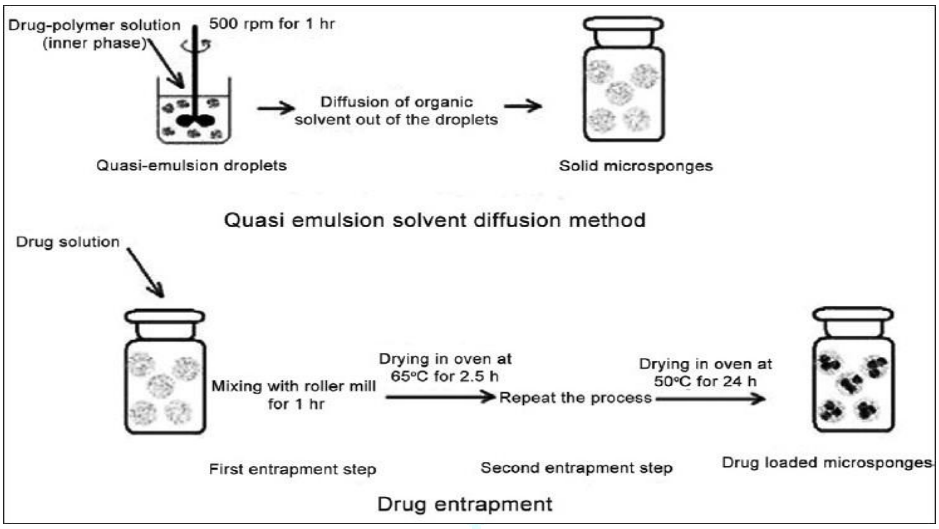

Fig. 3 Preparation of microsponges by quasi-emulsion solvent diffusion method[12,13]

Formulation Considerations

Active ingredients entrapped in microsponge delivery system then it can be incorporated into many products such as that soaps, creams, lotions and powders. Meanwhile formulating the vehicle, few opinions are taken into account in order to obtain required product characteristics. These are as follow below:

1. The solubility of actives in the vehicle must be limited. Otherwise the vehicle will deplete the microsponges before the application.

2. To avert cosmetic problems, not >10 to 12% w/w microsponges must be incorporated into the vehicle.

3. Polymer design and payload of the microsponges for the active must be optimized for required release rate for a given time period. There remains equilibrium between microsponge and vehicle and microsponge releases drug in response to the depletion of drug concentration in the vehicle. The concentration of the drug in the vehicle is depleted by absorption of the drug into the outer layer of the skin. Hereby continuous and steady release of active agents into the skin is efficient with this system.

Sustained release microsponges can also be developed. Several factors that are to be believed during development of such formulations comprise physical and chemical properties of entrapped active ingredients[14].

Effect of Formulation Variables on Physical Properties of Microsponges[15]

Effect of composition of internal and external phases

It is found that particle sizes of microsponges were directly proportional to the apparent viscosity of dispersed phase. If the difference between apparent viscosity of dispersed and continuous phase is high, the mean particle size of the microsponge is large. When the dispersed phase with higher viscosity is poured into the continuous phase (external phase), due to the higher viscosity of the internal phase, the globules of the formed emulsion can hardly be divided into smaller particles and bigger droplets are found resulting in an increase in mean particle size. Good microsponges can be produced only when 3 to 5 ml of internal phase is used. When increased the amount of internal phase from 5 to 15 ml, the production yield and drug content of the microsponges is found to be reduced. This happens because of the lower concentration of the drug in the higher volume of internal phase.

Effect of drug to polymer ratio

When the amount of polymer is kept constant however the ratio of drug to polymer is modified, the drug loading capacity is not much affected by drug to polymer ratio however production yield can be extremely altered from minimum ratio to a maximum one. Second parameter which is affected from drug: polymer ratio change is particle size. It

has been examined that when drug amount is increased so that particle size of the microsponges is also enhanced.

Effect of Process Variables on Physical Properties of Microsponges[15,16]

Effect of stirring rate

As the stirring rate is increased, the size of obtained microsponge is smaller. Increase in the stirring rate decreases the production yield but the drug content gets increased which indicates that the drug loss is decreased as the stirring rate is increased. This is due to the turbulence created within the external phase due to which polymer gets adhered to the paddle and production yield gets decreased.

Physical Characterization of Microsponges[17,18,19,20]

Particle Size Determination

Free-flowing powders with fine aesthetic properties are possible to achieve by controlling the size of particles during polymerization. Particle size examination of loaded and unloaded microsponges can be carried out by laser light diffractometry or by any other suitable method. The values (d 50) can be denoted for all formulations as mean size range. Cumulative percentage drug release from microsponges of different particle size is plotted against time to study the effect of particle size on drug release. Particles larger than 30 µm can give gritty feeling and hence particles of sizes between 10 and 25 µm are privileged to use in final topical formulation.

Morphology and Surface Topography of Microsponges

At room temperature microsponges can be coated with gold–palladium beneath an argon atmosphere for the purpose of morphology and surface topography, then the surface morphology of the microsponges can be well read by scanning electron microscopy. SEM of a fractured microsponge particle can also be taken to exemplify its ultrastructure.

Determination of Loading Efficiency and Production Yield

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

$$\text{Loading efficiency} = \frac{\text{Actual drug content in microsponges}}{\text{Theoretical drug content}} \times 100$$

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

Determination of true density

$$\text{Production Yield (PY)} = \frac{\text{Practical mass of microsponges}}{\text{Theoretical mass (polymer + mass)}} \times 100$$

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

Compatibility Studies

Thin layer chromatography and Fourier Transform Infra-red Spectroscopy can be used to study the compatibility of drugs with excipients. X-ray diffraction and Differential Scanning Colorimetry (DSC) used to study the polymerization on crystallinity of the drug.

Polymer/ Monomer Composition

Factors such as microsponge size, drug loading, and polymer design regulate the drug release from microsponge. Polymer creation of the microsponge drug delivery system can affect partition coefficient of the entrapped drug between the vehicle and the microsponge system, Hereby it has direct impact on the release rate of entrapped drug.

Release of drug from microsponge systems of different polymer compositions can be intended by plotting cumulative percent (%) drug release against time.

Selection of monomer is dictated both by characteristics of active ingredient ultimately to be entrapped and by the vehicle into which it will be dispersed. Polymers with varying electrical charges or degrees of hydrophobicity or lipophilicity may be prepared to confer flexibility in the release of active agents. Several monomer combinations will be screened for their suitability with the drugs by studying their drug release profile.

Resiliency (viscoelastic properties)

Resiliency (viscoelastic properties) of microsponges can be improved to produce beadlets that are softer or stable according to the requirements of the final formulation. The rate of release gets slow down by increased cross-linking. However, resiliency of microsponges will be studied and optimized as per the requirement by considering release as a function of cross-linking with time.

Applications of Microsponge Systems[21,22]

Microsponges are porous, polymeric microspheres that are used mostly for topical delivery of drug and recently it is used for oral administration. It proposed the formulator a range of substitute to drug and cosmetic products. Microsponges are designed to deliver an active pharmaceutical ingredient efficiently at the low dose and also to increased stability, reduce side effects and modify the drug release. Various applications of microsponge systems are summarized in Table 1.

TABLE 1: Applications of microsponge systems.

S. N.	Active agents	Applications
1.	Sunscreens	Sunscreens are the products which prolonged efficacy and protection against various sun injuries and sun burns. Which occurs at high concentration on the skin.
2.	Anti-acne e.g. Benzoyl peroxide	Benzoyl peroxide known for these products maintaining the efficacy with reduction in skin sensitization and irritation problems.
3.	Anti-inflammatory e.g. hydrocortisone	These provides reduction in the skin inflammation and certain allergic responses and dermatoses with long lasting effect.
4.	Anti-fungal e.g. Fluconazole	These products are well known for providing the active sustained effect of pharmaceutical active ingredients.
5.	Anti-dandruffs e.g. zinc pyrithione, selenium sulfide	These Anti-dandruff products provide reduction in the unpleasant and foul odour with extended safety and efficacy, in addition to the reduction in irritation of scalp also.
6.	Antipruritics	Extended and improved activity.
7.	Skin depigmenting agents e.g. hydroquinone	They are well known for providing stabilization against the various oxidation reactions with improvement in aesthetic properties.
8.	Rubefacients	They have long time activity with reduced irritancy greasiness and odour.

Microsponge delivery systems are used to increase the safety, efficacy and aesthetic properties of topical, over-the counter ("OTC") and personal care products. Products under development or in the market place make use of 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 that is excess skin oils.

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

(i) Topical drug delivery using microsponge technology[23,24]

Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne and athletes foots. Skin irritation is a common side effect, and it has been shown that controlled release of BPO from a drug delivery system to the skin could reduce the side effect while reducing percutaneous absorption. Benzoyl peroxide microparticles were prepared by using quasi emulsion solvent diffusion method then the addition of an internal phase (benzoyl peroxide, ethyl cellulose and dichloromethane) into a aqueous phase (polyvinyl alcohol).

Disorders of hyperpigmentation such as that melasma and post-inflammatory hyperpigmentation are common, especially among people with darker skin types. Hydroquinone bleaching creams are believed the gold standard for treating hyperpigmentation. Recently, a new formulation that is 4% Hydroquinone with 0.15% retinol entrapped in microsponge reservoir was evolved for the treatment of melasma and post-inflammatory hyperpigmentation. Microsponges were used to release HQ gradually to prolonged exposure to treatment and to minimize skin irritation.

Microsponges containing mupirocin were prepared by an quasi-emulsion solvent diffusion method. The optimized microsponge were incorporated into an emulgel base. Drug release through cellulose dialysis membrane showed diffusion controlled release pattern an drug deposition studies using rat abdominal skin exhibited significant retention of active in skin from microsponge based formulations by 24 hour. The optimized formulation were stable and non-irritant to the skin as demonstrated by Draize patch test. Microsponges-based emulgel formulation short prolonged efficacy in mouse surgical wound model infected with staphylococcus aureus. Formulation of mupirocin was best fitted in topical emulgel formulations and exhibit increased conception in the skin signalling better potential of the delivery system for treatment of primary and secondary skin infections such as impetigo, eczema, and atopic dermatitis.

(ii) In oral drug delivery using microsponge technology

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

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

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 decreased to microscopic particles and the considerable increase in the surface area hereby greatly increase the rate of solubilization.

(iii) In Bone tissue engineering using microsponge technology

3D biodegradable porous scaffold perform a very vital role in articular cartilage tissue engineering. The hybrid structure of 3D scaffolds was evolved the merits of natural type I collagen and synthetic PLGA knitted mesh. The mechanically strong PLGA mesh served as a skeleton meanwhile the collagen microsponges facilitated cell seeding and tissue formation. The scaffolds were divided into three sets:

(1) THIN: In this the collagen microsponge formed in interstices of PLGA mesh.

(2) SEMI: In this collagen microsponge formed on one side of PLGA mesh.

(3) SANDWICH: In this scaffold collagen sponge formed on both sides of PLGA mesh. Bovine chondrocytes were cultured in these scaffolds and transplanted subcutaneously into nude mice for two to eight weeks.

All three groups of transplants exhibit natural chondrocyte morphology, uniform cell distribution and abundant cartilaginous ECM deposition. Output of GAGs per DNA and the statement of type II collagen and aggrecan mRNA were too higher in the SEMI and SANDWICH groups than in the THIN group. When collate to native articular cartilage, the mechanical capacity of the engineered cartilage attain 54.8%, 49.3% in Young's modulus and 68.8%, 62.7% in stiffness, systematically, in SEMI and SANDWICH. These scaffolds could be employed for the tissue engineering of articular cartilage with adjustable fattening. The design of the hybrid structures confer a strategy for the preparation of 3D porous scaffolds.

A novel 3D porous scaffold has been evolved for bone tissue engineering by hybridizing synthetic poly (DL-lactic-co-glycolic acid), inorganic apatite and naturally derived collagen. Firstly, a porous PLGA sponge was prepared after that collagen microsponges were formed in the pores of the PLGA sponge. Finally, apatite particulates were deposits 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 well seen by optional immersion of PLGA–collagen sponge in calcium chloride and disodium hydrogen phosphate aqueous solutions and centrifugation. The deposited particulates were little and insignificant after one cycle of optional immersion. Their number and size increased with the number of alternate immersion cycles.

(iv) In cardiovascular engineering using microsponge technology

A biodegradable material with autologous cell seeding requires a complicated and invasive procedure that carries the risk of infection. To avoid these issues, a biodegradable graft material inclusive collagen microsponges that would allow the regeneration of autologous vessel tissue has developed. The capability of this material to accelerate in situ cellularization with autologous endothelial and smooth muscle cells was analysed with and without pre-cellularization.

Poly (lactic-co-glycolic acid) as a biodegradable scaffold was adjunct with collagen microsponge to form a vascular patch material. These poly (lactic-co-glycolic acid) collagen patches with or without n = 10 autologous containers cellularization were used to patch the canine pulmonary artery trunk. Histologic and biochemical assessments were performed 2 and 6 months after the implantation. There was no thrombus formation in either group, and the poly (lactic-co-glycolic acid) scaffold was almost completely absorbed in both groups.

Histologic results showed the formation of an endothelial cell monolayer, a parallel alignment of smooth muscle cells, and reconstructed vessel wall with elastin and collagen fibres. The cellular and extracellular components in the patch had increased to levels similar to those in native tissue at 6 months. This patch demonstrate statement as a bioengineered material for promoting in situ cellularization and the regeneration of autologous tissue in cardiovascular surgery.

(v) In 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 pre-cellularization 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 exhibit appropriate in situ cellularization by hematoxylin/eosin and immunostaining. The quantification of the cell population by polymerase chain reaction demonstrate a large number of endothelial and smooth muscle cells 2 months after implantation. In the huge graft model, the architecture of the patch was identical to that of native tissue 6 months after implantation and this patch can be employed as a surgical material for the repairing of the cardiovascular system.

The resulting advantages comprise extended efficacy, decreased skin irritation, cosmetic elegance, formulation flexibility and improved product stability.

Marketed Formulation Using the MDS[25,26]

Marketed formulation using the microsponge drug delivery system comprise Ethical Dermatological products (APS defined ethical dermatological products as prescriptional and non-prescriptional drugs that are encouraged primarily through the medical profession for the purpose of prevention and treatment of skin problems or diseases). Several ethical dermatology products approved by US FDA as over the counter (OTC) and personal care products are sold in the United States. Results from several human clinical studies affirmed that the technology proposed the potential to decrease the drug side effects, maintains the therapeutic efficacy and potentially enhanced the patient compliance with the treatment regimen. Ethical dermatological products that have been developed or are under development include,

Tretinoin Acne Medication

In February 1997, the food and drug administration approved the first ethical pharmaceutical product based on patented microsponge technology; Retin-A-Micro(TM), which has been licensed to Ortho-McNeil Pharmaceutical Corporation. This product was launched in March 1997. Although, skin irritation among sensitive individuals can extent patient compliance with the prescribed therapy. The company consider its patented influence to decrease the potentially irritating side effects of tretinoin. Ortho Dermatological began the marketing of this product in March 1997.

5-Fluorouracil (5-FU)

5-FU is an effective chemotherapeutic agent for treating actinic keratosis, a pre-cancerous, hardened skin condition

caused by excessive exposure to sunlight. Although, patient compliance with the treatment regimen is cheap, due to considerable adverse side effects. Microsponge-increased topical formulation, that potentially purpose a less irritating solution for treating actinic keratosis, is sold under the brand name of Carac.

Tretinoin Photo-damage Treatment

Product containing microsponge system for the treatment of photo-damage, which contributes to the premature aging of skin and in skin cancer, is also developed.

Cosmeceutical Product Retinol

Retinol is a highly pure form of vitamin A which has exhibit a remarkable capability for maintaining the skin's youthful appearance. Although, it has been achievable only on a moderate basis because it becomes unstable when mixed with other active ingredients. Stabilized retinol in a formulation which is cosmetically elegant and which has a low potential for skin irritation is successfully developed and marketed.

Personal Care and OTC Products

Microsponge drug delivery system is ideal for skin and personal care products. They can retain various times their weight in liquids, absorb large amounts of excess skin oil and respond to a variety of release stimuli. Hereby, retaining an aesthetic feel on the skin's surface. This technology is presently employed in nearly number of products sold by major cosmetic and toiletry companies worldwide. Among these products skin makeup, powders, cleansers, conditioners, oil control lotions, moisturizers, deodorants, razors, lipstick, and eye shadows are introduced. Which proposed various advantages, including improved physical and chemical stability, controlled release of the active ingredients, greater available concentrations, reduced skin irritation and sensitization, and unique tactile qualities[27]. Several marketed products utilizing microsponge drug delivery system summarizes in Table 2.

TABLE 2: Marketed products using microsponge drug delivery system

Product	Advantages	Manufacturer
Retin-A-Micro	Around 0.1% and 0.04% tretinoin entrapped in microsponge drug delivery for topical treatment of acne vulgaris. This formulation uses patented methyl methacrylate/ glycol dimethacrylate cross-polymer porous microspheres (MICROSPONGE® System) to enable inclusion of the actives, tretinoin, in an aqueous gel.	Ortho-McNeil Pharmaceutical, Inc.
Carac Cream, 0.5%	It consist of fluorouracil up-to 0.5 %, with 0.35% being inclusive into a patented microsponge that is composed of methyl methacrylate or glycol dimethacrylate cross-polymer and dimethicone. It is a topical prescription product for the treatment of actinic keratoses (AK) and used once-a-day, a common pre-cancerous skin condition caused by over-exposure to the sun.	Dermik Laboratories, Inc.
Retinol cream	The retinol molecule is kept in the microsponge system to protect the potency of the vitamin A. This helps to enhance retinol dosage meanwhile decreasing the possibility of irritation. Retinol is a topical vitamin A derivative which helps to maintain the healthy skin, hair and mucous membranes.	Biomedic, Inc.
Biomedic, Inc.	The Microsponge ® system uses the microscopic reservoirs that trap HQ and retinol. This confer the skin with continuous exposure to hydroquinone and retinol over time, which may reduced skin irritation.	SkinMedica Inc
Line Eliminator Dual Retinol Facial Treatment	Lightweight cream with a retinol in microsponge drug delivery system, it delivers both immediate and time released of drug and having wrinkle-fighting action.	Avon
Retinol 15 Nightcream	When we use Retinol 15 continuously in night will results in the visible diminishment of fine lines and wrinkles, a observable improvement in the skin discolorations due to aging and enhanced skin smoothness.	Sothys
EpiQuin Micro	This confer the skin with continuous exposure to hydroquinone and retinol over time, which may reduced skin irritation.	Skin medica inc.
Sports cream RS and XS	Topical analgesic-anti-inflammatory and counterirritant actives used for the management of musculoskeletal conditions in a Microsponge® Delivery System.	Embil pharmaceutical co. Ltd.

APS developed microsphere precursors to the microsponge for use as a testing standard for gauging the purity of municipal drinking water. Marketed nationwide, these microspheres are suspended in pure water to form an accurate, stable, reproducible turbidity standard for the graduation of turbidimeters used to examine water purity. The technology can have much broader applications than testing the turbidity of water and can even be used for the calibration of spectrophotometers and colorimeters.

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 exclusive technology for the controlled release of topical agents and it consists of microporous beads loaded with active ingredients. Thus, use for oral as well as biopharmaceutical drug delivery also. MDS can release its active agent on a time mode and in response to other stimuli also. Hereby, microsponge has got a lot of potential and is a very emerging field which is needed to be explored.

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CONFLICT OF INTEREST

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