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MICROSPONGE DELIVERY SYSTEM (MDS): A UNIQUE TECHNOLOGY FOR DELIVERY OF ACTIVE INGREDIENTS

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ABSTRACT

In pharmaceutical industry, various controlled released dosage forms like solid formulation, semi solid formulation and topical preparation have more importance due to efficacy and patient compliance. Topical preparations have some disadvantages like unpleasant odour, greasiness and skin irritation and fail to reach the systemic circulation in sufficient amounts in few cases. This problem is overcome by microsponge delivery system. Microsponges are tiny sponge like spherical and highly porous micro-sized particles with a unique ability for entrapping actives. They offers programmable release active drug into the skin in order to reduce systemic exposure and minimize local cutaneous reactions to active. These MDS's are closely related to microspheres, and used in the sun screens, creams, ointments, over- the-counter (OTC) skin care preparations, recently used in oral drug as well as biopharmaceuticals (peptides, proteins and DNA-based therapeutics) drug delivery. The present review introduces microsponge technology along with its synthesis, characterization, programmable parameters and release mechanism of MDS.

INTRODUCTION: The microsponge technology was developed by Won in 1987 and the original patents were assigned to Advanced Polymer Systems, Inc [1]. Several predictable and reliable systems were developed for systemic delivered through skin under the title of transdermal delivery system (TDS). It has improved the efficacy and safety of many drugs that may be better administered via skin. But transdermal delivery system is unrealistic for delivery of materials whose final target is skin itself [2].

No efficient vehicles have been developed for controlled and localized delivery of drugs into the stratum corneum and underlying skin layers and not beyond the epidermis [3]. 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 [4]. Furthermore, the significance of topical drugs suffers from various problems like greasiness, stickiness associated with the ointments and so on, that often result in lack of patient compliance.

These vehicles necessitate a high concentration 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 odour. The fundamental appeal of the microsponge technology stems from these difficulties experienced with conventional formulations in releasing active ingredients over an extended period of time.

Conventional dermatological products typically provide active ingredients in relatively high concentrations but with a short duration of action. This may lead to a cycle of short term over medication followed by long term under medication. In contrast, microsponge technology allows an even and sustained rate of release, reducing irritation while maintaining efficacy.

Microsponges are patented delivery systems composed 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. The size of the microsponges ranges from 5 - 300µm (**Figure 1**) in diameter and a typical 25µm sphere can have up to 250000 pores and an internal pore structure equivalent to 10ft in length, providing a total pore volume of about 1ml/g. These microsponges have the capacity to entrap a wide range of active ingredients such as emollients, fragrances, essential oils and anti-infective, etc. are used as a topical carrier system[5].

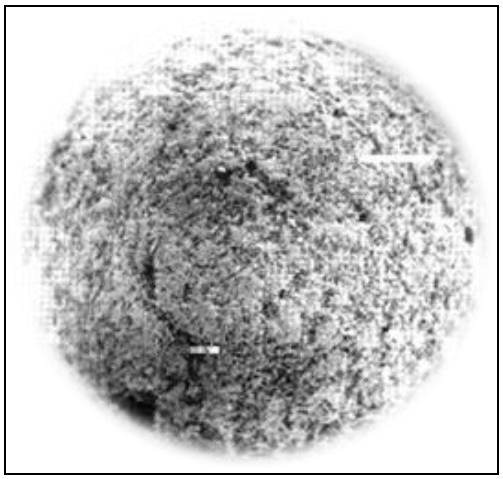


FIG. 1: POROUS NATURE OF A MICROSPONGE

Further, these porous microspheres with active ingredients can be incorporated in to formulations such as creams, lotions and powders. Release of drug into the skin is initiated by a variety of triggers, including rubbing and higher than ambient skin temperature [6]. Their high degree of cross-linking results in particles that are insoluble, inert and of sufficient strength to stand up to the high shear commonly used in manufacturing of creams, lotions, and powders. Their characteristic feature is the capacity to adsorb or "load" a high degree of active materials into the particle and on to its surface.

Its large capacity for entrapment of actives, up to three times its weight, differentiates microsponge products from other types of dermatological delivery systems. The active payload is protected in the formulation by the microsponge particle; it is delivered to skin through controlled diffusion. This sustained release of actives to skin over time is an extremely valuable tool to extend the efficacy and lessen the irritation.

Advantages of Microsponge Delivery System [5, 7]:

- Microsponges can absorb oil up to 6 times its weight without drying.
- It provides continuous action up to 12 hours i.e. extended release.
- Improved product elegancy.
- Lessen the irritation and better tolerance leads to improved patient compliance.
- It can also improve efficacy in treatment.
- They have better thermal, physical and chemical stability.
- These are non-irritating, non-mutagenic, non-allergenic and non-toxic.
- MDS allows the incorporation of immiscible products.
- They have superior formulation flexibility.
- In contrast to other technologies like microencapsulation and liposomes, MDS has wide range of chemical stability, higher payload and are easy to formulate.
- Liquids can be converted in to powders improving material processing.
- It has flexibility to develop novel product forms.
- MDS can improve bioavailability of the drugs.

Characteristics of Microsponges [8]**:**

- Microsponge formulations are stable over range of pH 1 to 11;
- Microsponge formulations are stable at the temperature up to 130^{o}C;
- Microsponge formulations are compatible with most vehicles and ingredients;
- Microsponge formulations are self sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate;
- Microsponge formulations have higher payload (50 to 60%), still free flowing and can be cost effective.

Characteristics of materials that are entrapped in Microsponges: Most liquid or soluble ingredients can be entrapped in the particles [9]. 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.
- It should be stable in contact with polymerization catalyst and conditions of polymerization.

Drugs explored in Microsponge Delivery System [9-17]:

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

Formulation Aids: Various polymers like Eudragit RS100, Dimethacrylate, Ethyl Cellulose, Polystyrene and PHEMA can form a microsponge 'cage'. In addition to actives; some microsponges contain plasticizers like Triethylcitrate (TEC) that help to stabilize their structure [18-21].

Preparation of Microsponges: Drug loading in microsponges drug delivery system done in two ways, one step process or by two step process as discussed in liquid-liquid suspension polymerization and quasi emulsion solvent diffusion techniques which are based on physicochemical properties of drug to be loaded. If the drug is typically an inert non-polar material, will create the porous structure it is called porogen. Porogen drug, which neither hinders the polymerization nor become activated by it and stable to free radicals is entrapped with one step process.

Liquid-Liquid Suspension Polymerization: The porous microspheres are prepared by suspension polymerization method in liquid-liquid systems [22]. In their preparation, the monomers are first dissolved along with active ingredients in a suitable solvent solution of monomer and 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 (**Figure 2**).

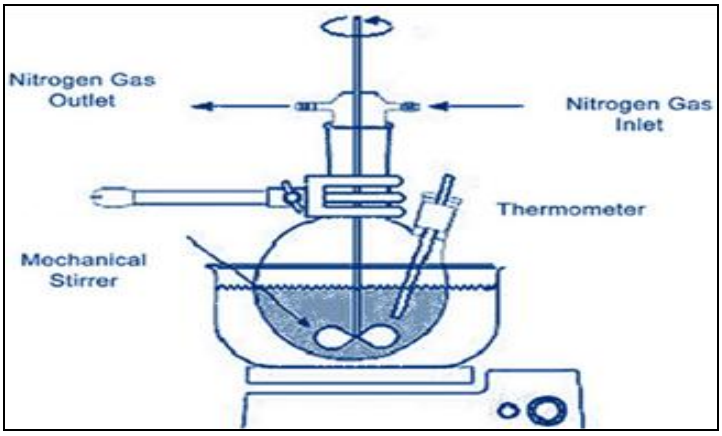
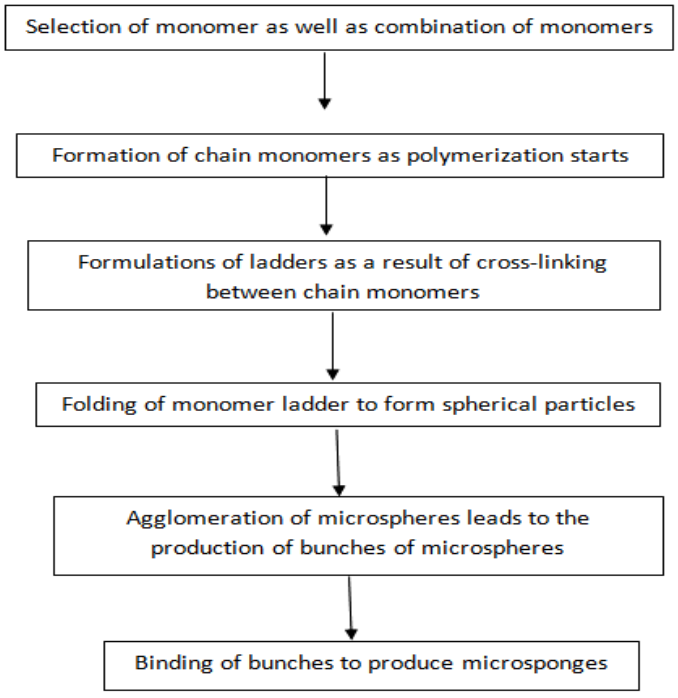


FIG. 2: REACTION VESSEL FOR MICROSPONGE PREPARATION BY LIQUID-LIQUID SUSPENSION METHOD

The polymerization process continues the formation of a reservoir type of system with spherical structure. After the polymerization process the solvent is removed leaving the spherical structured porous microspheres, i.e., microsponges. The various steps involved in the preparation of microsponges are summarized in **scheme 1** as follows [12]:



SCHEME 1: STEPS IN THE PREPARATION OF MICROSPONGES

Quasi-emulsion Solvent Diffusion: All microsponges were prepared by a quasi-emulsion solvent diffusion method (**Figure 3**) using an external phase of containing distilled water and polyvinyl alcohol (PVA) 72 000. The internal phase consisted of Drug, ethyl alcohol, polymer and TEC, which was added at an amount of 20% of the polymer in order to facilitate the plasticity. At first, the internal phase was prepared at 60°C and added to the external phase at room temperature. After emulsification, the mixture was continuously stirred for 2 hours. Then the mixture was filtered to separate the microsponges. The product was washed and dried by vacuum oven at 40°C for 24 hours [19].

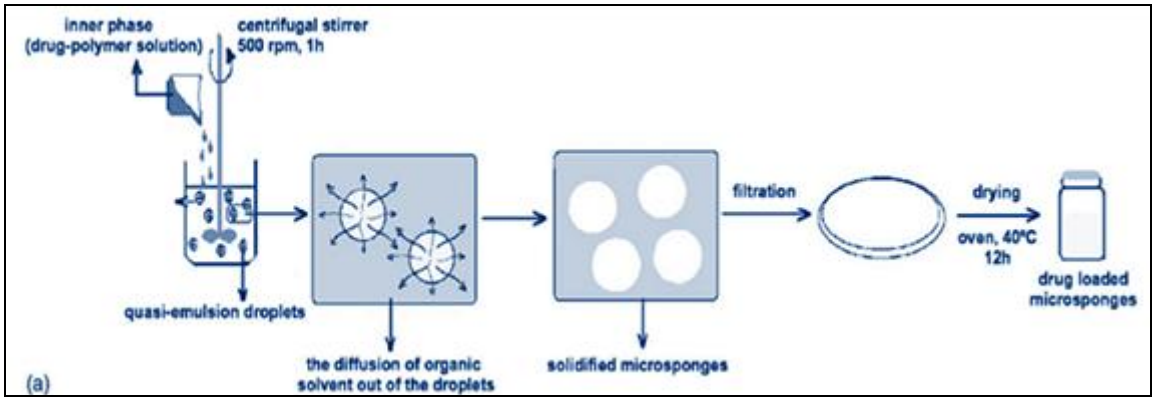


FIG. 3: PREPARATION OF MICROSPONGES BY QUASI-EMULSION SOLVENT DIFFUSION METHOD

Evaluation Parameters of Microsponges:

- Particle size (Microscopy)
- Morphology and Surface topography
- Characterization of pore structure
- Loading efficiency and production yield
- Characterization of pore structure
- Compatibility studies
- Resiliency
- Drug release study

Physical Characterization of Microsponges:

Particle Size Determination [21]**:** Particle size analysis of loaded and unloaded microsponges can be performed by laser light diffractometry or any other suitable method. The values can be expressed for all formulations as mean particle size range. Cumulative percentage drug release from microsponges of different particle size will be plotted against time to study effect of particle size on drug release. Particles larger than 30µm can impart gritty feeling and hence particles of sizes between 10 and 25µm are preferred to use in final topical formulation.

Morphology and Surface Topography of Microsponges [23]**:** 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.

Determination of Loading Efficiency and Production Yield [24]**:** 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 microparticles can be determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponge obtained.

$$\text{Production Yield} = \frac{\text{Practical Mass of Microsponges}}{\text{Theoretical Mass (Polymer + Drug)}} \times 100$$

Determination of True Density [25]**:** The true density of microparticles is measured using an ultra-pycnometer under helium gas and is calculated from a mean of repeated determinations.

Characterization of Pore Structure [26]**:** Porosity parameters of microsponges such as intrusion extrusion isotherms, pore size distribution, total pore surface area, average pore diameters, shape and morphology of the pores, bulk and apparent density

can be determined by using mercury intrusion porosimetry. Incremental intrusion volumes can be plotted against pore diameters that represented pore size distributions. The pore diameter of microsponges can be calculated by using Washburn equation:

$$D = \frac{-4\gamma\cos\theta}{P}$$

Here; D is the pore diameter (µm), γ is the surface tension of mercury (485 dyn cm−1), θ is the contact angle (130°), and P is the pressure (psia).

Total pore area (A_{tot}) was calculated by using equation,

$$A_{tot} = \frac{1}{\gamma\cos\theta}\int_0^{V_{tot}} P.\,dV$$

Here, P is the pressure (psia), V is the intrusion volume (ml g−1), Vtot is the total specific intrusion volume (ml g−1). The average pore diameter (Dm) was calculated by using equation:

$$Dm = \frac{4V_{tot}}{A_{tot}}$$

Envelope (bulk) density (ρse) of the microsponges was calculated by using equation:

$$\rho_{se} = \frac{Ws}{V_p - V_{Hg}}$$

Here, Ws is the weight of the microsponge sample (g), Vp is the empty penetrometer (ml), VHgis the volume of mercury (ml). Absolute (skeletal) density (ρsa) of microsponges was calculated by using equation:

$$\rho_{sa} = \frac{Ws}{Vse - Vtot}$$

Here, Vse is the volume of the penetrometer minus the volume of the mercury (ml). Finally, the percent porosity of the sample was found from equation,

$$\text{Porosity}(\%) = \left(1 - \frac{\rho_{se}}{\rho_{sa}}\right) \times 100$$

Pore morphology can be characterized from the intrusion–extrusion profiles of mercury in the microsponges as described by Orr.

Compatibility Studies: Compatibility of drug with reaction adjuncts can be studied by thin layer chromatography (TLC) and Fourier Transform Infra-red spectroscopy (FT-IR) [27]. Effect of polymerization on crystallinity of the drug can be studied by powder X-ray diffraction (XRD) and Differential Scanning Colorimetry (DSC) [28]. For DSC approximately 5mg samples can be accurately weighed into aluminium pans and sealed and can be run at a heating rate of 15°C/min over a temperature range 25–430°C in atmosphere of nitrogen [29-30].

Polymer/Monomer Composition: Factors such as microsponge size, drug loading, and polymer composition govern the drug release from microsponges. Polymer composition of the MDS can affect partition coefficient of the entrapped drug between the vehicle and the microsponge system and hence have direct influence on the release rate of entrapped drug. Release of drug from microsponge systems of different polymer compositions can be studied by plotting cumulative % drug release against time. Release rate and total amount of drug released from the system composed of methyl methacrylate/ ethylene glycol dimethacrylate is slower than styrene/divinyl benzene system. [3]

Resiliency: Resiliency (viscoelastic properties) of microsponges can be modified to produce beadlets that is softer or firmer according to the needs of the final formulation. Increased cross-linking tends to slow down the rate of release. Hence resiliency of microsponges will be studied and optimized as per the requirement by considering release as a function of cross-linking with time [31].

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. 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 [32].

Kinetics of Release: To determine the drug release mechanism and to compare the release profile differences among microsponges, the drug released

amount versus time was used. The release data were analyzed with the following mathematical models:

$$Q = k_1 t^n \quad \text{OR} \quad logQ = logk_1 + n \log t$$

Where, Q is the amount of the released at time (h), n is a diffusion exponent which indicates the release mechanism, and k_1 is a constant characteristic of the drug–polymer interaction. From the slope and intercept of the plot of log Q versus log t, kinetic parameters n and k_1 were calculated.

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

$$Q = k_2 t^{0.5} + C$$

Above Eq. 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.

Mechanism of Drug Release: By proper manipulation of the aforementioned programmable parameters, microsponge can be designed to release given amount of active ingredients over time in response to one or more external triggers.

Temperature Change [33]**:** 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 [34]**:** Rubbing or pressure applied can release the active ingredient from microsponges onto skin.

Solubility [35]**:** 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 [36]**:** Triggering the pH-based release of the active can be achieved by modifying the coating on the microsponge. This has many applications in drug delivery.

Safety Considerations [33, 37-38]: Safety studies of microsponges can be confirmed by:

- Allergenicity in guinea pigs
- Eye irritation studies in rabbits
- Mutagenicity in bacteria
- Oral toxicity studies in rats
- Skin irritation studies in rabbits

Applications of Microsponge Systems: 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. Microsponges are porous, polymeric microspheres that are used mostly for topical but recently used for oral administration (**Table 1**).

TABLE 1: APPLICATIONS OF MICROSPONGE SYSTEM

ACTIVE AGENTS	APPLICATIONS
Anti-acne	Maintained efficacy with decreased skin irritation and sensitization.
Anti-dandruffs	Reduced unpleasant odour with lowered irritation with extended safety and efficacy.
Anti-fungals	Sustained release of actives.
Anti-inflammatory	Long lasting activity with reduction of skin allergic response and dermatoses.
Antipruritics	Extended and improved activity.
Rubefacients	Prolonged activity with reduced irritancy greasiness and odour.
Skin de-pigmenting agents	Improved stabilization against oxidation with improved efficacy and aesthetic appeal.
Sunscreens	Long lasting product efficacy, with improved protection against sunburns and sun related injuries even at elevated concentration and with reduced irritancy and sensitization.

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 [39].

Jelvehgari *et al*., developed Benzoyl peroxide microsponges by using emulsion solvent diffusion method and investigate the parameters affecting the morphology and other characteristics by using scanning electron microscopy (SEM). The morphology and particle size of microsponges were affected by drug: polymer ratio, amount of emulsifier used and stirring rate. The results showed that with increase in the ratio of drug: polymer resulted in a reduction in the rate of release of Benzoyl peroxide from the microsponges. The release data showed that the highest and the lowest release rates were obtained from lotions containing plain Benzoyl peroxide particles and Benzoyl peroxide microsponges with the drug: polymer ratio (13:1) respectively [19].

Amrutiya *et al*., developed microsponge based topical delivery system of mupirocin by using emulsion solvent diffusion method for sustained release and enhanced drug deposition in the skin. In-vitro drug release, ex-vivo drug deposition, and in-vivo antibacterial activity of mupirocin loaded formulations were studied. Microsponges were spherical and porous, and there was no interaction between drug and polymer molecules. Emulgels containing microsponges showed desired physical properties. 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 [40].

D'souza *et al*., developed topical anti-inflammatory gels of fluocinolone acetonide entrapped in eudragit based microsponge delivery system. Fluocinolone acetonide (FA) is a corticosteroid chiefly used in dermatology to lessen skin inflammation and relieve itching. The percutaneous absorption increases risk related with systemic absorption of topically applied formulation.

Thus, the goal of the study was to produce FA entrapped microsponges which were prepared by quasi-emulsion solvent diffusion method in order to control release of drug to the skin which in turn lessens the side effect whereas also reducing percutaneous absorption. FTIR and DSC studies showed that there is no incompatibility between formulation adjuvant and process parameters.

Surface morphology can be done by SEM which showed microporous nature of microsponges. Drug release was also observed controlled with comparative anti-inflammatory activity with the gels that contains free drug [41].

Grimes *et al*., developed microsponge based delivery of hydroquinone 4% and retinol 0.15% for the treatment of melasma and post-inflammatory hyper-pigmentation and also to minimize skin irritation. Hydroquinone (HQ) bleaching creams are generally considered as the gold standard for treating hyper-pigmentation. The formulation was evaluated in a 12 week open label study for safety and efficacy. The study included pigmentation intensity, disease severity, lesion area and colorimetry assessments. Adverse events were also recorded. Patients were applied the microsponge formulation entrapped HQ 4% to the full face in morning and evening (twice) daily. After 15 minutes of application of the test product, a broad-spectrum sunscreen was applied once in the morning. Then, patients were evaluated at baseline and at 4, 8, and 12 weeks. The study showed that microentrapped HQ 4% with retinol 0.15% formulation produced improvement at all study end points. The open-label study concluded that microentrapped HQ 4% with retinol 0.15% was safe and effective.[17]

Microsponge for Oral Delivery: A Microsponge system offers the potential for active ingredients to remain within 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. If this approach is successful then it should open up entirely new opportunities for MDS. It has been shown that microsponge system enhances the solubilization of drugs which are poorly soluble by entrapping these drugs in their pores.

As these pores are very small, the drug is in effect reduced to microscopic particles and drastically increased surface area consequently, increases the rate of solubilization. Additionally, the time it takes the microsponge system to pass through the small and large intestine is considerably increased as a result maximizing the amount of drug that is absorbed.

Jain *et al*., prepared paracetamol loaded eudragit RS 100 based microsponges by quasi-emulsion solvent diffusion method. The compatibility of the drug with different formulation components was demonstrated. Surface morphology and shape of the microsponges were analyzed using SEM. Compression coating of microsponges with pectin: Hydroxypropylmethyl cellulose (HPMC) mixture followed by tableting was used for colon specific formulations. *In-vitro* drug release studies were done on all the formulations and the results were evaluated kinetically and statistically. The study concluded that the release data followed Higuchi matrix but diffusion was the main mechanism of drug release from microsponges. *In-vitro* studies showed that compression coated colon specific tablet formulations started the release of drug at the 6th hour resultant to the arrival time to proximal colon. [13]

Jain *et al*., developed dicyclomine loaded eudragit RS100 based microsponge for colonic delivery by using quasi-emulsion solvent diffusion method. Differential Scanning Calorimetry and Fourier Transform Infra-Red was done to study the compatibility of the drug with various formulation components. SEM was used for demonstration of surface morphology and shape of the microsponges. The formulations were subjected to in vitro release studies, and the results were evaluated kinetically and statistically. Kinetic studies showed that the Higuchi matrix controlled diffusion was the main mechanism of drug release. With an initial burst effect, the drug release was biphasic with 16 - 30 % of the drug was released in the 1st hour. Cumulative release for the microsponges over 8 hours was ranged from 59 - 86 %. This study concluded an approach for the alteration of microsponges of dicyclomine for prolonged drug release. The distinctive compressibility of microsponges can be applied to get efficient local action as microsponges may be taken up by macrophages which are present in colon [14].

Orlu *et al*., prepared a novel colon specific drug delivery system containing flurbiprofen microsponges. Flurbiprofen loaded Eudragit RS 100 based microsponge were prepared by quasi-emulsion solvent diffusion method. Additionally, Flurbiprofen was entrapped into a commercial Microsponge® 5640 system using entrapment method. Then, the effects of drug: polymer ratio, amount of inner phase solvent, stirring speed and time and stirrer type on the physical characteristics of microsponges was examined and investigate the surface morphology, thermal behaviour, particle size and pore structure of microsponges.

The Compression Coating with Pectin: HPMC mixture followed by tableting was used for colon specific delivery of microsponge formulations. In vitro studies exhibited that compression coated colon specific tablet formulations started to release the drug at the 8th hrs corresponding to the proximal colon arrival time due to the addition of enzyme. [15]

Gonul *et al*., developed microsponge of ketoprofen by quasi-emulsion solvent diffusion method with Eudragit RS 100 and tablets of microsponges were prepared by direct compression method and studied the effects of pressure and direct compression on tableting of microsponges. In order to determine the optimum pressure value for the compression of the tablets, different pressure values were applied to the tablet powder mass. Results of the study indicated that microsponge compressibility was much better over the physical mixture of the drug and polymer and due to the plastic deformation of sponge-like structure; microsponges can produce mechanically strong tablets [42].

Microsponges for Biopharmaceuticals Delivery: The microsponge delivery system (MDS) is employed for both in the delivery of biopharmaceuticals as well as in tissue engineering. Dai 2010 *et al*., developed 3D scaffolds hybrid structures that have advantages of natural type I collagen and synthetic PLGA knitted mesh. The collagen microsponges facilitated cell seeding and tissue formation and mechanically strong PLGA mesh served as a skeleton. The scaffolds were divided into three groups:

a) *Thin*: collagen microsponge formed in interstices of PLGA mesh;

b) *Semi*: collagen microsponge formed on one side of PLGA mesh;

c) *Sandwich*: collagen sponge formed on both sides of PLGA mesh.

In the scaffolds Bovine chondrocytes were cultured and transplanted subcutaneously into nude mice for 2, 4, and 8 weeks. All transplants showed natural chondrocyte morphology, homogeneous cell distribution, 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. Young's modulus showed 54.8 49.3% mechanical strength of the engineered cartilage and in stiffness 68.8 62.7%, respectively, in *Semi* and *Sandwich* when compared to native articular cartilage. These scaffolds could be used for the tissue engineering of articular cartilage with adjustable thickness [43].

Iwai *et al*., developed a biodegradable graft material containing collagen microsponge that would allow the regeneration of autologous vessel tissue in order to avoid these problems. Poly (lactic-co-glycolic acid) has been used as a biodegradable scaffold which was compounded with collagen microsponge to form a vascular patch material. The poly (lactic-co-glycolic acid) collagen patches with or without autologous vessel cellularization were used to patch the canine pulmonary artery trunk. Biochemical and histologic assessments were performed 2nd and 6th months after the implantation.

Resulting, there was no thrombus formation in either group but the poly (lactic-co-glycolic acid) scaffold was approximately 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 extra-cellular components in the patch had enlarged to levels analogous to those in native tissue at 6 months. This patch also shows promise as a bioengineered material for promoting *in-situ* cellularization and the regeneration of autologous tissue in cardiovascular surgery. [44]

Tateishi *et al*., has also been studied developed biodegradable porous scaffolds for tissue engineering. 3D biodegradable porous scaffolds play a vital role in tissue engineering. A novel method were used for preparing porous scaffolds which consists of synthetic biodegradable polymers and developed by combining porogen leaching and freeze-drying techniques utilizing pre-prepared ice particulates as the porogen material. Biodegradable hybrid porous sponges of synthetic polymer and collagen have been prepared by hybridizing synthetic polymer sponges with collagen microsponges. The collagen microsponges were produced in the pores of synthetic polymer sponges. Hybrid sponges of synthetic polymer, collagen and inorganic hydroxyapatite were prepared by depositing hydroxyapatite particulates on the surfaces of the collagen microsponges in the synthetic polymer-collagen sponges. The synthetic polymer sponge were used as a mechanical skeleton to aid the formation of these hybrid sponges into desired shapes and contributed good mechanical strength and handling whereas the collagen and hydroxyapatite are used to promote cell interaction and facilitate cell seeding [45].

Patents Information: In 1st September 1987, Won R (Palo Alto, CA) of Advanced Polymer Systems, Inc. (Redwood City, CA) received (United States Patent 4,690,825) for developing method to deliver an active ingredient by controlled time release using a novel delivery vehicle that can be prepared by a process utilizing the active ingredient as a porogen [1]. On 8th September 1992, Won R (Palo Alto, CA) of Advanced Polymer Systems, In (Redwood City, CA) received (United States Patent 5,145,675) for developing a two-step method for the preparation of controlled release formulations [45]. Advanced Polymer Systems, Inc. and subsidiaries is using its patented microsponge$^{(R)}$ delivery systems and related proprietary technologies to increase the safety, aesthetic quality and effectiveness of topical prescription, over-the-counter ("OTC") and personal care products like Vitamin- A, tretinoin and 5-fluorouracil etc. As on 23th July 2006, the Company has a total of 10 issued U.S. patents and an additional 92 issued foreign patents. 21 patent applications are pending worldwide.

Dean JR *et al*., received US patent no. 4863856 for the development of weighted collagen microsponges having a highly cross-linked collagen matrix that is suitable for use in culturing organisms in motive reactor systems. The microsponges have an open to the surface pore structure, pore volumes and pore sizes suitable for immobilizing a range of bioactive materials [46].

Marketed Formulations: MDS is best for skin and personal care products. They can take up large amounts of excess of skin oil while retaining an elegant feel on the surface of skin. This technology is presently employed in approximately number of products (**Table 2**) sold by leading cosmetic and toiletry companies worldwide.

Among these products include moisturizers, skin cleansers, deodorants, oil control lotions, conditioners, razors, lipstick, powders, makeup and eye shadows which offer various advantages including improved physical and chemical stability, greater available concentrations, reduced skin irritation and sensitization and controlled release of the active ingredients and unique tactile qualities [47-50].

TABLE 2: LIST OF MARKETED PRODUCTS USING MICROSPONGE DRUG DELIVERY SYSTEM

Product name	Manufacturer	Advantages
Retin-A-Micro	Ortho-McNeil Pharmaceutical, Inc.	For topical treatment of *acne vulgaris* tretinoin (0.1% and 0.04%) entrapped in MDS. This formulation uses patented methyl methacrylate/ glycol dimethacrylate cross-polymer porous microspheres (MICROSPONGE® System) to enable inclusion of the active ingredient, tretinoin, in an aqueous gel.
Carac Cream, 0.5%	Dermik Laboratories, Inc. Berwyn , PA 19312 USA	Carac is a once-a-day topical prescription product for the treatment of actinic keratoses (AK). It contains 0.5% fluorouracil, with 0.35% being incorporated into a patented porous microsphere composed of methyl methacrylate/glycol dimethacrylate cross-polymer and dimethicone. The product has a number of advantages over existing topical therapies, including reduced dosage frequency and less irritation with shorter duration of therapy.
Retinol cream	Biomedic	Retinol is a topical vitamin A derivative which helps maintain healthy skin, hair and mucous membranes. For protect the potency of the vitamin A, retinol molecule is entrapped in the MDS. This helps to maximize retinol dosage while reducing the possibility of irritation.
Line Eliminator Dual Retinol Facial Treatment	Avon	Lightweight cream with a retinol (pure Vitamin A) in MDS, delivers both immediate and time released wrinkle-fighting action.
EpiQuin Micro	SkinMedica Inc	The Microsponge® system uses microscopic reservoirs that entrap hydroquinone and retinol. The MDS release these ingredients into the skin gradually throughout the day. This provides the skin with continuous exposure to hydroquinone and retinol over time, which may minimize skin irritation. [49]
Sportscream RS and XS	Embil Pharmaceutical Co. Ltd.	Topical analgesic, anti-inflammatory and counterirritant actives in a MDS for the management of musculoskeletal conditions. [48]
Salicylic Peel 20 and 30	Biophora.	Salicylic acid 20% and 30%, microsponge technology has excellent exfoliation and used for stimulation of the skin for more resistant skin types or for faster results. It will considerably improve pigmentation, fine lines and acne concerns. Salicylic acid moves easily through the pores, clearing them out while reducing inflammation. This treatment effectively combats acne leaving an amazingly smooth and clear complexion.
Micro Peel Plus	Biomedic	The MicroPeel® Plus procedure stimulates cell turnover through the application of salicylic acid in the form of microcrystals using Microsponge® technology. These microcrystals target on exact areas of the skin that need improvement. The MicroPeel® Plus aggressively outperforms other superficial chemical peels by freeing the skin of all dead cells while doing no damage to the skin.
Oil free matte block spf20	Dermalogica	Protect the skin from damaging UV rays and control oil production with this invisible sunscreen. Microsponge technology absorbs oil, maintaining an all day matte finish and preventing shine without any powdery residue. Cornstarch and Vinyl Dimethicone/Methicone Silsesquioxane Cross-polymer act as microsponges to absorb excess surface oils on skin.
Oil Control Lotion	Fountain Cosmetics	A feature-light lotion with technically advanced microsponges that absorb oil on the skin's surface during the day, for a matte finish. Eliminate shine for hours with this feature-weight lotion, formulated with oil-absorbing Microsponge technology and hydrating botanicals. The naturally antibiotic Skin Response Complexes soothes inflammation and tightness to promote healing. Acne-Prone, oily skin conditions.

Lactrex™ 12% Moisturizing Cream	SDR Pharmaceuticals, Inc., Andover , NJ , U.S.A. 07821	It contains 12% lactic acid as the neutral ammonium salt, ammonium lactate. Microsponge® technology has been included for comfortable application and long lasting moisturization. Lactrex™ also contains water and glycerin, a natural humectant, to soften and help moisturize dry, flaky, cracked skin.
NeoBenz® Micro, Neo® MicroSD NeoBenz® Microwash	Intendis Inc. Morristown NJ07962 USA	NeoBenz® Micro 5.5% cream, NeoBenz® Micro SD 5.5% single dose cream pre-filled sponge applicator and NeoBenz®Microwash 7% are topical preparations containing Benzoyl peroxide incorporated into patented porous Microsponge® composed of methyl methacrylate/glycol dimethacrylate crosspolymer. This system has been shown to provide gradual release of active ingredient into skin and absorb natural skin oils. Benzoyl peroxide is an oxidizing agent that posses antibacterial properties and is classified as keratolytic.
Dermalogica Oil Control Lotion	John and Ginger Dermalogica Skin Care Products	Exclusive skin response complex soothes and purifies, provides effective skin hydration, without adding excess oil; eliminate shine for hours with Dermalogica Oil Control Lotion. Oil Control Lotion is a feather-light lotion, formulated with oil absorbing Microsponge technology and hydrating botanicals.
Aramis fragrances	Aramis Inc.	24 Hour High Performance Antiperspirant Spray Sustained release of fragrance in the microsponge. The microsponge comes in the form of an ultra light powder, and because it is micro in size, it can absorb fragrance oil easily while maintaining a free-flowing powder characteristic where release is controlled due to moisture and temperature.
Ultra Guard	Scott Paper Company	Microsponge system that contains dimethicone to help protect a baby's skin from diaper rash.

CONCLUSION: The microsponge drug delivery technology is widely applicable to the dermatological drug delivery products. The microsponge delivery technology of controlled release system in which active pharmaceutical ingredients are loaded in the microporous beads and initiates reduction in side effects with improved therapeutic efficacy. The microsponge drug delivery system has properties like improved stability and enhanced flexibility in formulation.

MDS is originally developed for topical delivery of drugs like anti-acne, anti-inflammatory, anti-fungal, anti-dandruffs, antipruritics, rubefacients etc. but MDS also expands its application in oral drug delivery and in bone and tissue engineering. Hence, the microsponge drug delivery system focus as an important tool for future inventions in controlled drug delivery system.

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