REVIEW ARTICLE
Department of Pharmaceutics

Mantry et.al / UJPSR / 1 (1), 2015, 32-38
e ISSN: 2454-3764
Print ISSN: 2454-3756

MICROSPONGE AS A NOVEL STRATERGY OF DRUG DELIVERY SYSTEM

[1]Shubhrajit Mantry*, [1]Arnab Bagchi, [1]Sujit Das, [1]Sudip Das

*Department of Pharmaceutics, Himalayan Pharmacy Institute, Majhitar, Rangpo, E. Sikkim – 737136, **INDIA***

ARTICLE INFO:
Article history:
Received: 1 April 2015
Received in revised form:
15 May 2015
Accepted: 15 June 2015
Available online: 15 July 2015

Corresponding Author:
Mr. Shubhrajit Mantry
Department of Pharmaceutics
Himalayan Pharmacy Institute
*Majhitar, E. Sikkim, **INDIA***
***Email:** manu28pharmcy@gmail.com*
***Phone:** +91-7384205300*

Abstract
Microsponge is recent novel technique for control release and target specific drug delivery system. Therefore many scientist or researcher attracted towards the microsponge drug delivery system. Also Microsponge technology has been introduced in topical drug products to facilitate the controlled release of active drug into the skin in order to reduce systemic exposure and minimize local cutaneous reactions to active drugs. More and more developments in delivery systems are being integrated to optimize the efficacy and cost-effectiveness of the therapy. This review is focused on method of preparation, characterization and application of microsponge.

Key words
Microsponges,
Liquid-Liquid Suspension Polymerization
Quasi-Emulsion Solvent Diffusion Method

INTRODUCTION

Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge-like spherical particles with a large porous surface. Moreover, they may enhance stability, reduce side effects and modify drug release favorably. Microsponge technology has many favourable characteristics, which make it a versatile drug delivery vehicle. Microsponge Systems are based on microscopic, polymer-based microspheres that can suspend or entrap a wide variety of substances, and can then be incorporated into a formulated product such as a gel, cream, liquid or powder. It can provide increased efficacy for topically active agents with enhanced safety, extended product stability and improved aesthetic properties in an efficient manner [1-3]. Microsponges consist of non-collapsible structures with porous surface through which active ingredients are released in controlled manner. Depending upon the size, the total pore length may range up to 10 ft. and pore volume up to 1 ml/g. 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 such as rubbing, temperature, and pH Microsponges have the capacity to absorb or load a high degree of active materials into the particle or onto its surface. Its large capacity for entrapment of actives up to 3 times its weight differentiates microsponges from other types of dermatological delivery systems. Mostly microsponge is use for transdermal drug delivery system [4,5]. The microsponge technology was developed by Won in 1987, and the original patents were assigned to Advanced Polymer Systems. This company developed a large number of variations of the technique and applied those to the cosmetic as well as over-the-counter (OTC) and prescription pharmaceutical products. At the present time, this interesting technology has been licensed to Cardinal Health, Inc., for use in topical products. The size of the microsponges can be varied, usually from 5 – 300 µm in diameter, depending upon the degree of smoothness or after-feel required for the end formula. Although the microsponge size may vary, a typical 25 µm sphere can have up to 250000 pores and an internal pore structure equivalent to 10 ft in length, providing a total pore volume of about 1 ml/g.

e ISSN: 2454-3764
Print ISSN: 2454-3756

This results in a large reservoir within each microsponge, which can be loaded with up to its own weight of active agent. The microsponge particles themselves are too large to be absorbed into the skin and this adds a measure of safety to these microsponge materials. Another safety concern is the potential bacterial contamination of the materials entrapped in the microsponge. As the size of the pore diameter is smaller, the bacteria ranging from 0.007 to 0.2 µm cannot penetrate into the tunnel structure of the microsponges [6].

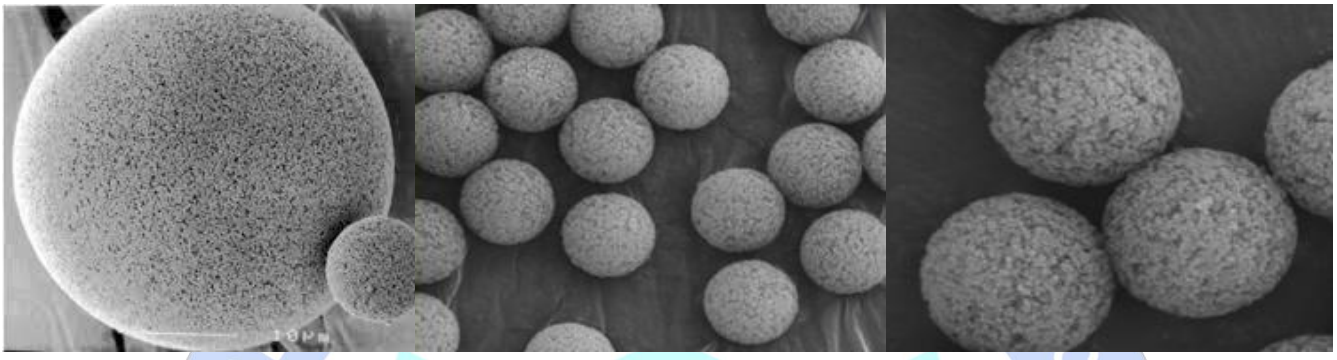

Fig.1: Various Sizes of Microsponges

CHARACTERISTICS OF MICROSPONGES [7]

- Microsponge formulations are stable over range of pH 1 to 11.
- Microsponge formulations are stable at the temperature up to 130oC.
- 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 is entrapped in Microsponges [7]

- Most liquid or soluble ingredients can be entrapped in the particles. Actives that can be entrapped in microsponges must meet following requirements,
- It should be either fully miscible in monomer or capable of being made miscible by addition of small amount of a water immiscible solvent.
- It should be water immiscible or at most only slightly soluble.
- It should be inert to monomers.
- The solubility of actives in the vehicle must be limited to avoid cosmetic problems; not more than 10 to 12% w/w microsponges must be incorporated into the vehicle.
- Otherwise the vehicle will deplete the microsponges before the application.
- The spherical structure of microsponges should not collapse.
- Polymer design and payload of the microsponges for the active must be optimized for required release rate for given time period.
- It should be stable in contact with polymerization catalyst and conditions of polymerization.
- Have the capacity to absorb or load a high degree of active materials into the particle or unto its surface.
- Microsponges are stable over a ph range of 1-11 and upto temperature of 130^0c
- They are self sterilizing as average pore size is 0.25 µm where bacteria cannot penetrate.

Advantages of Microsponges [8]

- Microsponges are biologically safe and offer unique advantage of programmable release.
- They offer entrapment of numerous ingredients and is believed to contribute
- Elegance and enhanced formulation flexibility.

- Microsponges are capable of absorbing skin secretions so reducing the oiliness of the skin upto 6 times of its weight.
- With size 10-25 microns in diameter it is capable of entrapping the various ingredients in asingle microsphere.
- The drug releases in microsponges the external stimuli like ph, temperature, and rubbing.
- Microsponges have several advantages over topical preparations in being non-allergic, non-toxic, non-irritant and non-mutagenic.
- Microsponges are all ways stable i.e, thermal, physical and chemical.
- These are compatible with the majority of vehicles and ingredients.
- These systems have higher payload up to 50 to 60%.

APPLICATION OF MICROSPONGE [9]

Microsponges are porous, polymeric microspheres that are used mostly for topical and recently for oral administration. It offers the formulator a range of alternatives to develop drug and cosmetic products. Microsponges are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects and modify drug release.

FORMULATION USED FOR MICROSPONGES [11]

The MDS contain drug, polymer, vehicle and other additives like plasticizers that help stabilize the structure. Various drugs used in MDS are :-

- Benzoyl peroxide,
- Dicyclomine,
- Fluconazole,
- Paracetamol,
- Retinol,
- Tretinoin,
- Flucinolone acetonide,
- Ketoprofen,
- Ibuprofen,
- Flurbiprofen

Various polymers can form a microsponge cage. These include Ethyl cellulose, Eudragit RS 100, Polystyrene, acrylic polymers and PHEMA etc In addition to actives; some microsponges contain plasticizers like Triethylcitrate (TEC) that help to stabilize their structure.

Table 1: Application of Microsponges [9]

Active agents	Applications
Sunscreens	Long lasting product efficacy, with improved protection against un burns and sun related injuries even at elevated concentration and with reduced irritancy and sensitization.
Anti-acne e.g.Benzoyl peroxide	Maintained efficacy with decreased skin irritation and sensitization.
Anti inflammatory e.g. hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatoses.
Anti-fungals	Sustained release of actives.
Anti-dandruffs e.g. zinc pyrithione, selenium sulfide	Reduced unpleasant odour with lowered irritation with extended safetyand efficacy.
Antipruritics	Extended and improved activity.
Skin depigmenting agents e.g. hydroquinone	Improved stabilization against oxidation with improved efficacy and aesthetic appeal.
Rubefacients	Prolonged activity with reduced irritancy greasiness and odour.

PREPARATION OF MICROSPONGES [8]

Initially, drug loading in microsponges is mainly take place in two ways depending upon the physicochemical properties of 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 become activated by it and also it is stable to free radicals is entrapped with one-step process (liquid-liquid suspension polymerization). Microsponges are suitably prepared by the following methods:

1. Liquid-liquid suspension polymerization.
2. Quasi-emulsion solvent diffusion method (Top down approach).

LIQUID-LIQUID SUSPENSION POLYMERIZATION

The porous microspheres are prepared by suspension polymerization method in liquid liquid systems. In their preparation, the monomers are first dissolved along with active ingredients in a suitable solvent solution of monomer and are then dispersed in the aqueous phase, which consist of additives (surfactant, suspending agents, etc. to aid in formation of suspension). The polymerization is then initiated by adding catalyst or by increasing temperature or irradiation. The various steps in the preparation of microsponges are as follows:

- Selection of monomer or combination of monomers.
- Formation of chain monomers as polymerization begins.
- Formations of ladders as a result of cross linking between chain monomers.
- Folding of monomer ladder to form spherical particles.
- Agglomeration of microspheres, which give rise to formation of bunches of microspheres.
- Binding of bunches to form microsponges.

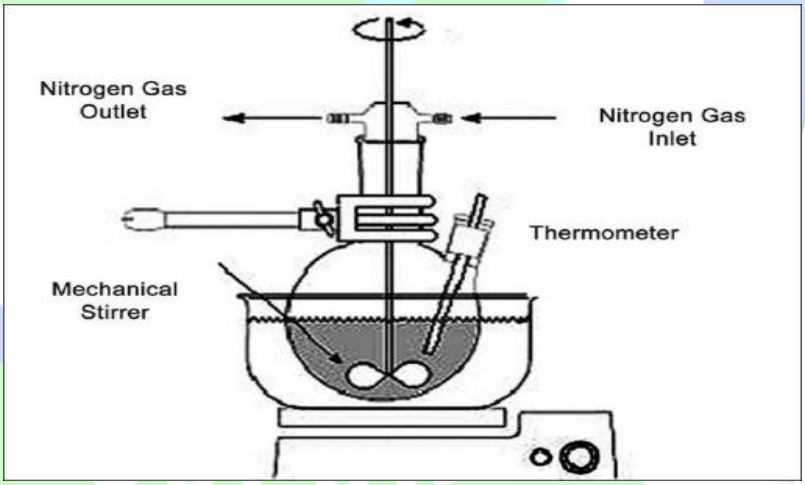

Fig.2: instrument set up for suspension polymerization technique

QUASI-EMULSION SOLVENT DIFFUSION METHOD (TOP DOWN APPROACH)

This is top-down approach starting with preformed polymer. This process involved formation of quasi-emulsion of two different phases i.e. internal phase and external phase similar to emulsions. The internal phase of drug polymer solution made in a volatile solvent like ethanol or acetone or dichloromethane was added to external phase comprising the aqueous polyvinyl alcohol (PVA) solution with vigorous stirring. Triethylcitrate (TEC), which was added at an adequate amount in order to facilitate plasticity. Stirring lead to the formation of discrete emulsion globules called quasi-emulsion globules. Solvent was then extracted out from these globules to form insoluble, rigid microparticles i.e. microsponges. Following sufficient stirring, the mixture was then filtered to separate the microsponges. The microsponges

Mantry et.al / UJPSR / 1 (1), 2015, 32-38
e ISSN: 2454-3764
Print ISSN: 2454-3756

were 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 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 with liquid liquid suspension polymerization method, this method offered the advantage of less exposure of the drug to the ambient conditions, low solvent residues in the product because the solvent get extracted out due to its solubility in aqueous media or due to its volatile nature.

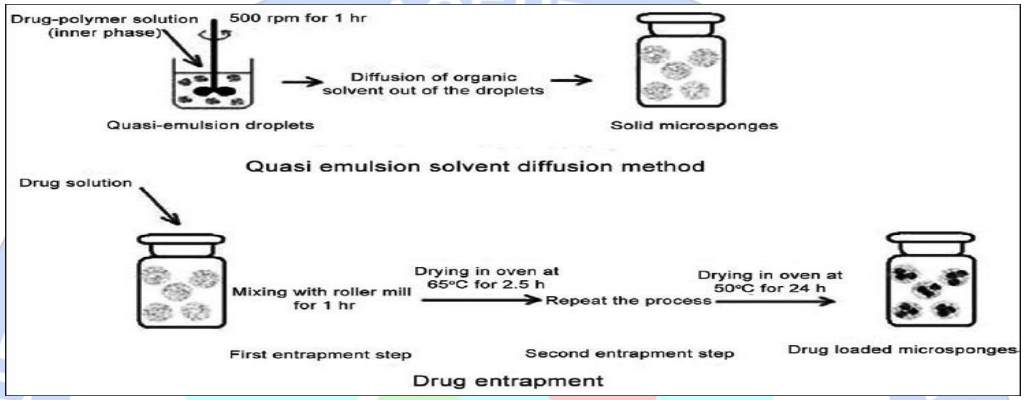

Fig.3: Quasi-emulsion solvent diffusion method (Top down approach)

EVALUATION OF MICROSPONGE [12]

a) 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, 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 PMμm can impart gritty feeling and hence particles of sizes between NM and 25μm are preferred to use in final topical formulation.

b) Morphology and surface topography of microsponges

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.

c) Determination of loading efficiency and production yield

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

Loading efficiency =Actual Drug Content in Microsponge / Therotical Drug Content

Theoretical Drug Content:

The production yield of the micro particles can be determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponge obtained.

Production Yeild (PY) =Practical Mass of Microsponges × 100/ Therotical Mass

Theoretical mass (Polymer+drug).

d) Characterization of pore structure

Pore volume and diameter are vital in controlling the intensity and duration of effectiveness of the active ingredient. Pore diameter also affects the migration of active ingredients from microsponges into the vehicle in which the material is dispersed. Mercury intrusion porosimetry can be employed to study effect of pore diameter and volume with rate of drug release from microsponges. Porosity parameters of microsponges such as intrusion extrusion isotherms pore size distribution, total pore surface area, average pore diameters, interstitial void volume, percent porosity,

percent porosity filled, shape and morphology of the pores, bulk and apparent density can be determined by using mercury intrusion porosimetry.

e) Polymer/monomer composition

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 % drug release against time.

f) Dissolution tests

Dissolution release rate of microsponges can be studied by use of dissolution apparatus USP XXIII with a modified basket consisted of 5µm stainless steel mesh. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. At various intervals the samples from the dissolution medium was analyzed by suitable analytical methods.

g) Determination of true density

The true density of micro particles is measured using an ultra-pycnometer under helium gas and is calculated from a mean of repeated determinations.

h) Resiliency (viscoelastic properties)

Resiliency (visco elastic 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.

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

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

j) *In-vitro* diffusion studies

The in vitro diffusion studies of prepared microsponge gel were carried out in Keshary–Chien diffusion cell using through a cellophane membrane. 100 ml of phosphate buffer was used as receptor compartment, and then 500 mg of gel containing 10 mg of drug was spread uniformly on the membrane. The donor compartment was kept in contact with a receptor compartment and the temperature was maintained at 37±0.50. The solution on the receptor side were stirred by externally driven Teflon coated magnetic bars at predetermined time intervals, pipette out 5 ml of solution from the receptor compartment and immediately replaced with the fresh 5 ml phosphate buffer. The drug concentration on the receptor fluid was determined spectrophotometrically against appropriate blank. The experiment was carried out in triplicate.

Table 2: List of marketed products using microsponge drug delivery system [10]

Product name	Advantages
Retin-A-Micro	0.1% and 0.04% tretinoin entrapped in MDS for topical treatment of acne vulgaris. 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%	Carac Cream contains 0.5% fluorouracil, with 0.35% being incorporated into a patented porous microsphere (Microsponge) composed of methyl methacrylate / glycol dimethacrylate cross-polymer and dimethicone. Carac is a once-a-day topical prescription product for the treatment of

	actinic keratoses
Line Eliminator Dual Retinol Facial Treatment	Lightweight cream with a retinol in MDS delivers both immediate and time released wrinkle-fighting action.
Retinol cream	The retinol molecule is kept in the microsponge system to protect the potency of the vitamin A by reducing the possibility of irritation.
Retinol 15 Nightcream	A nighttime treatment cream with Microsponge technology using a stabilized formula of pure (visible diminishment of fine lines and wrinkles.
EpiQuin Micro	The Microsponge ® system entraping hydroquinone and retinol release drug into the skin gradually throughout the day(minimize skin irritation). [49]
Sportscream RS and XS	Topical analgesic-anti-inflammatory and counterirritant actives in a Microsponge® Delivery System for the management of musculoskeletal conditions. [48]
Salicylic Peel 20	Salicylic acid 20%, Microsponge Technology, Excellent exfoliation and stimulation of the skin to improve fine lines, pigmentation, and acne concerns.

CONCLUSION

The microsponge delivery system is a unique technology for the controlled release of macro porous beads, loaded with active agent, offering a potential reduction in side effects, while maintaining their therapeutic efficacy. A microsponge delivery system can release its active ingredient on a time mode and also in response to other stimuli. Therefore, microsponge has got a lot of potential 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. Shivani Nanda, Mandeep Kaur, Nikhil Sood, Sahil Nagpal, Microsponge drug delivery system: an overview, *World Journal of Pharmacy and Pharmaceutical Sciences*, Volume 2, Issue 3, 1032-1043.
2. aity, S., et al., Microsponges: A novel strategy for drug delivery system. *J Adv Pharm Technol Res*, 2010. 1(3): p. 90-283.
3. Chadawar, V. and J. Shaji, Microsponge delivery system. *Curr Drug Deliv*, 2007. 4(2): p. 9-123.
4. Anderson D.L., Cheng C.H., Nacht S (1994). Flow Characteristics of Loosely Compacted Macroporous Microsponge(R) Polymeric Systems. Powder Technol78: 15-18.
5. Barkai A., Pathak V., Benita S (1990). Polyacrylate (Eudragit retard) microspheres for oral controlled release of nifedipine. I. Formulation design and process optimization. Drug Dev Ind Pharm 16: 2057-2075.
6. Kaity, et al.: Microsponges: Journal of Advanced Pharmaceutical Technology & Research | Jul-Sep 2010 | Vol 1 | Issue 3, page no. 283-290.
7. International Journal of Universal Pharmacy and Life Sciences 3(4): July-August 2013, Page No. 1-17.
8. Dhyani Archana et al / Indian Journal of Novel Drug Delivery 6(3), Jul-Sep, 2014, 198-207.
9. http://www.pharmatutor.org/articles/recent-advancement-microsponge-drug-delivery-system-review?page=0,0`
10. http://www.pharmatutor.org/articles/recent-advancement-microsponge-drug-delivery-system-review?page=0,1
11. Pathan et al. Microsponge drug delivery system as an innovation in Cosmetic world: A Review. AJPER October-December 2012, Vol 1, Issue 2 (67-87).
12. Raju. Manda et al.,: A Review: Microsponge a Novel New Drug Delivery System, J. Sci. Res. Phar., 2015; 4(1): 1-5.