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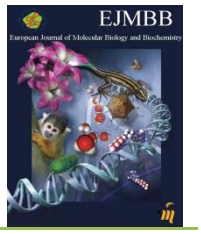

A CURRENT VIEW ON MICROSPONGE DRUG DELIVERY SYSTEM

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ABSTRACT
The drug delivery technology landscape has become highly competitive and rapidly evolving. More and more developments in delivery systems are being integrated to optimize the efficacy and cost-effectiveness of the therapy In recent times, microsponge delivery system (MDS) has been successively addressed for the controlled release of drugs onto the epidermis. Microsponge is recent novel technique for control release and target specific drug delivery system. Drug loaded microsponge consist of microporous beads, typically 10-25 µm in diameter that possess a versatility to entrap wide range of active agents. Microsponge Systems are based on microscopic, polymer-based microspheres that can suspend or entrap a wide variety of substance. Microsponge technology offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility. In addition, numerous studies have confirmed that microsponge systems are non-irritating, non-allergenic and non-toxic. MDS technology is being used currently in cosmetics skin care, sunscreens. One of the best feature is it is self-sterilizing. it also expands its application in oral drug delivery, bone and tissue engineering. The versatile and unique properties of MDS made it ideal carrier of drugs with shorter half-lives and drugs which are suffering from first pass metabolism.

INTRODUCTION

Drug delivery system

Increased developments in drug delivery systems are being integrated to optimize the efficacy and cost effectiveness of the therapy. With increasing competition and increased need for customer friendliness, in transdermal drug delivery systems have gained a lot of importance. Further controlled release of drugs through the epidermis with sureness that the drug remains mainly localized and that does not enter the systemic circulation in significant amounts is thought to be an area of research that has only recently been addressed with success.

Defining Microsponge

The Microsponges Delivery System (MDS) is a patented polymeric system consisting of porous microspheres. They are tiny sponge like spherical particles that consist of a myriad of interconnecting voids within a non-collapsible structure with a large porous surface as shown in figure 1 through which active ingredient are released in a controlled manner [1].

Microsponge was originally developed for topical delivery of drugs. They are colloidal carriers have recently been developed and proposed for drug delivery. since their use can solubilize poorly water soluble drug and provide prolonged release as well as improving drugs bioavailability and in some case modifying its pharmacokinetics parameters. They can also decrease side effect and protect drug from degradation. 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

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profile. The microsponges are macroporous beads typically 10-25 microns in diameter loaded with active agent. Microsponges are porous, polymeric microspheres that are mostly used for prolonged topical administration.

Microsponges consisting of non-collapsible structure with porous surface through which active ingredients are released in a controlled manner. Microsponges are porous microsphere having interconnected voids of particle size range 5300µm. They are uniform, spherical polymer particles. 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.

Microsponge delivery systems (MDS) that can precisely control the release rates or target drugs to a specific body site have an enormous impact on the health care system. The microsponge drug delivery technology is widely applicable to the dermatological drug delivery products. But MDS also expands its application in oral drug delivery, bone and tissue engineering, in detecting the diseases and in RNAi silencing.

Microsponges are highly crosslinked, patented, porous, polymeric microspheres having myriad of interconnected voids of particle size range 5-300µm was shown in figure 2 that acquire the flexibility to entrap a wide variety of active ingredients that are mostly used for prolonged topical administration and but recently they are also investigating for oral drug administration [2].

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. 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.

These criteria serve as porogen or pore forming agent. Such drugs can be entrapped while polymerization takes place by one-step process. When the material is sensitive to the polymerizing conditions, polymerization is performed using substitute porogen. The porogen is then removed and replaced by contact absorption assisted by solvents to enhance absorption rate.

PREPARATION OF MICROSPONGES

Drug loading in microsponges drug delivery system done in two ways, one step process or by two step process. They are

- Liquid-liquid suspension polymerization
- Quasi emulsion solvent diffusion method

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 [3].

Liquid-liquid suspension polymerization

Microsponges are prepared by suspension polymerization process in liquid-liquid systems (one-step process). Firstly, the monomers are dissolved along with active ingredients (non-polar drug) in an appropriate solvent solution of monomer, which are then dispersed in the aqueous phase with agitation. Aqueous phase typically consist of additives such as surfactants and dispersants (suspending agents) etc in order to facilitate the formation of suspension. Once the suspension is established with distinct droplets of the preferred size then, polymerization is initiated by the addition of catalyst or by increasing temperature as well as irradiation was shown in figure 4. The polymerization method leads to the development of a reservoir type of system that opens at the surface through pores. During the polymerization, an inert liquid immiscible with water however completely miscible with monomer is used to form the pore network in some cases. Once the polymerization process is complete, the liquid is removed leaving the microsponges which is permeate within preformed microsponges then, incorporates the variety of active substance like anti fungal, rubefacients, anti-acne, anti inflammatory etc and act as a topical carriers. In some cases, solvent can be used for efficient and faster inclusion of the functional substances. If the drug is susceptible to the condition of polymerization then, two-step process is used and the polymerization is performed by means of alternate porogen and it is replaced by the functional substance under mild conditions.several parts as raw materials to produce cosmetics [7].

The seeds of lotus decrease blood lipids induced by a high-fat diet in rats [8]. It also inhibits platelet aggregation [9]; anti fertility effect [10] and free radical scavenger [11]. The lotus rhizome showed the isolation of active fraction of amino acid tryptophan that reduced the blood glucose level [12] and CNS - depressant effect [13] in hyperglycemic mice. Stalk extracts of *N.nucifera* showed antipyretic effect [14]. The lotus plumuleis a potent antioxidant [15] and it is recognized as a cooling food with anti-inflammatory activities [16]. The leaves are used in the treatment of bleeding disorders [17]. The embryo of *N. nucifera* extract increases the heart rate and contraction [18]. The flower extract of *N.nucifera* possess.

Quasi-Emulsion Solvent Diffusion Method

Microsponges were also prepared by a quasi-emulsion solvent diffusion method (two-step process) using an internal phase containing polymer such as Eudragit RS 100 which is dissolved in ethyl alcohol. Then, the drug is slowly added to the polymer solution and dissolved under ultrasonication at 35°C and plasticizer such as triethylcitrate (TEC) was added as shown in figure 3 in order to aid the plasticity. The inner phase is then poured into external phase containing polyvinyl alcohol and distilled water with continuous stirring for 2 hours11. Then, the mixture was filtered to separate the microsponges. The product (microsponges) was washed and dried in an air heated oven at 40°C for 12 hrs [4].

Mechanism of releasing

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

Temperature Change: At room temperature, few entrapped active ingredients can be too viscous to flow suddenly from microsponges onto the skin. With increase in skin temperature, flow rate is also increased and therefore release is also enhanced.

Pressure: Rubbing or pressure applied can release the active ingredient from microsponges onto skin.

Solubility: Microsponges loaded with water miscible ingredients like antiseptics and antiperspirants will release the ingredient in the presence of water. The release can also be activated by diffusion but taking into consideration, the partition coefficient of the ingredient between the microsponges and the external system.

pH Triggered Systems: Triggering the pH-based release of the active can be achieved by modifying the coating on the microsponge [5].

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 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.

Microsponges for Bone and Tissue Engineering Bone-substitute

Compounds were obtained by mixing pre polymerized powders of polymethyl methacrylate and liquid methyl methacrylate monomer with two aqueous dispersions of tricalcium phosphate grains and calcium deficient hydroxyapatite powders. The final composites appeared to be porous and acted as microsponges. Basic fibroblast growth factor (bFGF) incorporated in a collagen sponge sheet was sustained released in the mouse sub-cutis according to the biodegradation of the sponge matrix and exhibited local angiogenic activity in a dose-dependent manner. The injection of collagen microsponges incorporating bFGF induced a significant increase in the blood flow in the murine ischemic hind limb, which could never have been attained by the bolus injection of bFGF. These results suggest the significance and therapeutic utility of the type I collagen as a reservoir of bFGF.

Microsponges in Oral Care Cosmetics

An interesting application of the microsponge technology could be in oral cosmetics, such as to sustain the release of volatile ingredients. Thus increasing the duration of the fresh feel Microsponges of such volatile ingredients may be easily incorporated in tooth pastes or mouth washes [6].

Long lasting Coloured Cosmetics

A new application for Microsponges Colours entrapped in microsponges may be used in a variety of coloured cosmetic products such as rouge or lipsticks to make them long lasting. As stated above, microsponges help in uniform spreading and improving covering power. Thus, colored cosmetics formulated with microsponges would be highly elegant.

Microsponge for Topical Delivery

Benzoyl peroxide is mainly used in the treatment of mild to moderate acne and athlete's foot and the most common side effect associated with Benzoyl peroxide is skin irritation and it has been shown that controlled release of Benzoyl peroxide from a delivery system to the skin could lessen the side effect while reducing percutaneous absorption. Topical delivery system with reduced irritancy was successfully developed [7].

EVALUATION OF MICROSPONGES DELIVERY SYSTEM

Particle size and shape

The most widely used procedures to visualize micro particles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine the shape and outer structure of micro particles. LM provides a control over coating parameters in case of double walled micro particles. The micro particles structures can be visualized before and after coating and the change can be measured microscopically. SEM provides higher resolution in contrast to the LM. SEM allows investigations of the microparticles surfaces and after particles are cross-sectioned, it can also be used for the investigation of double walled systems. Conflocal fluorescence microscopy is used for the structure characterization of multiple walled microparticles. Laser light scattering and multi size coulter counter other than instrumental methods, which can be used for the characterization of size, shape and morphology of microsponges.

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 ultra structure.

The size of the microsponges usually ranges from 5-300µm in diameter and a typical 25µm sphere can have as many as 250000 pores and an internal pore structure equivalent to 10 ft in length, providing a total pore volume of about 1 ml/g. These microsponges have the excellent capacity to entrap a wide range of active ingredients such as emollients, fragrances, essential oils, anti-infective, etc that are used as a topical carrier system.

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.

Drug release from the semi solid dosage forms and drug deposition studies

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

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 [8].

DRUGS EXPLORED IN MICROSPONGE DRUG DELIVERY SYSTEM

- Ibuprofen
- Fluconazole
- Benzyl peroxide
- Ketoprofen
- Paracetamol
- Dicyclomine
- Flurbiprofen
- Ketoconazole
- Tretinoin
- Trolamine
- Retinol

APPLICATIONS OF MICROSPONGES

Microsponges are designed to deliver the pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects and modify drug release. Microsponge drug delivery systems offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, reduces systemic exposure and minimize local cutaneous reactions, increased elegance, and enhanced formulation flexibility [9].

ADVANTAGES OF MICROSPONGES

This technology offers entrapment of ingredients and reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility Microsponge systems are non-irritating, non-mutagenic, non-allergenic, and non-toxic. Extended release - continuous action up to12 hours. Allows incorporation of immiscible liquid. Improves material processing - liquid can be converted to powders.

Microsponge formulations are stable over range of pH 1 to 11; 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 as it is stable at the temperature up to 130°C. Microsponge formulations have higher payload (50 to 60%), still free flowing and can be cost effective. This technology offers entrapment of ingredients and reduced side effects, Improved stability, increased elegance, and enhanced formulation flexibility. Extended release - continuous action up to 12 hours allows incorporation of immiscible liquid Improves material processing - liquid can be converted to powders.

- Advanced oil control, absorb up to 6 times its weight without drying
- Improved product elegancy.
- MDS allows the incorporation of immiscible products.
- Reduced irritation
- Allows novel product form
- Improved product aesthetics gives product an elegant feel
- Better tolerance means broader consumer acceptance

- Improves thermal, physical and chemical stability
- In contrast to other technologies like microencapsulation and liposomes, MDS has wide range of chemical stability, higher payload and are easy to formulate.
- Microsponges are microscopic spheres capable of absorbing skin secretions, therefore, reducing oiliness and shine from the skin. Flexibility to develop novel product forms. Microsponges offer better control of drug release than microcapsules. Microcapsules cannot usually control the release rate of the active pharmaceutical ingredients (API). Once the wall is ruptured, the API contained within the microcapsules will be released [10].

ADVANTAGES OVER CONVENTIONAL FORMULATION

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.

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 to1300C; 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. It has a property of self sterilization as their average pore size is 0.25m where bacteria cannot penetrate. It is compatible with vehicles and ingredients.

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.

Table 1. Important Microsponge Preparation

Retin-A-Microtm	0.04% tertinoin entrapped in MDS, for topical treatment of acne vulgaris.
Carac cream, 0.5%	Carac cream contains 0.5% flurouracil,with0.35 being incorporated into a patented porous microsponge composed of methyl methacrylate cross polymer and dimethicone
Line eliminator dual retinal Facial treatment	Lightweight cream with a retinal in MDS, Delivers both immediate and time released Wrinkle-fighting action
Retinol cream	The retinol molecule is kept in microsponge System to protect the potency of vitamin A. This helps to maximize the retinol dosage. While reducing the possibility of irritation
Retinol 15 night cream	A night time treatment with microsponge Technology using a stabilize formula of pure Retinol and vitamin
EpiQuin micro	The microsponge system uses microscopic. Reserviours that entrap hydroquionone and Retinol
Spots cream RS and X	Topical analgesic-anti inflammatory and Counter Irritant activities in microsponge delivery System for management of musculoskeletal Condition.
Salicylic peel 20	Deep BHA peeling agent for salicylic acid 20% microsponge technology. Excellent Exfoliations and stimulation of skin for more Resistant skin types or for faster results.
Oil free matte block spf20	The invisible sun screen provides a shield for the skin from damaging UV rays and controls oil production. Microsponge technology absorbs the oil. Maintain an all day matte finish and preventing shine without any powdery residue
Anti-acne e.g. Benzoyl peroxide	Maintained efficacy with decreased skin irritation and sensitization
Anti-fungals	Sustained release of actives
Anti-inflammatory e.g. hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatoses.
Anti-dandruffs e.g. zinc	Reduced unpleasant odour with lowered irritation with extended safety and efficacy

pyrithione, sele-nium sulfide	
Anti-pruritics	Extended and improved activity
Rubefacients	Prolonged activity with reduced irritancy greasiness and odour
Sunscreens	Long lasting product efficacy, with improved protection against sunburns and sun related injuries even at elevated concentration and with reduced irritancy and sensitization.

Fig 1. Porous Structure of Microsponges

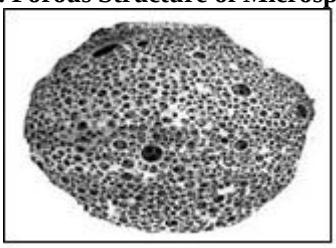
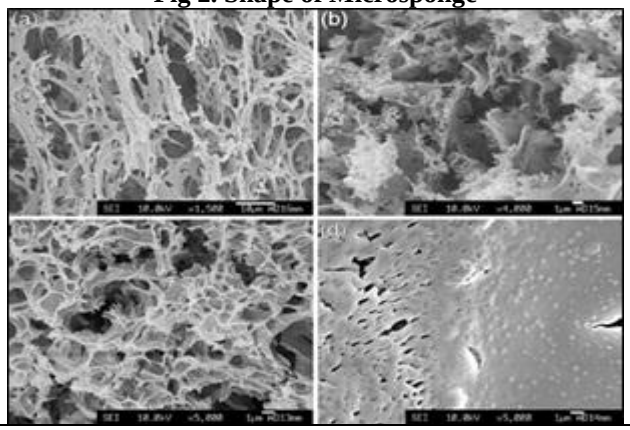


Fig 2. Shape of Microsponge



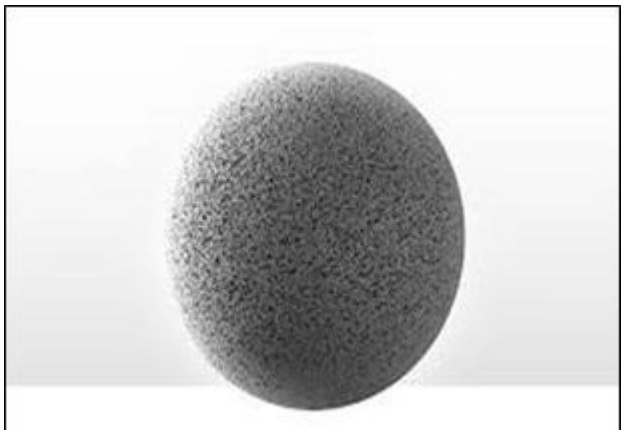


Fig 3. Preparation of Microsponges by Liquid-liquid suspension polymerization

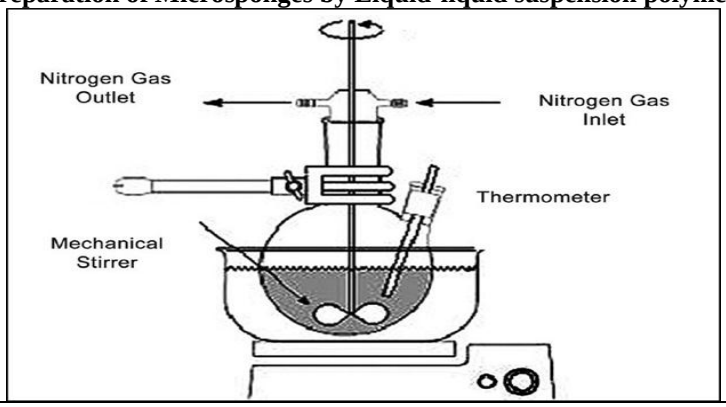


Fig 4. Preparation of Microsponges by Quasi-Emulsion Solvent Diffusion Method

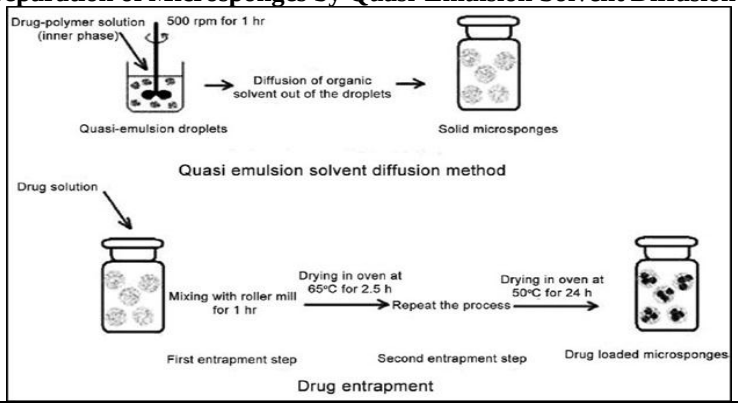


Fig 5. SEM Images of Microsponge

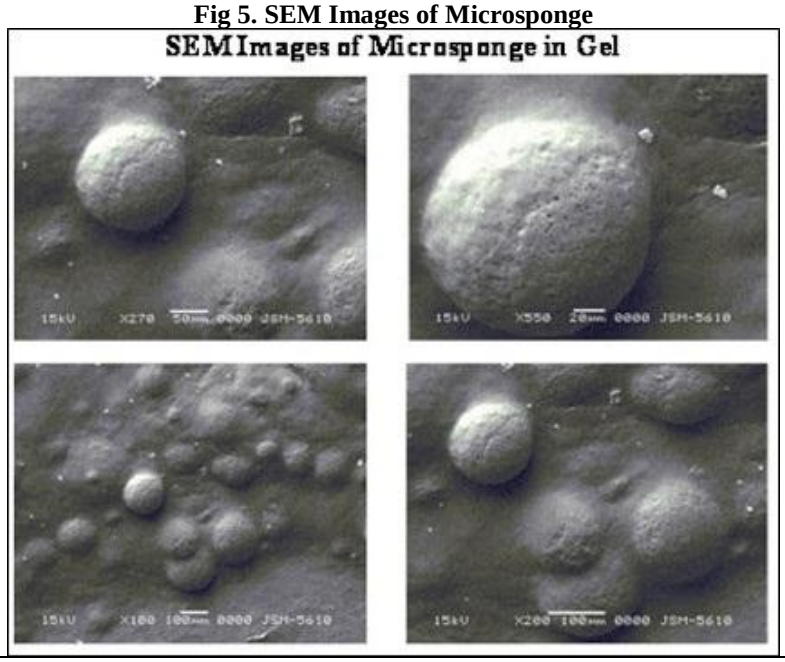
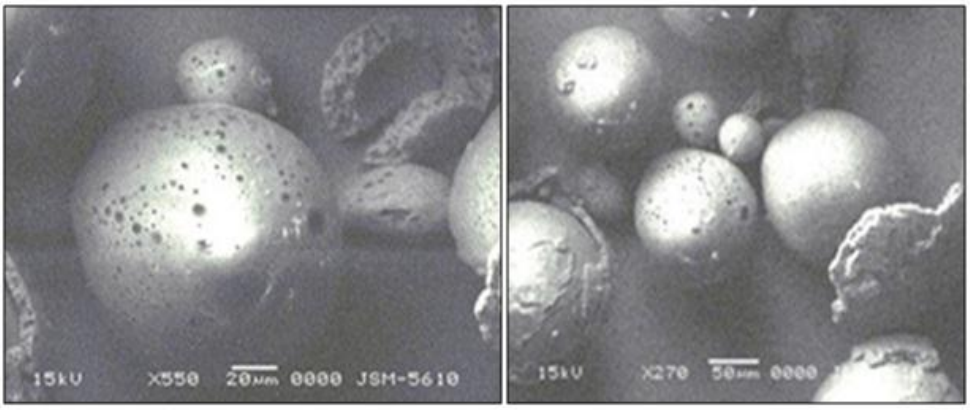


Fig 6. Morphology and surface topography of microsponges



SUMMARY AND CONCLUSION

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. Microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Researchers are continuously trying to develop a drug delivery system which is cost effective and having better therapeutic efficacy. MDS technology showed such promises to meet researcher's expectations. It is a very unique technology to control drug release of topical agents as well as oral drug delivery. The MDS system offers entrapment of its ingredients with reduced side effects, improved stability and increased eleganic. The versatile and unique properties of MDS made it ideal carrier of drugs with shorter half-lives and drugs which are suffering from first pass metabolism. 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. 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. Especially for colon specific delivery and controlled release drug delivery system thus improving patient compliance by providing site specific drug delivery system and prolonging dosage intervals.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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