IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
December 2018 Vol.:14, Issue:1

Microsponge – Aeon in the Field of Topical Formulation

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Madhvi Ghadge*, Dipayan Purakasythya, Anup Pramanik, Shiv K. Garg

Department of Pharmaceutics, Maharishi Arvind College of Pharmacy, Ambabari, Jaipur, Rajasthan, India

Submission: 21 November 2018
Accepted: 26 November 2018
Published: 30 December 2018

Keywords: Microsponges, Release mechanism, Quasi-emulsion solvent diffusion, Liquid-liquid suspension polymerization, pore characterization, Over the counter (OTC)

ABSTRACT

Microsponge an ulta-innovative drug delivery system has been formulated for topical and/or oral administration. Microsponges are porous microspheres, biologically inert particles that are made up of polymer and serves to protect entrapped drug compound from physical and environmental degradation. Size of microsponge varies from 5-300 µm in diameter. Recently, microsponge delivery system (MDS) has been successively addressed for the controlled release of drugs onto the epidermis with an assurance that the drug remains chiefly localized and does not enter the systemic circulation in major amounts. MDS is an idiosyncratic technology for the controlled release of topical agents, also used for oral as well as biopharmaceuticals (peptides, proteins, and DNA-based therapeutics) drug delivery. It consists of microporous beads having a range of 10-25 microns in diameter that boast a versatility to entrap wide range of active agents. This review article covers methods of preparation, release mechanism, characterization and applications of microsponge delivery system with patent information and marketed formulations.

INTRODUCTION

Microsponges have been tremendous innovation in the pharmaceutical field. A microsponge delivery system (MDS) is highly cross-linked, patented, porous, polymeric microspheres that acquire the flexibility to entrap a wide variety of active ingredients such as emollients, fragrances, sunscreens, essential oils, anti-infective, anti-fungal and anti-inflammatory agents etc and are used as a topical carrier system. Akin a true sponge, each microsphere consists of an innumerable of interconnecting voids within a non-collapsible structure with a large porous surface. It is an outlandish technology for the controlled release of topical agents which consists of microporous beads normally 10-25 microns in diameter. They can accurately control the release rates or target drugs to a specific body site have a massive effect on the health care system. By coupling the drug to a carrier it regulates the release and absorption characteristics of the drug. When applied to the skin, the drug release can be controlled through diffusion. This controlled release of active ingredient onto the skin over time is an enormously important tool for providing the benefits of enhanced product efficacy, tolerability, mildness and lessen. The irritation is usually associated with powerful therapeutic agents like retinoids or benzoyl peroxide and extended wear to a wide range of skin therapies. This system has been automated for the enhancement of topically applied drug. MDS technology is now being presently used in cosmetics, over-the-counter (OTC) skin care, sunscreens, and prescription products.

Microsponges are porous microspheres that are proficient to absorb skin secretions consequently, reducing oiliness and shine from the skin. Microsponge particles are utterly small, inert, indestructible spheres that do not pass through the skin. To a certain extent, they pile up in the tiny nooks and crannies of skin and slowly release the entrapped drug, as the skin needs it. The microsponge system can also avoid unnecessary stockpiling of ingredients within the epidermis and the dermis. Potentially, they can reduce the irritation of effective drugs without reducing their efficacy. These products normally exit in conventional forms like creams, gels, lotions, ointments, powders and share a broad package of benefits.

HISTORY OF MICROSPONGES:

The microsponges technology was developed by Won in 1987 and the original patent was assigned to advanced polymer system, Inc. This company developed a large number of varieties of the procedures and those are as well as applied to the cosmetic over the counter (OTC) and prescription pharmaceutical product.

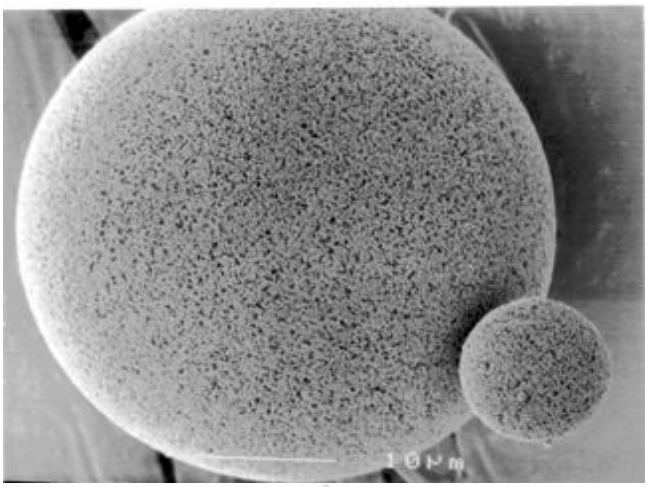

Figure 1: View of Microsponges

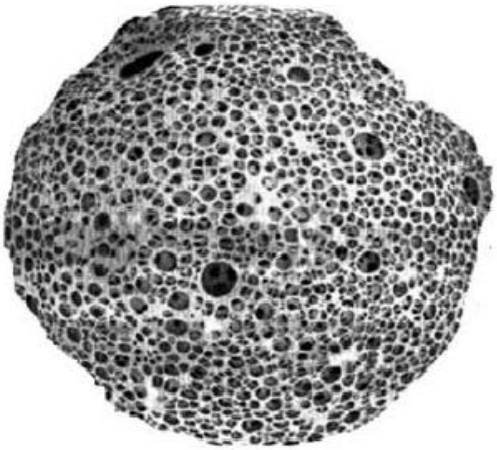

Figure 2: Highly microporous nature of microsponge

Figure 3: Hypothetical Mechanism of Microsponge

Microsponges composed of non-collapsible structures with the porous surface through which active ingredients are released in a controlled manner. Reliant upon the size, the total pore length may range up to 10 ft and pore volume up to 1 ml/gm. When applied to the skin, the microsponge drug delivery system (MDS) releases its active ingredient on a time mode and also in response to other stimuli (rubbing, temperature, pH, etc). Microsponges have the capacity to soak-up or load a high degree of active materials into the particle or onto its surface. Its large capacity for entrapment of actives is up to 3 times its weight differentiates microsponges from other types of dermatological delivery systems. Currently, microsponge delivery system has been successively addressed for the controlled release of drugs onto the epidermis with the assurance that the drug remains chiefly localized and does not enter the systemic circulation in major lots and resulted in a new creation of highly efficacious and well tolerated novel products.

Ascendancy of MDS:

- Microsponges can imbibe oil up to 6 times its weight without drying. Eg:- oil-free matte block spf20.
- It equip continuous action up to 12 hours i.e. extended release. Eg :- Epi Quin Micro
- Ameliorate product elegance.
- Lessen the irritation and better tolerance leads to improved patient compliance.
- They have better thermal, physical and chemical stability.

- These are non-irritating, non-mutagenic, non-allergenic and non-toxic. Eg:- carac cream, 0.5%
- MDS endure the incorporation of immiscible products.
- They have superior formulation flexibility.
- In contrast to other technologies like microencapsulation and liposome's, MDS has a wide range of chemical stability, higher payload and are effortless to formulate.
- Liquids can be converted into powders ameliorating material processing.
- It has the flexibility to develop novel product forms.
- MDS can improve the bioavailability of some drugs.
- It can also improve efficacy in treatment.
- Uniqueness of microsponges
- MDS is stable over the range of pH 1 to 11.
- These are stable at the temperature up to 130˚C.
- These are compatible with the majority of vehicles and ingredients.
- Self-sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.
- Systems have higher payload up to 50 to 60%.
- These are free-flowing and can be cost-effective.
- Its entrapment capacity of actives is up to three times its weight,

Characteristics of actives/API entrapped into microsponges:

Active ingredients that are entrapped in microsponges can then be incorporated into many products such as creams, gels, powders, lotions, and soaps. Certain considerations are taken into account while, formulating the vehicle in order to achieve the desired product characteristics:

- It should be either fully miscible in monomer as well as capable of being made miscible by addition of small amount of a water immiscible solvent.
- It should be inert to monomers and should not increase the viscosity of the mixture during formulation.
- It should be water immiscible or nearly only slightly soluble.
- It should not collapse the spherical structure of the microsponges.
- It should be stable in contact with a polymerization catalyst and also in conditions of polymerization.
- The solubility of actives in the vehicle must be limited. Otherwise, the vehicle will deplete the microsponges before the application.
- Not more than 10 to 12% w/w microsponges must be incorporated into the vehicle in order to avoid cosmetic problems.
- Payload and polymer design of the microsponges for the action must be optimized for the required release rate for the given period of time.

METHODS OF PREPARATION OF MICROSPONGES:

Initially, drug loading in microsponges is mainly taken place in two ways depending upon the physicochemical properties of a drug to be loaded. If the drug is consistently an inert non-polar material which will generate the porous structure then, it is known as the porogen. A Porogen drug neither hinders the polymerization process nor become activated and is stable to free radicals entrapped within a one-step process (liquid-liquid suspension polymerization). Microsponges are suitably prepared by the following methods:

A. Liquid-liquid suspension polymerization

The porous microspheres are prepared by suspension polymerization method in liquid-liquid systems. In this method the monomers which are immiscible are first dissolved along with active ingredients in a suitable solvent monomer and are then dispersed in the aqueous phases which consist of additives like surfactant, suspending agents to facilitate the formation of the suspension. The polymerization is then activated by increasing temperature or irradiation or by addition of catalyst. The polymerization process continues the formation of a reservoir type of system with a spherical structure. After the polymerization process the solvent is withdrawn leaving the spherical structured porous microspheres, i.e., microsponges. The various steps involved in the preparation of microsponges are summarized as follows:

Step 1: Selection of monomer as well as a combination of monomers.

Step 2: Formation of chain monomers as polymerization starts.

Step 3: Formations of ladders as a result of cross-linking between chain monomers.

Step 4: Folding of monomer ladder to form spherical particles.

Step 5: Agglomeration of microspheres leads to the production of bunches of microspheres.

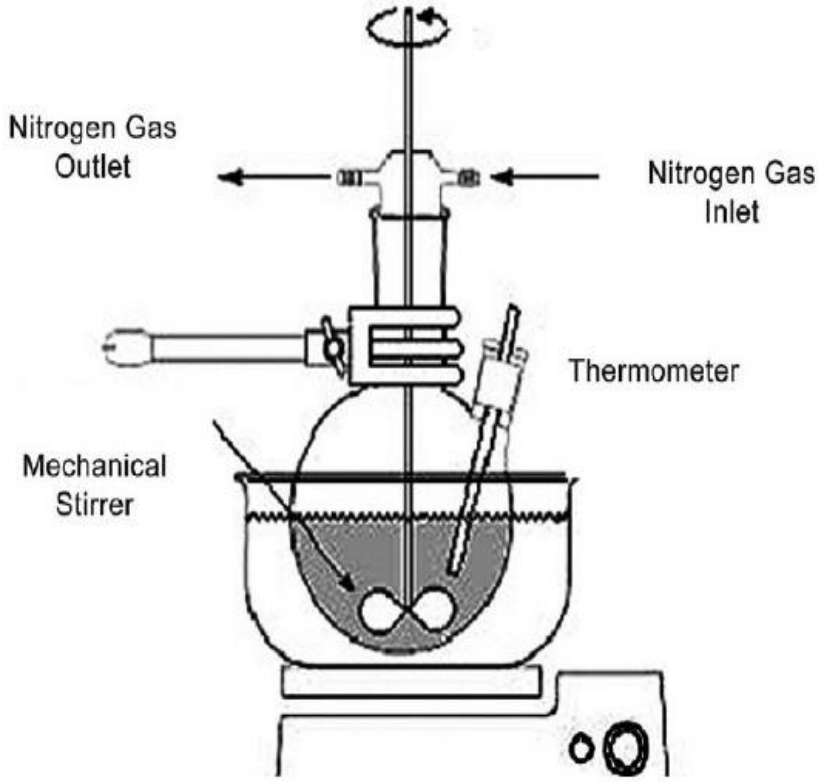

Figure 4: Microsponge preparation of liquid liquid suspension polymerization

B. The quasi-emulsion solvent diffusion method

This is a top-down approach starting with a preformed polymer. This operation involves the formation of quasi-emulsion of two different phases' i.e. internal phase and an external phase similar to emulsions. The internal phase of a drug-polymer solution made in a volatile solvent like ethanol or acetone or dichloromethane was added to the external phase comprising the aqueous polyvinyl alcohol (PVA) solution with vigorous stirring. Triethyl citrate (TEC), which was added at an adequate amount in order to facilitate plasticity. Stirring lead to the emergence of discrete emulsion globules called quasi-emulsion globules. The solvent is then extracted out from these globules to form insoluble, rigid microparticles i.e. microsponges. Following sufficient stirring, the mixture is then filtered to isolate the microsponges. The microsponges are then dried in an air heated oven. Conceptually, the finely dispersed droplets of the polymeric solution of the drug (dispersed phase) get solidified in aqueous phase via counter diffusion of organic solvent and water out of and into the droplets. The diffused aqueous phase within the droplets. The diffused aqueous phase within the droplets decreased the drug and polymer solubility resulting in the co-precipitation of both the components and continued diffusion of the organic phase results in further solidification, producing matrix-

type porous microspheres. In comparison to liquid-liquid suspension polymerization method, this method offers the advantage of less exposure of the drug to the ambient conditions, low solvent residues in the product because the solvent gets extracted out due to its solubility in aqueous media or due to its volatile nature.

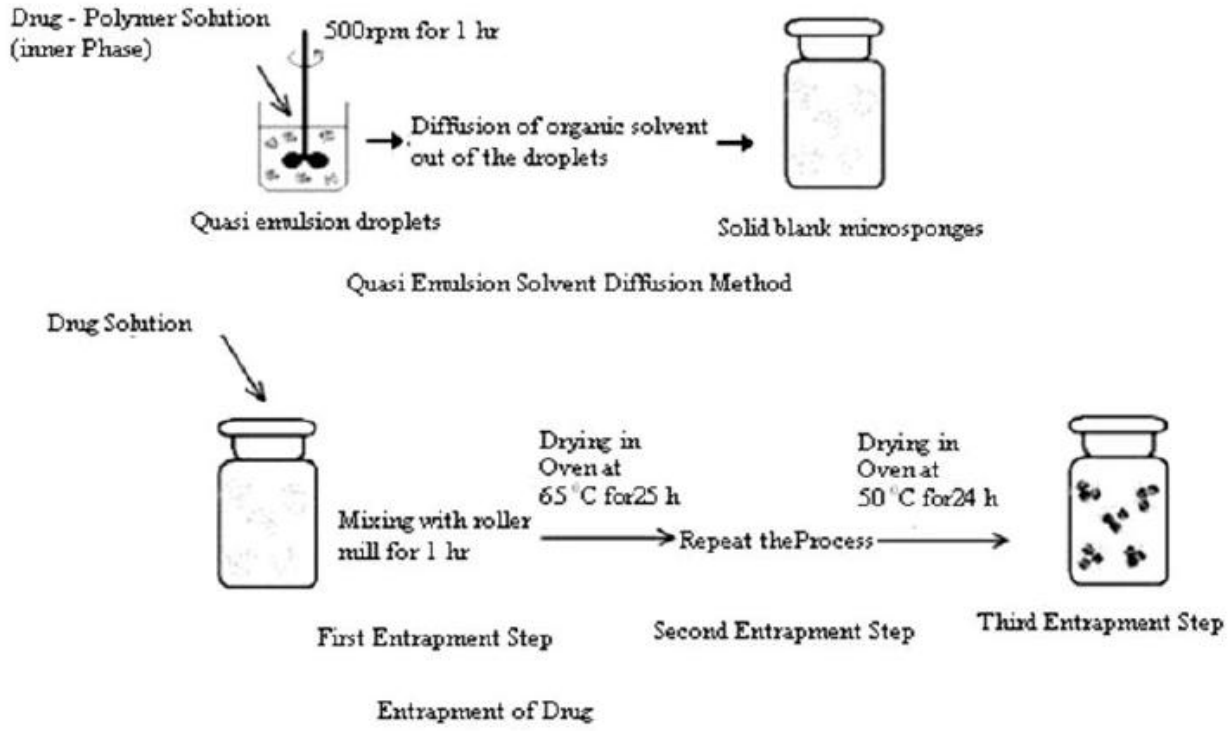

Figure 5: Quasi-Emulsion solvent diffusion method

DRUG RELEASE MECHANISM:

Temperature change: At room temperature, a few active ingredients can be too viscous to flow suddenly from microsponges onto the skin. With the rise in skin temperature, flow rate also increases and therefore release is also enhanced.

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

Solubility: Microsponges loaded with water miscible ingredients like antiseptics and antiperspirants 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.

PHYSICAL CHARACTERIZATION OF MICROSPONGES:

Particle Size Determination: 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 the 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 the final topical formulation.

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

Determination of Loading Efficiency and Production Yield: The loading efficiency (%) of the microsponges can be calculated according to the following equation:

$$\text{Loading efficiency} = \frac{\text{Actual Drug Contentin Microsponge}}{\text{Theoritical Drug Content}} \times 100$$

$$\text{Production Yeild(PY)} = \frac{\text{Practical Mass of Microsponges}}{\text{Theoritical Mass(polymer + Drug)}} \times 100$$

Determination of True Density: 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: 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 operating **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 the Washburn equation:

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

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

Here; D is the pore diameter (μm), is the surface tension of mercury (485 dyn cm−1), θ is the contact angle (130^0), and P is the pressure (psia). Total pore area (A_{tot}) was calculated by using the equation,

Here, P is the pressure (psia), V is the intrusion volume (ml g−1), V_{tot} is the total specific intrusion volume (ml g−1). The average pore diameter (Dm) is estimated by using the equation:

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

Envelope (bulk) density (ρ_{se}) of the microsponges was calculated by using the equation:

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

$$\rho_{sa} = \frac{Ws}{Vse - V_{tot}}$$

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 the equation:

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 the equation,

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

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

Compatibility Studies: Compatibility of the drug with reaction adjuncts can be studied by thin layer chromatography (TLC) and Fourier Transform Infra-red spectroscopy (FT-IR). Effect of polymerization on the crystallinity of the drug can be studied by powder X-ray diffraction (XRD) and Differential Scanning Colorimetry (DSC). For DSC approximately 5mg samples can be accurately weighed into aluminum pans and sealed and can be run at a heating rate of 15^0C/min over a temperature range 25-43^0C in an atmosphere of nitrogen.

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

Resiliency: Resiliency (viscoelastic properties) of microsponges can be altered to produce beadlets that are 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.

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:

$$Q = k_1 t^n \; OR \log Q = \log k_1 + n \log t$$

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

Where Q is the amount of the released at the time (h), n is a diffusion exponent which indicates the release mechanism, and k1 is a constant characteristic of the drug-polymer interaction. From the slope and intercept of the plot of log Q versus log t, kinetic parameters n and k1 were calculated. For comparison purposes, the data was also subjected to Eq., which may be considered a simple, Higuchi type equation;

Above Eq. for release data dependent on the square root of time, would give a straight line release profile, with k2 presented as a root time dissolution rate constant and C as a constant.

APPLICATIONS OF MICROSPONGES:

Sr. No.	Active agents	Applications
1.	Sunscreens	Long lasting product efficacy, with improved protection against sunburns and sun related injuries even atelevated concentration and with reduced irritancy and sensitization.
2.	Anti-acne e.g. Benzoyl peroxide	Maintained efficacy with decreased skin irritation and sensitization.
3.	Anti-fungals	Sustained release of actives.
4.	Anti-inflammatory e.g. hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatoses.
5.	Anti-dandruffs e.g. zinc pyri-thione, sele-nium sulfide	Reduced unpleasant odour with lowered irritation with extended safety and efficacy.
6.	Antipruritics	Extended and improved activity.
7.	Rubefacients	Prolonged activity with reduced irritancy greasiness and odour.
8.	Skin depig-menting agents e.g. hydroquinone	Improved stabilization against oxidation with improved efficacy and aesthetic appeal.

PATENT INFORMATION:

In September 1, 1987, Won R (Palo Alto, CA) of Advanced Polymer Systems, Inc. (Redwood City, CA) received (the 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.

On September 8, 1992, Won R (Palo Alto, CA) of Advanced Polymer Systems, In (Redwood City, CA) received (the United States Patent 5,145,675) for developing a two-step method for the preparation of controlled release formulations.

Advanced Polymer Systems, Inc. and subsidiaries ("APS" or the "Company") 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 July 23, 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*39 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.

LIST OF MARKETED PRODUCTS:

Product Name	Manufacturer	Advantages
Retinol cream	Biomedic	Microspongesystem helps to maximize retinol dosage while reducing the possibility of irritation. Retinol is a topical vitamin A derivative which helps maintain healthy skin, hair and mucous membranes.
Dermalogica oil control lotion	John & Ginger Dermalogica skin care products	Microsponge technology has exclusive skin response complex soothes and purifies, provides effective skin hydration, without adding excess oil.
Oil free matte block spf 20	Dermalogica	Microsponge technology absorbs oil, maintaining an all-day matte finish and preventing shine without any powdery residue. Oil free formula contains soothing Green Tea to help calm inflammation caused by breakouts. Contains no artificial fragrance or color.

FUTURE PROSPECT:

MDS holds a favorable future in various pharmaceutical applications in the coming years as they have peculiar properties like enhanced product performance and elegance, extended release, reduced irritation, improved physical, chemical, and thermal stability so flexible to develop novel product forms. MDS was originally developed for topical delivery of drugs

like anti-acne, anti-inflammatory, anti-fungal, anti-dandruff, antipruritics, rubefacients etc. The genuine challenge of microsponge delivery system in the future is gaining the advance core/shell delivery of the drug-loaded microsponges for oral peptide delivery by varying ratio of polymers. These days it is also being used for controlled oral delivery of drugs exerting bioerodible polymers for colon-specific delivery and also for biopharmaceutical delivery as well as in tissue engineering. Modern classes of pharmaceuticals, biopharmaceuticals (peptides, proteins, and DNA-based therapeutics) are fueling the rapid evolution of drug delivery technology.

CONCLUSION:

MDS has grown into vastly competitive and rapidly evolving technology and more and more research are carrying out to optimize the cost-effectiveness and efficacy of the therapy. It's a solitaire technology for the controlled release of topical agents and consists of microporous beads loaded with the active agent and also used for oral as well as biopharmaceutical drug delivery. Microsponge delivery systems that can precisely control the release rates or target drugs to a particular body site have a vast impression on the health care system. A microsponge delivery system can release its active ingredient on a time mode and also in response to other stimuli. Therefore, microsponge has a lot of potentials and is a very emerging field which is needed to be explored. Microsponges constitute a significant part by virtue of their small size and efficient carrier characteristics.

REFERENCES

1. Patel A.*, Upadhyay Pratik, Trivedi.J, Shah.Sheeraj and Patel J. *"Microsponge as the versatile tool for the topical route: A Review*"; IJPSR, 2012; Vol. 3(9): 2926-2937.
2. Jain N*, Sharma P.K, Banik.A, "*Recent advances on Microsponge delivery system";* International Journal of Pharmaceutical Sciences Review and Research,2011, Vol.8(003):13-23.
3. Maiti S*, Kaity S,Ray. S,Biswanath SA,"*Development and evaluation of xanthan gum-facilitated ethyl cellulose microsponges for controlled percutaneous delivery of diclofenac sodium"; Acta Pharm,2011, Vol.61:257-260.*
4. Jain.V, Singh.R, "*Development & Characterization of Eudragit RS 100 loaded microsponges & its colonic delivery using natural polysaccharides";*Acta Poloniae Pharmaceutica n Drug Research,2010, Vol.67(4):407-415.
5. Giri.V,Matreja.PS,"Sertaconazole Nitrate 2% Cream for the treatment of Tinea pedis";National Journal of Laboratory Medicine, 2016, Vol.5 (4):01-05.
6. Yerram Chandramouli*, Shaik Firoz1, R. Rajalakshmi1, Amaravathi Vikram1, B. Rubia Yasmeen1, R. Naveen Chakravarthi2, *"Preparation and evaluation of microsponges loaded controlled release topical gel of acyclovir sodium";*International Journal of Biopharmaceutics,2012, Vol.3(2):96-102.
7. Shital S. Patil*, Vaishali Dandekar, Asawari Kale, and Dr. S. D. Barhate; "*Microsponges drug delivery system: An overview";ejpmr, 2016, Vol.*3(8):212-221.

8. Kapoor D, Vyas RB, Lad C, Patel M, Tyagi BL, "A *Review On Microsponge Drug Delivery System",* Journal of Drug Delivery & Therapeutics., 2014, Vol.4(5): 29-35.
9. Jaya Raja Kumar, Selvadurai Muralidharan, Sanggetha Ramasamy, *"Microsponges Enriched Gel (MEGs): A Novel Strategy for Ophthalmic Drug Delivery System Containing Ketotifen",J. Pharm. Sci. & Res,* 2013; Vol.5 (4): 97–102.
10. D'souza JI, Harinath NM, *"Topical anti-inflammatory gels of fluocinolone acetonide entrapped in eudragit based microsponge delivery system"*, Research J Pharm and Tech, 2008, Vol.1: 502-506.
11. M. Orlu, E. Cevher, and A. Araman, *"Design and evaluation of colon-specific drug delivery system containing flurbiprofen microsponges"*, *Int. J. Pharm.*, 2006, Vol.318: 103–117.
12. Hong J, Chen H, Xiang S, Zuo T, Cao S, "Toward Application of Microsponges in Transdermal Drug Delivery System". MOJ Bioequiv Availab, 2015, Vol 1(1):216-217.
13. Aritomi H, Yamasaki Y, Yamada K, Honda H, Koshi M, "Development of sustained release formulation of chlorpheniramine maleate using powder coated microsponges prepared by dry impact blending method", J Pharm Sci Tech,1996, Vol 56:49-56.
14. Jain V, Singh R, "Dicyclomine loaded eudragit based microsponge with potential for colonic delivery: Preparation and characterization", Trop J Pharm Res, 2010, Vol.9: 67-72.
15. N.H, Aloorkar, A.S. Kulkarni, D.J. Ingale, "Microsponge As Innovative Drug Delivery System", International Journal Of Pharmaceutical Sciences and Nanotechnology, 2012, Vol.5 (1):1597-1605.
16. Mehta M, Panchal A, Shah VH, Upadhyay U. "Formulation and in-vitro evaluation of controlled release microsponge gel for topical delivery of clotrimazole", Int. J. Adv. Pharm; 2012,Vol.2(2):93-101.