IJPSR (2021), Volume 12, Issue 9 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 19 June 2020; received in revised form, 30 January 2021; accepted, 21 May 2021; published 01 September 2021

MICROSPONGES DRUG DELIVERY SYSTEM

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Keywords:

Microsponges, Controlled release, Liquid-Liquid Suspension Polymerization, Quasi-Emulsion Solvent Diffusion

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ABSTRACT: Microsponges are novel drug delivery systems made up of cross-linked spongy, polymeric, porous, spherical microspheres particles which vary in size from 5-300 µm. This delivery system as the advantage of producing controlled release formulations of poorly soluble drugs. It increases drug stability, reduces side effects and modifies drug release profiles making it a versatile drug delivery vehicle. These active micro sponges can entrap a wide variety of substances and be incorporated into formulations, such as capsules, gels, liquids, creams and powders and share a broad package of benefits. This article presents a broad review of Micro sponges delivery system (MDS), discussing its characteristics, benefits, different preparation methods (Liquid-Liquid Suspension Polymerization, Quasi-Emulsion Solvent Diffusion) and release mechanisms. It also covers different characterization parameters like particle size, size distribution, morphology, surface topography, loading efficiency, production yield, compatibility studies, true density, *in-vitro* release studies and MDS systems applications in oral, topical cosmetics bone and tissue.

INTRODUCTION: In conventional drug delivery systems, medication has many problems as it requires multi-dose therapy and the absorption of the drug across a biological membrane, whereas the targeted release system releases the drug in a dosage form. In traditional intravascular injection or oral ingestion, the medication is distributed throughout the body through the systemic blood circulation for most therapeutic agents and only a small portion of the medication reaches the organ to be affected. The newer approach, however, delivers the drug into the systemic circulation at a pre-determined rate, known as controlled release drug delivery system [1, 3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(9).4697-07

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(9).4697-07

In today's time, the main focus of pharmaceutical industry is to develop formulations which have controlled or sustained release drug delivery system. In this system the active ingredients resides in a carrier system, which allows changing the time duration of the drug and its therapeutic index [4]. The micro-sponges technology was first developed by Won in 1987 and the original patent was assigned to advance polymer systems, Inc [5, 6].

Micro-sponge drug delivery systems (MDS) are spherical, porous, polymeric and patented delivery systems that are used for prolonged topical administration. They are spongy tiny like spherical articles of 5 – 300 µm **Fig. 1**. [7] The surface and pore volume can be varied from 20 to 500 m^2/g and 0.1 to 0.3 cm^{-3}/g, respectively. Due to their non-collapsible structure made of interconnecting voids, they are inert and stand in a high degree of shear and hence can be used in the manufacturing of powders, lotions, and creams [8, 9]. Micro sponges are designed to deliver a pharmaceutically active

ingredient efficiently at a minimum dose and enhance stability, reduce side effects and modify drug release profiles [10, 11]. Release of the drug into the skin is facilitated by various factors like pressurizing or rubbing, changes in skin temperature, pH and solubility [9]. The benefits and limitations of microsponges drug delivery system are mentioned in **Table 1**.

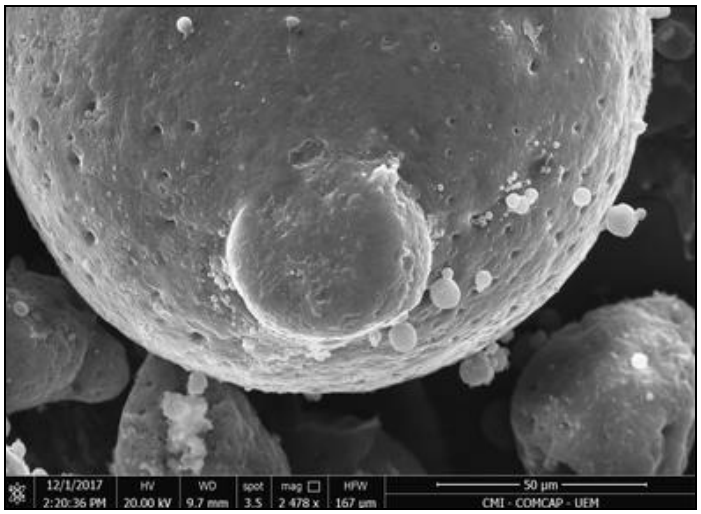

FIG. 1: IMAGE OF MICROSPONGE

Characteristics of Microsponges:

- MDS system is stable over range of pH 1 to 11 and temperature up to 130 ℃.
- They are compatible with most ingredients and vehicles.
- Micro sponge formulations have small pore size of 0.25 µm which inhibit the entry of bacteria so they are self-sterilizing.
- Micro sponge formulations have higher payload (50 to 60%), still free flowing and can be cost effective [12].

TABLE 1: BENEFITS AND LIMITATIONS OF MICROSPONGE DRUG DELIVERY SYSTEMS [13, 16]

Benefits	Limitations
MDS provides continuous action up to 12 h, extends the drug release and enhances product performance.	During the preparation of microsponges organic solvents are used as porogens and some of them are highly inflammable which cause environment and safety hazard.
Improved product elegancy and Lessen the irritation, and better tolerance leads to improved patient compliance.	In some cases, the traces of residual monomers have been observed, which may be toxic and hazardous to health.
MDS improved oil control as it can absorb oil up to 6 times its weight without drying.	
MDS formulation increases the cure faster, resulting in improved treatment efficacy.	
Drugs prepared by the MDS method have more bioavailability than the conventional method.	
They have superior formulation flexibility help to develop novel product forms and stable over the range 1 -11 pH	
MDS product have better thermal and chemical stability and are non-toxic in nature	
With the help of MDS system we can prepare the formulation of immiscible products and also improves material processing *e.g.* liquid can be converted to powders.	

Approaches for Formulation of Micro-sponges: Liquid-Liquid Suspension Polymerization (Bottom-up approach) this method of micro-sponges formation is a polymerization method that starts by mixing immiscible polymer (monomer) with the active ingredient in a suitable solvent forming a solution phase. This phase is then dispersed in an aqueous phase containing additives such as surfactants and suspending agents to form suspension. Once the suspension is formed,

polymerization is increased by activating the monomers; it can be done by either increasing the temperature or by adding a catalyst [17]. The polymerization process leads to forming a solid spherical structure that has an open-pore surface in reservoir type of system. The solvent is removed, and solid material is then washed and processed to get microsponges. 18Thereaction vessel for micro sponge preparation by liquid-liquid suspension polymerization is shown in **Fig. 2**.

The Various Steps Involved In the Preparation of Microspongesare [17, 21]:

- Picking of monomer and merging of the monomers.
- Chain monomers are formed as polymerization starts.
- Monomer ladder is formed due to cross-linking between chain monomer
- Formation of spherical particles by folding monomer ladder.
- Microsphere bunches are formed by the agglomeration of the microsphere.
- The binding of these bunches leads to the formation of a microsponge.

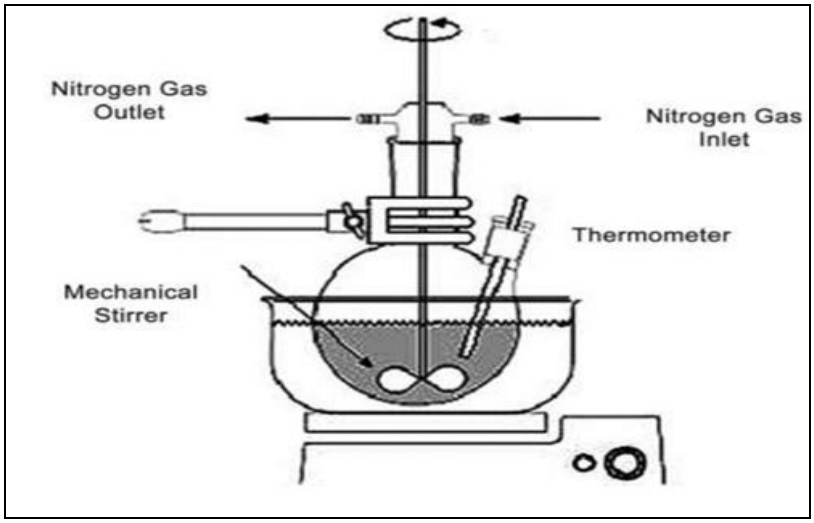

FIG. 2: REACTION VESSEL FOR MICROSPONGE PREPARATION BY LIQUID-LIQUID SUSPENSION POLYMERIZATION

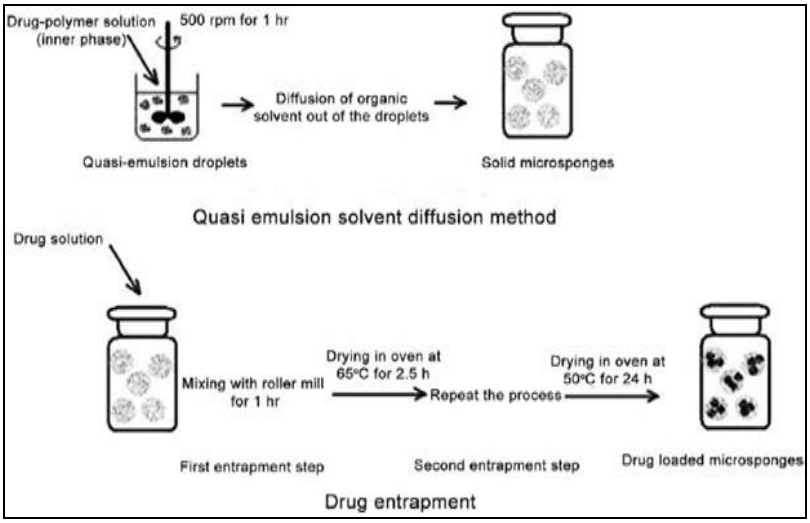

FIG. 3: METHOD OF QUASI-EMULSION SOLVENT DIFFUSION.

Quasi-Emulsion Solvent Diffusion: [22-24]

- This method is a two-step process known as top-down approach as it starts with preformed polymer, as shown in **Fig. 3**.
- The first step involves the preparation of the inner phase: polymer (Eudragit RS 100) dissolved in solvent (ethyl alcohol). Then

the drug is added to the solution and dissolved under ultrasonication at 35 ºC.

- A plasticizer can be added to this solution, such as triethyl citrate (TEC), to enhance plasticity.
- Preparation of external phase: the polyvinyl alcohol solution in distilled water.
- The inner phase is poured into the external phase.
- This mixture is stirred for 60 min and filtered to separate the microsponges.
- The microsponges are then dried in an air-heated oven at 40 ℃ for 12 h. and weighed to determine production yield.
- Ingredients can be entrapped in micro-sponge polymers at the time of synthesis. They can be post-loaded after the microsphere structure has been pre-formed. The latter process is the preferred mode since many pharmaceuticals, and cosmetic ingredients would decompose at the temperature used for polymerization

Release Mechanism of Microsponge: In micro sponge drug delivery system, the active ingredients are free to move in and out from the particles into the vehicle due to their open structure. This process continues till equilibrium is reached. When the final product is applied to the skin surface, the vehicle starts depleting due to unsaturation disturbing the equilibrium. This causes the flow of the active ingredients from the microspheres into a vehicle and then into the skin surface. In MDS formulations, the sustained release effect can be achieved by altering the release rate of the active ingredients. This can be achieved by modifying the diameter of the pores, the extent of cross-linking of the polymers, the difference in concentration of the active ingredient between the microspheres and the vehicle in which these spheres are entrapped. The release of active ingredients from the microsponges is triggered by external factors, which include pressure, temperature, pH and solubility [25, 26].

Pressure: MDS releases the active ingredient when it is pressurized or rubbed into the skin surface. The released amount of active ingredient depends on the features of microsponges. We can get optimized microsponges for a particular application by varying in different process variables and types of material [27, 29].

Temperature Change: The change in skin temperature affects the release of active ingredients from microsponges onto the skin surface, especially for those MDS formulations which have viscous active ingredients at room temperature and needs high temperature for the sudden flow of active ingredients onto the skin. For example, viscous sunscreens were found to show a higher release from micro-sponges when exposed to higher temperatures; thus, sunscreen would be released from a micro-sponge only upon exposure to heat from the sun [30, 31].

Solubility: The solubility of an active ingredient in MDS depends on dissolving medium, concentration gradient diffusion in consideration with the partition coefficient of the ingredient between the microsponges and the outside system. The antiseptics and antiperspirants are water-miscible active ingredients, and release of these active ingredients will occur only in water medium. The release can also be activated by diffusion, taking into consideration the partition coefficient of the ingredients between the microsponges and the outside system [30, 32].

pH: By applying a pH-specific coating on the microsponges, we can trigger the release of active ingredients at a particular pH [27].

Characterization of Micro-sponges:

Particle Size and Size Distribution: Particle size and size distribution of microsponges affect the texture and stability of the formulation and affect drug release. So, it is a very crucial step for microsponge formulation. Particle size and size distribution of loaded and unloaded microsponges are evaluated by using laser light diffract geometry. To study the effect of particle size on drug release, a graph of cumulative percentage drug release *vs.* particle size will be plotted against time [26, 33].

Morphology and Surface Topography: To study morphology and surface topography, micro sponges are coated with gold-palladium under an argon atmosphere at room temperature, then examined using Scanning electron microscopy (SEM) or Transmission electron microscopy (TEM) [34].

Determination of Loading Efficiency and Production Yield: The loading efficiency percentage of microsponges can be calculated by using the following equation [35]:

Loading Efficiency (%) = (Actual Drug Content in Microsponges) / (Theoretical Drug Content) × 100

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

Production yield = (Practical mass of microsponges) / (Theoretical mass (polymer + drug) × 100

Compatibility Studies: Compatibility study of drugs with excipients can be studied by Fourier Transform Infra-red spectroscopy (FT-IR). Differential scanning colorimetry (DSC) and powder X-ray diffraction (XRD) are used to study the effect of polymerization on the crystallinity of the drug. For DSC, approximately weigh and seal 5 mg of sample in an aluminum pan and then run it at a heating rate of 15 °C/min over a temperature range 25-430 °C in nitrogen atmosphere [36].

Characterization of Pore Structure: Pore volume and diameter of microsponges are crucial in controlling the intensity and duration of action of active ingredients. Pore diameter of microsponges also shows the effect in the movement of active ingredients into the vehicle in which the material is dispersed.

The effect of pore diameter and volume on release rate of drug can be studied by Mercury intrusion porosime try. It also helps in determining total pore surface area, average pore diameters, pore size distribution, shape, morphology, bulk and apparent density of the pores [34].

Determination of True Density: The true density of micro-spherical particles can be determined using an ultra-pycnometer under helium gas and is calculated from a mean of repeated determinations [37].

Resiliency Viscoelastic Properties: Micro sponges can be made softer or rigid according to the needs of formulation by modifying its Resiliency viscoelastic properties. Increased cross-linking leads to a slow drug release rate. Hence resiliency of Micro sponges is studied and optimized as per the need by considering release as a function of cross-linking with time [38].

***In-vitro* Release Studies:** USP XXIII dissolution apparatus equipped with a modified basket consisted of 5 µm stainless steel mesh is used to perform the *In-vitro* release studies of mico sponges. The apparatus is run at 150 rpm at37 °C to measure dissolution rate. The selection of dissolution medium depends upon the solubility of active ingredients to maintain sink conditions. The samples are withdrawn at regular time intervals and analyzed by suitable analytical methods (UV spectrophotometer [39].

Polymer / Monomer Composition: The selection of monomer is done depending on the characteristics of the drug which reside inside it and the vehicle in which the drug gets dispersed. The partition coefficient between the vehicle and the microsponge system and the release rate of the drug depends on polymer composition. The drug release also depends on several factors such as particle size, drug loading, and polymer composition. The release of drugs from micro-sponge systems of different polymer compositions can be studied by plotting cumulative percentage drug release against time. To check the compatibility of drug with the polymer, different drug-polymer combinations are made, and their drug release profile is studied [40, 41].

Stability Studies: Stability studies are performed to ensure that there is no change in the physical, chemical, microbiological, therapeutic, and toxicological properties of formulation during its storage in a particular container or closure system. The prepared formulation os tested for stability on storing them at 4 ± 1 ºC, 25 ± 2 ºC and 37 ± 5 ºC & RH (Relative Humidity) 75%. After one month and three months, they are evaluated for the following parameters-appearance, pH, drug content analysis, drug release profiles, rheological properties, *etc.* [42, 43]

Applications of Microsponges Drug Delivery System: MDS are used to modify drug release; they deliver the drug efficiently in low dose with enhanced stability and low side effects. This system is used to prepare oral, topical and bio-

pharmaceutical formulations. It also offers the formulator a range of alternatives to develop drug and cosmetic products. This is due to the high loading capacity and sustained release ability of micro sponges [44, 45]. The applications of different active ingredients in a microsponge formulation is given in **Table 2**. Its marketed formulations are mentioned in **Table 3**; examples of microsponge drug delivery with their formulations are given in **Table 4** and Patents filed in **Table 5**.

TABLE 2: APPLICATIONS OF DIFFERENT ACTIVE INGREDIENTS IN MICROSPONGES FORMULATION [44, 45].

S. no	Active ingredients	Applications
1	Anti-inflammatory *e.g.* hydrocortisone	Prolonged activity with reduction of skin allergic response and dermatoses
2	Anti-acne *e.g.* Benzoyl peroxide	Maintained efficacy with reduced skin irritancy and sensitization
3	Skindepigmenting agentse.g.hydroquinone	Enhanced stability against oxidation with improved efficacy and aesthetic appeal
4	Antipruritics	Extended and improved activity
5	Anti-dandruffs *e.g.* zinc pyrithione, selenium sulfide	lowered unpleasant odour with decreased irritation with enhanced safety and efficacy
6	Rubefacients	prolonged activity with reduced irritancy greasiness, and odour
7	Anti-fungals	Sustained release of actives
8	Sunscreens	Prolonged product efficacy, with improved protection against sunburns and sun-related injuries even at high concentration and with decreased irritations and sensitization

For Topical Administration: Release of the drug into the skin is facilitated by a various factor like pressuring or rubbing, change in skin temperature, pH and solubility[9]. Genetically engineered melanin is incorporated in microsponges (sunscreens), melanosponge-α to spread it evenly hence providing protection against UV-A and UV-B radiation 46 Fluocinolone Acetonide (FA) is a corticosteroid primarily used in dermatology to reduce skin inflammation and relieve itching [16].

For Oral Administration: In the oral drug delivery system, MDS is used to increase the solubility of poorly water-soluble drugs by entrapping such drugs in its pores. Due to tiny pores of microsponges the drug is reduced to microscopic particles, hence increased surface area, thus greatly increasing the solubility. The drug in the microsponges resides in a protected environment, which provides controlled delivery of the drug to the lower gastrointestinal (GI) tract, where it is released upon exposure to specific enzymes in the colon. Additionally, the MDS system increases the GI retention time of the drug, thus increasing absorption [47, 48, 49, 50].

Microsponge for Bone and Tissue Engineering: The microsponges for the bone substituted compound are prepared in pre-polymerized powders of polymethyl-methacrylate and liquid methylmethacrylate monomer with two aqueous dispersions of a-tri calcium phosphate (a-TCP) grains and calcium-deficient hydroxylapatite (CDHA) powders. The fibroblast growth factor (bFGF) incorporated in a collagen sponge sheet was sustained release in the mouse subcutis according to the biodegradation of the sponge matrix and exhibited local angiogenic activity in a dose-dependent manner 51 A biodegradable graft material containing the collagen micro sponge was developed for cardiovascular tissue grafting, as it would permit the regeneration of the autologous vessel tissue [52].

Long-Lasting Coloured Cosmetics: Coloured cosmetics formulated with micro-sponges entrapment are highly graceful due to uniform spreading and improved covering; it includes coloured cosmetic products such as rouge or lipsticks [53, 54]. Some marketed formulations of microsponges are given in **Table 3**.

Recent Advances in Microsponge Drug Delivery System: With the development of nanotechnology, the Pharmaceutical Industry has become very advanced; they shifted the formulation process from micro to nanosized particles. Nanosponges are hyper cross-linked polymer based colloidal

structures, consisting of countless interconnecting voids within a collapsible structure with porous surface [72]. These sponges are incorporated in cosmetics and sunscreens as antioxidants and antireflectants [76]. 77β - CD nanosponges were developed that can be used for hydrophilic as well as hydrophobic drugs like Flurbiprofen, dexamethasone, itraconazole, doxorubicin hydrochloride and serum albumins model drug. These nanosponges were developed by cross-linking the β CD molecule by reacting it with Biphenylcarbonate. Some researchers also observed nanosponges as a good carrier for the delivery of gases. Researchers also observed that incorporating a cytotoxic in a nanosponge carrier system can increase the potency of the drug, suggesting that these carriers can be potentially used for targeting the cancerous cells [78]. Swaminanthan *et al.*, 2007 formulated cyclodextrin nanosponges for solubility enhancement of itraconazole, a poorly water-soluble drug [79]. Sharma and Pathak, 2011 fabricated ethyl cellulose nanosponges as an alternative system for targeting econazole nitrate to the skin through hydrogel formulation [80]. Improved stability of RNA and a relatively effective encapsulation process of siRNA was prepared. The approach could lead to novel therapeutic routes for siRNA delivery [81]. The babchi oil-loaded cyclodextrin nanosponges were also fabricated by a research group for solubility and photostability enhancement of entrapped essential oils [82].

TABLE 3: MARKETED FORMULATIONS OF MICROSPONGES [55, 62]

S. no.	Product name	Therapeutic effect	Manufacture
1	Lactrextm 12% moisturizing cream	Moisturizer	SDR pharmaceuticals, Inc
2	Glycolic acid moisturizer w/SPF 15	Anti-wrinkles soothing	AMCOL Health &Beauty Solution
3	Sports cream RS and XS	Topical analgesic, anti-inflammatory	Embil Pharmaceutical Co. Ltd
4	Retinol cream	Vitamin A derivative which helps maintain healthy skin, hair and mucous membranes.	Biomedic
5	Carac Cream, 0.5%	treatment of actinic keratoses	Dermik Laboratories, Inc. Berwyn, PA 19312 USA
6	NeoBenz®Micro, Neo®MicroSD, eo Benz®Microwash	Used to absorb natural skin oils	Intendis Inc. Morristown NJ07962 USA
7	EpiQuin Micro	Hyperpigmentation	Skin Medica Inc
8	Oil free matte block spf20	Sunscreen	Dermalogica
9	Oil Control Lotion	Absorb oil on the skin's surface during the day, for a matte finish	Fountain Cosmetics
10	Micro Peel Plus	Freezing the skin of all dead cells while doing no damage top skin.	Biomedic
11	Aramis fragrances	24 H High-Performance Antiperspirant Spray Sustained release of fragrance in the microsponge	Aramis Inc.
12	Salicylic Peel 20 and 30	excellent exfoliation	Biophora
13	Dermalogica Oil Control Lotion	Skin protectant	John and Ginger Dermalogica Skin Care Products
14	Retin A micro	Acne vulgaris	Ortho McNeil Pharmaceutical, Inc.
15	Line Eliminator Dual Retinol Facial Treatment	Anti-wrinkle	Avon
16	Ultra-Guard	Protects baby skin	Scott Paper Company
17	Retinol 15-night cream	Anti-wrinkle	Sothys

TABLE 4: EXAMPLES OF MICROSPONGE DRUG DELIVERY WITH THEIR FORMULATIONS [63, 65]

S. no.	Microsponge delivery systems	Drug	Disease
1	Lotions	Benzoyl peroxide	Anti-Acne Treatment
2	Grafts	Poly (lactic-co glycolic acid)	Cardiovascular surgery
3	Tablets	Meloxicam	Arthritis
		Ketoprofen	Musculoskeletal pain
		Chlorpheniramine maleate	Hay Fever
		Fenofibrate	Gout

		Indomethacin	Inflammation
		Paracetamol	Anti-pyretic
4	Gels	Mupirocin	Antibacterial activity
		Terbinafine HCl	Anti-fungal
		Fluconazole	Inflammation
		Hydroxyzine HCl	Urticaria and atopic dermatitis
5	Creams	Hydroquinone and Retinol	Melanoma
6	Implants	Poly(DL-lactic-co-glycolic acid)	Skin tissue engineering
7	Injection	Benzoyl peroxide	Anti-Acne Treatment
		Diclofenac sodium	Inflammation
		Basic fibroblast growth fact	Growth factor
		Acyclovir	Viral infections

TABLE 5: PATENTS FILED RELATED TO MICROSPONGES [66, 74]

S. no.	Patent number	Inventor
1	US4690825	WON, 1987
2	US4863856	Dean *et al.*, 1989
3	US5292512	Schaefer *et al.*, 1989
4	US5135740	Katz et al 1992
5	US5679374	Chantal *et al.*, 1994
6	US5316774	Robert *et al.*, 1994
7	US5725869	Ray, 1996
8	US6395300	Straub *et al.*, 1999
9	US6211250	Tomlinson *et al.*, 2001
10	US20030232091	Shefer *et al.*, 2002
11	US20030008851	Singh, 2003
12	US20040247632	Maurizio, 2004
13	US20050271702	Steven et al 2005
14	US20070141004	Malek, 2007
15	US20080160065	Halliday, 2008
16	US76044814	Karyion Inc., 2009
17	US7740886	Sara Vargas 2010
18	US7749489	Celmatrix corporation, 2011
19	US8323672	Karykion corporation 2012
20	US8361273	Ferring B. V, 2013
21	US8758728	Stiefel research Australia Pvt. Ltd., 2014
22	US8936800	Galderma research & Development, 2015

CONCLUSION: MDS is a spherical, porous, polymeric, and patented delivery system used for prolonged topical administration. It is used to increase the solubility of poorly water-soluble drugs by entrapping such drugs in the micro sponges pores. Due to the tiny pores of microsponges, the drug is reduced to microscopic particles, hence increased surface area thus, this greatly increases the solubility. Micro sponges are designed to deliver a pharmaceutically active ingredient efficiently at a minimum dose with enhanced stability, reduced side effects and modified drug release profiles. In this system, the active ingredient resides in a carrier system, which allows us to change the time duration of the drug and its therapeutic index. With the help of MDS system, we can prepare the formulation of immiscible products and also improves material processing, e.g., liquid can be converted to powders. This system is used to prepare oral, topical and biopharmaceutical formulations. It also offers the formulator a range of alternatives to develop drug and cosmetic products. This is due to the high loading capacity and sustained release ability of microsponges. Hence, microsponge-based formulations are control released and have better therapeutic effects than conventional formulation.

ACKNOWLEDGEMENT: Nil

CONFLICTS OF INTEREST: Nil

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How to cite this article:
Tomar M and Pahwa S: Microsponges drug delivery system. Int J Pharm Sci & Res 2021; 12(9): 4697-07. doi: 10.13040/IJPSR.0975-8232.12(9).4697-07.