AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Microsponges: A Novel Drug Delivery System

Vasavan Reshmy[1*], Vyas Sridhar[1], Nayak Shashank[1], Shabaraya AR[1]

1.Srinivas College of Pharmacy, Valachil, Post Parengipete, Mangalore- 574143

ABSTRACT

The Microsponge Delivery System (MDS) is a unique technology used for controlled release and prolonged topical administration. Due to the difficulty that arouse in the release of the active ingredient over an extended period of time the fundamental need for the Microsponge technology arouse. The MDS consists of macroporous beads typically 10 – 25 microns in diameter loaded with the active pharmaceutical ingredient. When applied to the skin the MDS releases its active ingredient on a time mode and also in response to different stimuli like rubbing, temperature, pH etc. This technology is currently being used in sunscreens, skin care, cosmetics and prescription products. It offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, increased elegance and enhanced formulation flexibility. Innumerable studies have confirmed that microsponge systems are non irritating, non mutagenic, non allergic and non toxic. Microsponges are used mostly for topical drug delivery and have been recently used for oral administration and tissue engineering.

Keywords: Microsponge, Controlled release, Topical drug delivery.

*Corresponding Author Email: reshmyvasavan@gmail.com

Received 06 February 2014, Accepted 13 February 2014

Please cite this article in press as: Reshmy V *et al.*, Microsponges: A Novel Drug Delivery System. American Journal of PharmTech Research 2014.

INTRODUCTION

Several predictable and reliable system were developed for systemic drugs under the heading of transdermal delivery system (TDS) using the skin as portal of entry. It has improved the efficacy and safety of many drugs that may be better administered through skin[1]. Microsponges are designed to deliver a pharmaceutically active ingredient efficiently at minimum dose and also to enhance stability, reduce side effects, and modify drug release profiles. These attributes have been successfully demonstrated in the FDA-approved Retin-A Micro® (0.1% or 0.04% tretinoin) and Carac (0.5% 5-flurouracil) products for acne treatment and actinic keratoses, respectively[3].

Application of topical drugs suffers many problems such as ointments, which are often aesthetically unappealing, greasiness, stickiness etc. that often results into lack of patient compliance. These vehicles require high concentrations of active agents for effective therapy because of their low efficiency of delivery system, resulting into irritation and allergic reactions in significant users. Other drawbacks of topical formulations are uncontrolled evaporation of active ingredient, unpleasant odour and potential in- compatibility of drugs with the vehicles. Thus the need exists for system to maximize amount of time that an active ingredient is present either on skin surface or within the epidermis, while minimizing its transdermal penetration into the body. The microsponge delivery system fulfils these requirements[2].

Microsponge

The microsponge technology was developed by Won in 1987 and the original patents were assigned to Advanced Polymer Systems, Inc[3]. Microsponge deli- very systems are uniform, spherical polymer particles. Their high degree of cross-linking results in particles that are insoluble, inert and of sufficient strength to stand up to the high shear commonly used in manufacturing 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 micro- sponge products from other types of dermatological delivery systems. The size of the microsponge varies from 5-300 µm in diameter. Although the microsponge size may vary, a typical 25 µm sphere can have upto 250000 pores and an internal pore structure equivalent to 10 ft in length providing a total pore volume of about 1 ml/g. Its large capacity for entrapment of actives, up to three times its weight, differentiates microsponge products from other types of dermatological delivery systems[4]. The active payload is protected in the

formulation by the microsponge particle; it is delivered to skin via controlled diffusion. This sustained release of actives to skin over time is an extremely valuable tool to extend the efficacy and lessen the irritation commonly associated with powerful therapeutic agents like α- hydroxy acids which may produce burning, stinging or redness in individuals with sensitive skin

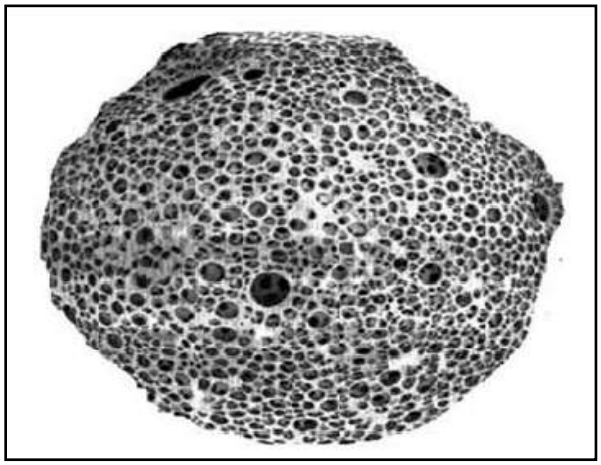

Figure 1: Porous nature of the microsponges

Microsponge polymers possess the versatility to load a wide range of actives providing the benefits of enhanced product efficacy, mildness, tolerability, and extended wear to a wide range of skin therapies. The microsponge particles are too large to be absorbed into the skin and this adds a measure of safety to these microsponge materials[5]. Bacterial contamination of the materials entrapped in the microsponge, because the size of pore diameter is smaller than bacteria, ranging from 0.007 to 0.2 µm. Microsponge delivery system applied to the skin, the release of drug can be controlled through diffusion or other variety of triggers, including rubbing, moisture, pH, friction, or ambient skin temperature[4].

Characteristics of microsponges[13]

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

- Microsponges absorb skin secretions up to 6 times its weight without drying and reduce the oiliness.

Advantages of microsponges[11]

- Extended release, continuous up to 12 hours;
- Reduced irritation formulas, better tolerance means broader consumer acceptance;
- Allows novel product form;
- Improved product aesthetics, gives product an elegant feel;
- Improves stability i.e. thermal, physical and chemical stability;
- Allows incorporation of immiscible products;

  Improves material processing e.g. Liquids can be converted to powders.

CHARACTERISTICS OF THE DRUGS ENTRAPPED INTO MICROSPONGE SYSTEM[6]

Most liquids or soluble ingredients can be entrapped in the particles. Actives that can be entrapped in microsponges must meet the following requirements,

- It should be either fully miscible in the monomer or capable of being made miscible by addition of a small amount of a water immiscible solvent.
- It should be water immiscible or at most only slightly soluble.
- It should be inert to monomers.
- The solubility of actives in the vehicle must be limited to avoid cosmetic problems; not more than 10 to 12% microsponges must be incorporated into the vehicles. Otherwise the vehicle will deplete the microsponges before the application.
- The spherical structure of the microsponges should not collapse.
- Polymer design and the payload of the microsponges for the active must be optimized for required release rate for given time period.

  It should be stable in contact with polymerization catalyst and conditions of polymerization.

Drugs Explored In MDS[15]

- Diclofenac sodium
- Ketoprofen
- Retinol
- Fluconazole
- Ibuprofen

- Tretinoin
- Trolamine
- Benzyl peroxide

Formulation Aids

Various polymers can form a microsponge 'cage'. These include a wide variety of natural and synthetic polymers. In natural there are Alginates (which are capable of forming hydrogels in the presence of divalent cations like Ca^{2+}) and Chitosan. Under synthetic there are Ethyl cellulose, Eudragit RS 100, Polystyrene and PHEMA; some microsponges contain plasticizer that help stabilize their structure[15].

Advantages Over Conventional Formulation

Conventional formulations of topical drugs are intended to work on the outer layers of the skin. Such products release their active ingredients upon application, producing a highly concentrated layer of active ingredient that is rapidly absorbed. In comparison Microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Potentially, the Microsponge system can significantly reduce the irritation of effective drugs without reducing their efficacy[15]. For example, by delivering the active ingredient gradually to the skin like MDS-Benzoyl peroxide have excellent efficacy with minimum irritation[12]. There properties are superior to microcapsules and liposomes as their walls have the tendency to rupture and likewise liposomes have lower payload than microsponges. Ointments on the other hand are aesthetically unappealing, greasy and sticky in nature. Also they require a larger amount of the vehicle thus increasing the ability to cause irritation and side effects. Other drawbacks of topical formulations are uncontrolled evaporation of active ingredient, unpleasant odour and potential incompatibility of drugs with the vehicles. The Microsponge system maximize the amount of time that a active ingredient is present either on skin surface or within the epidermis, while minimizing its transdermal penetration into the body[7].

Release Mechanisms[8]

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

i. **Pressure**: Rubbing/ pressure applied can release active ingredient from microsponges onto skin.

ii. **Solubility**: Microsponges loaded with water-soluble ingredients like anti-prespirants and antiseptics will release the ingredient in the presence of water. The release can

also be activated by diffusion taking into consideration the partition coefficient of the ingredient between the microsponges and the outside system.

iii. **Temperature change**: Some entrapped active ingredients can be too viscous at room temperature to flow spontaneously from microsponges onto the skin. Increased in skin temperature can result in an increased flow rate and hence release. Drug release from the topical semisolid formulation can be studied by using Franz-type static diffusion cells.

iv. **pH triggered systems**: 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.

Method of Preparation of Microsponges

Drug entrapment in microsponges can be done by two methods, depending on the physiochemical properties of the drug to be loaded. If the drug is typically an inert non-polar material which will generate the porous structure then, it is known as Porogen. A Porogen drug neither hinders the polymerization process nor becomes activated by it and also it is stable to free radicals and can be entrapped by one-step process (liquid-liquid suspension polymerization). Microsponges are suitably prepared by the following methods[9]:

Quasi-emulsion solvent diffusion[14]

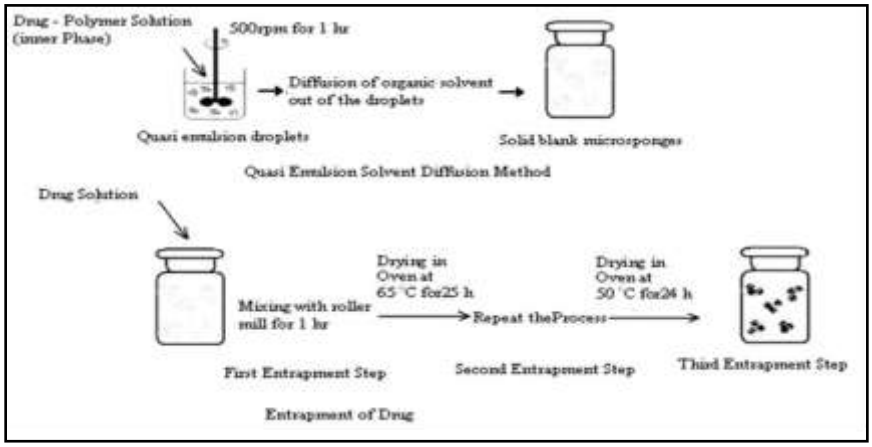

Figure 2: Preparation of microsponges by Quassi emulsion diffusion method

This is a two step process where the microsponges can be prepared by quasi- emulsion solvent diffusion method using the different polymer amounts. To prepare the inner phase, Eudragit RS 100 was dissolved in ethyl alcohol. Then, drug can be then added to solution and dissolved under ultrasonication at 35˚C. The inner phase was poured into the PVA solution in water (outer phase). Following 60 min of stirring, the mixture is filtered to separate the microsponges. The

microsponges are dried in an air-heated oven at 40˚C for 12 hrs and weighed to determine production yield (PY).

Solvent evaporation method[17]

This method was employed first for the preparation of microspheres, but now has been used for preparation of microsponge esp. which incorporates water soluble drugs. The inner polymeric phase consists of drug and the polymer (Ethylcellulose or Eudragit RS 100) made to a solution in equal amount (10 ml) of acetone and ethanol (1:1 ratio). This was stirred till a clear uniform mixture was obtained. The outer phase consisted of 50 ml of coconut oil and 50 ml of light liquid paraffin and 4 drops of Tween 80. The inner phase was poured into the outer phase by using a 22 gauge needle. The dispersion was stirred using a mechanical stirrer at 970 rpm for 4 hrs in case of ethyl cellulose and at 1200 rpm for 6 hrs for Eudragit RS 100. The resultant microsponges that were obtained were filtered using Whatmann filter paper, washed 3 times with n-hexane and then with water, dried and stored in a air tight container for further analysis. During the preparation procedure, emphasis is to be given on rpm and temperature for size and spherecity of the microspheres.

Liquid-liquid suspension polymerization[14]

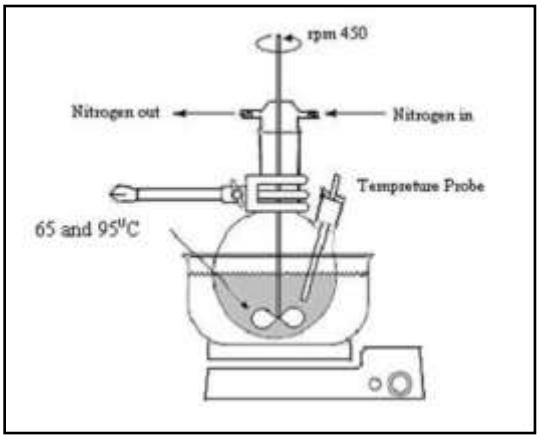

Figure 3: Reaction vessel for the preparation of Microsponges by liquid -liquid suspension polymerization

In this technique polymerization of styrene or methyl methacrylate is carried out in a round bottom flask. In their preparation, the monomers are first dissolved along with non-polar active ingredients in a suitable solvent solution of monomer and then dispersed in the aqueous phase, which consist of additives such as surfactant, suspending agents' etc. help in formation of suspension. Once suspension with the discrete droplets of the desired size is established; polymerization is effected by activating the monomers either by catalysis or increased temperature or irradiation.

The various steps in the preparation of microsponges are summarized as:

- Selection of monomer or combination of monomers.
- Formation of chain monomers as polymerization begins.
- Formation of ladders as a result of cross linking between them.
- Folding of monomer ladder to form spherical particles.
- •Agglomeration of microspheres, thus forming their bunches.
- • Binding of bunches to form microsponges.

The polymerization process leads to the formation of a reservoir type of system, which opens at the surface through pores. In some cases an inert liquid immiscible with water but completely miscible with monomer is used during polymerization to form the pore network. After the polymerization the liquid is removed leaving the porous microspheres, i.e., microsponges.

Factors Affecting Mechanism Of Drug Release[12]

- Physical and chemical properties of entrapped actives.
- Physical properties of Microsponge system like pore diameter, pore volume, resiliency etc. Properties of vehicle in which the microsponges are finally dispersed.
- Particle size, pore characteristics, resiliency and monomer compositions can be considered as programmable parameters and microsponges can be designed to release given amount of actives in response to one or more external triggers like; pressure, temperature and solubility of actives.
- Pressure Rubbing/ pressure applied can release active ingredient from microsponges onto skin.
- Temperature change some entrapped actives can be too viscous at room temperature to flow spontaneously from microsponges onto the skin. Increased in skin temperature can result in an increased flow rate and hence release.
- Microsponges loaded with water-soluble ingredients like antiperspirants and antiseptics will release the ingredient in the presence of water. The release can also be activated by diffusion taking into consideration the partition coefficient of the ingredient between the microsponges and the outside system.

Evaluation Parameters of Microsponges

Particle size and shape[10]

The most widely used procedures to visualize microparticles are conventional light microscopy

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

Morphology and surface topography of the microsponges[10]

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[10]

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

$$Loading\ Efficiency = \frac{Actual\ Drug\ Content\ in\ microsponge}{Theoretical\ Drug\ content}\ 100$$

The production yield of the microsponges can be calculated by accurately weighing the initial weight of the raw materials and the final weight of the microsponges obtained.

$$\text{Production yield} = \frac{\text{Actual Mass of microsponge}}{\text{Theoretical Mass (Drug + Polymer)}}\ 100$$

Determination of true Density[10]

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[10]

Pore volume and diameter are vital in controlling the intensity and duration of effectiveness of the active ingredient. Pore diameter also affects the migration of active ingredients from the microsponges into the vehicle in which the material is dispersed. Mercury intrusion porosimetry can be employed to study the effect of pore diameter and volume with rate of drug release from the microsponges. 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.

Compatibility studies[10]

Compatibility of drug with reaction adjuncts can be studied by thin layer chromatography (TLC) and Fourier Transform Infra-red spectroscopy (FTIR). Effect of polymerization on 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 aluminium pans and sealed and can be run at a heating rate of 15˚C/min over a temperature range 25–430˚C in an atmosphere of nitrogen.

Polymer/monomer composition[10]

Factors such as microsphere size, drug loading, and polymer composition govern the drug release from microspheres. 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 percentage drug release against time.

Resiliency (Viscoelastic properties)[10]

Resiliency 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.

Dissolution studies[10]

Dissolution profile of microsponges can be studied by use of dissolution apparatus USP XXIII with a modified basket consisted of 5µm stainless steel mesh. The speed of the rotation is 150 rpm. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. Samples from the dissolution medium can be analysed by suitable analytical method at various intervals.

Kinetics of Release[10]

The dissolution profile of each formulation have been subjected to various models such as Zero order kinetics (percentage drug release against time), First order kinetics (log percentage drug unreleased against time), Higuchi (percentage drug released against square root of time) and Korsemeyer-Peppas (log percent drug released against log of time) were applied to access the kinetics of drug release from prepared microsponges.

Safety Considerations[16]

Safety substantiation of microsponges can be confirmed by skin irritation and eye irritation studies on rabbits, oral toxicity studies in rats, mutagenicity in bacteria and allergenicity in guinea pigs.

Formulation Considerations

Actives entrapped in MDS can then be incorporated into many products such as creams, lotions, powders and soaps. When formulating the vehicle, certain considerations are taken into account in other to achieve desired product characteristics,

- The solubility of actives in the vehicle must be limited, otherwise the vehicle will deplete the microsponge before application.
- To avoid cosmetic problems, not more than 10%-20% w/w microsponges must be incorporated into the vehicle.
- Polymer design and payload of microsponges for the active must be optimized for required release rate for the given time period[18].

There remains equilibrium between microsponge and vehicle, and microsponge release drug in response to the depletion of drug concentration in the vehicle. Drug concentration in the vehicle is depleted by absorption of the drug into the skin. Hence continuous and steady release of active onto the skin is accomplished with this system. Drug release from the topical semisolid formulation can be studied by using Franz diffusion cells[17].

Applications Of Microsponges

Microsponge delivery systems are used to enhance the safety, effectiveness and also the aesthetic quality of topical prescription, over-the-counter and personal care products. Products under development or in the market place utilize the topical microsponge systems in three primary ways:

1. As reservoirs releasing active ingredients over an extended period of time,
2. As receptacles for absorbing undesirable substances, such as excess skin oils, or
3. As closed containers holding ingredients away from the skin for superficial action[20].

Releasing of active ingredients from conventional topical formulations over an extended period of time is quite difficult. Cosmetics and skin care preparations are intended to work only on the outer layers of the skin. The typical active ingredient in conventional products is present in a relatively high concentration and, when applied to the skin, may be rapidly absorbed. The common result is over-medication, followed by a period of under-medication until the next application. Rashes and more serious side effects can occur when the active ingredients rapidly

penetrate below the skin's surface[12]. Microsponge technology is designed to allow a prolonged rate of release of the active ingredients, thereby offering potential reduction in the side effects while maintaining the therapeutic efficacy[6].

FUTURE PERSPECTIVE

Nanosponges[4]

Today, as we realize the immense advantages offered by the nano-size, the micro sized products are likely to be outdated. The nanosized particles have a very high surface area to size ratio and a greater potential to modulate the release of actives compared to micro-sized particles. While inorganic nanosponges have many applications in electronics, the first pharmaceutical nanosponges based on cross linked cyclodextrins have been reported. These are Nano sized, highly porous materials composed of beta-cyclodextrins cross linked with carbonate bonds. Econazole nitrate nanosponges loaded carbopol hydrogel were recently developed. These are prepared using ethyl cellulose and poly vinyl alcohol by emulsion solvent evaporation method.

Oral care cosmetics[13]

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

Incorporating natural ingredients[13]

Nowadays multifunctional natural ingredients are been used recently in the formulation of microsponges. For example, Marinosomes®, liposomes made from natural anti- inflammatory lipid extracts, have set a new paradigm in using such functional 'active excipients'. The possibility of using such substances for constructing a microsponge structure appears to be cost effective and innovative.

In long lasting coloured cosmetics[4]

Colours entrapped in microsponges may be used in a variety of coloured cosmetic products such as rouge or lipsticks to make them long lasting thus they help in uniform spreading and improving covering power. Hence, coloured cosmetics formulated with microsponges would be highly elegant

MARKETED FORMULATIONS OF MICROSPONGES[9]

Product Name	Advantages	Manufacturer
Retin-A-Micro^{tm}	0.1% and 0.04% Tertinoin entrapped in MDS, for topical treatment of acne vulgaris	Ortho-Mcneil pharmaceutical, inc
Carac cream, 0.5%	Carac cream contains 0.5% flurouracil,with0.35 being incorporated into a patented porous microsponge composed of methyl methacrylate cross polymer and dimethicone	Dermik Labratories, inc.
Line eliminator dual retinal Facial treatment	Lightweight cream with a retinal in MDS, Deliver both immediate and time released Wrinkle-fighting action.	Avon
Retinol cream	The retinol molecule is kept in microsponge System to protect the potency of vitamin A. This helps to maximize the retinol dosage. While reducing the possibility of irritation	Biomedic
Retinol 15 night cream	A night time treatment with microsponge Technology using a stabilize formula of pure Retinol and vitamin A	Sothys
EpiQuin micro	The microsponge system uses microscopic. Reservoirs that entrap hydroquinone and Retinol.	Skin Medica inc
Spots cream RS and XS	Topical analgesic-anti-inflammatory and Counter Irritant activities in microsponge delivery System for management of musculoskeletal Conditin.	Embil Co. Inc.
Salicylic peel 20	Deep BHA peeling agent for salicylic acid 20% microsponge technology. Excellent Exfoliations and stimulation of skin for more resistant skin types for faster action.	Biophora
Salicylic peel 30	Deep BHA peeling agent for salicylic acid 30% microsponge technology. Excellent Exfoliation and stimulation of skin for more resistant skin types for faster action.	Biomedic
Oil free matte block spf-20	The invisible sun screen provides a shield for the skin from damaging uv rays and controls oil production. Microsponge technology absorbs the oil. Maintain an all day matte finish.	Dermalogica
Lactrex^{TM} 12%moisturizing cream	Lactrex^{TM} 12% moisturizing Cream contains 12% lactic acid as the neutral Ammonium salt and lactate microsponge Technology has been included for comfortable Application and long lasting moisturization.	SDR pharmaceuticals, inc.

CONCLUSION

A Microsponge Delivery System can entrap wide range of actives and then release them onto the skin over a time and in response to trigger. It is a unique technology for the controlled release of topical agents and consists of microporous beads loaded with active agent and also

use for oral as well as biopharmaceutical drug delivery. A Microsponge Delivery System can release its active ingredient on a time mode and also in response to other stimuli. Thus microsponge has got a lot of potential and is a very emerging field which is needed to be explored.

REFERENCES

1. Patel SB, Patel HJ, Seth AK. Microsponge drug delivery system: An overview. J Global Pharm Tech.2010; 2(8): 1-9.
2. Viral Shaha, Hitesh Jain, Jethva Krishna, Pramit Patel. Microsponge drug delivery: A review. Int J Res Pharm Sci. 2010; 1(2): 212-218.
3. Patidar K, Soni M, Saxena C, Soni P, Sharma DK. Microsponges versatile vesicular approach for transdermal drug delivery system. J Global Pharm Tech. 2010; 2(3): 154-164.
4. Saroj KP, Microsponge as the versatile tool for drug delivery system. IJRPC. 2011; 1(2): 243-258.
5. Mahajan AG, Jagtap LS, Chaudhari AL, Swami SP, Mali PR. Formulation and evaluation of drug delivery system using indomethacin. IRJP. 2011; 2(10): 64-69.
6. Transel C, Omog L, Nursin G, Tamer B. Preparation and *in vitro* evaluation of modified release ketoprofen microsponges. Il Farmaco. 2003; 58: 101-106.
7. Santanu K, Sabyasachi M, Ashok kumar G, Shubham B. Microsponge: A novel strategy for drug delivery system. J Adv Pharm Tech Res. 2010; 1(3): 283-290.
8. Shyamsunder MVT. Novel approach: Microsponge drug delivery system. IJPSR. 2012; 3(4): 967-980.
9. Parikh BN *et al.* J Global Pharm Tech. 2010; 2(1): 17-29.
10. Vyas SP, Khar RK. Targeted and Controlled drug delivery-Novel carrier system, New delhi, CBS Publication. 2002; 1st Ed: 453.
11. D'souza JI, Harinath NM. Topical anti-inflammatory gels of fluocinolone acetonide entrapped in Eudragit based microsponge delivery system. Res J Pharm Tech. 2008; 1(4): 502-506.
12. Patel G, Patel JK. Use of a microsponge in drug delivery systems, available at: http://www.pharmpro.com/ShowPR.aspx?PUBCODE=021&ACCT=0000100&ISSUE=0602&RELTYPE=PR&ORIGRELTYPE&ATO&PRODCODE=0000&PRODLETT=B&CommonCount=0

13. A.P.Pharma Inc. Microsponge Technology, Topical Technology December 2001. Available at: http://www.appharma.com/PDFs/topicalsht.pdf
14. D'souza JL. *In vitro* antibacterial and skin irritation studies of microsponges of benzoyl peroxide. Indian drugs. 2001; 38(7):104-109.
15. Amrutiya N, Bajaj A, Madan M. Development of Microsponges for topical delivery of Mupirocin. AAPS Pharm Sci Tech. 2009; 10(2): 402-408.
16. Jelvahgari M, Siahi-shadbad MR, Azarmi A, Martin GP, Nokhodchi A. The microsponge delivery system of benoilperoksit: Preparation, characterization and release studies. Int J Pharm. 2006; 308: 124-132.
17. Nacht S, Katz M. The microsponge: A novel topical programmable delivery system in
18. Shah VP. Determination of *In vitro* release from Hydrocortisone creams. Int J Pharmaceutics. 1989; 53: 53-59.
19. Wester R, Patel R, Natch S, Leyden J, Melendres J, Maibach H. Controlled release of benzoylperoxide from a porous microsphere polymeric system can reduce topical irritancy. 1991; 24: 720-726.
20. Grimes PE. A microsponge formulation of hydroquinone 4% and retinol 0.15% in the treatment of melisma and post inflammatory hyperpigmentation. 2004; 74(6): 362-368.