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REVIEW ARTICLE

MICROSPONGE:A NOVEL TOPICAL DRUG DELIVERY SYSTEM

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ABSTRACT

Microsponge technology is novel technique generally used for transfer of active drug into the skin. It is a controlled release secretion system also helps to reduce systemic exposure and minimize local cutaneous reactions to active drugs. Microsponges used to control delivery of drug at specific predetermined site in body. The Microsponge Delivery System (MDS) is a unique technology for the controlled release of topical agents and consists of macroporous beads, typically 10-25 microns in diameter, loaded with active agent. Microsponges can entrapped various types of drug and incorporated in formulation such as cream, powder, gels and lotions. When applied to the skin; the microsponge releases its active ingredient on a time mode and also in response to other stimuli (rubbing, temperature, pH, etc) also microsponges are taken orally route. Microsponge technology offers entrapment of active drug ingredients and is used in to reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility. The microsponge systems are non-irritating, non-mutagenic, non-allergenic, and non-toxic. Microsponges also inhibit the various problems than other formulation problem such as need of regular dosing, drug reaction; incompatibility with environmental condition also easily stop the treatment and no need of special knowledge. The present review introduces Microsponge technology along with its method of preparation, characterization, advantages and release mechanism of MDS.

Keywords: Microsponge, Controlled release, Topical drug delivery, Oral drug delivery.

INTRODUCTION

Various systems were developed for systemic drugs under the class of trans-dermal delivery system (TDS) using the skin as portal of entry. Topical drugs while applying having many problems such as ointments, which are often aesthetically unappealing, greasiness, stickiness etc. that often results into lack of patient compliance. Also gels, powders, lotion has low time of contact with skin therefore these vehicles require high concentrations of active agents for effective therapy because of their low efficiency of delivery system no longer drug can be absorb form skin. This problem can be recovered by the microsponges. Microsponges require low drug content but having the longtime of contact with skin. Resulting into no irritation and allergic reactions are observed in some patient. A Microsponge Delivery System (MDS) is patented, highly cross-linked, porous, polymeric microspheres that can entrap wide range of actives and then release them with desired rate[1].This system is useful for the improvement of performance of topically applied drugs. It is a unique technology for the controlled release of topical agents and consists of microporous beads, typically 10-25 microns in diameter, loaded with active agent. 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, gels, 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[2].Microsponges should be

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uniform, spherical having the cross linked polymeric system, non-collapsible structure consisting of porous void space for the large entrapment of various active ingredients in the spaces and it offers higher shear strength which are commonly used in the area of creams, lotions, powders, having maximum payload of (50% to 60%), and inter connected void space of particle size range 5-500µm[3].The loaded active compound can be protected by microsponge formulation and diffuses long time. Its large capacity for entrapment of actives, up to three times its weight, differentiates microsponge products from other types of dermatological delivery systems. 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.

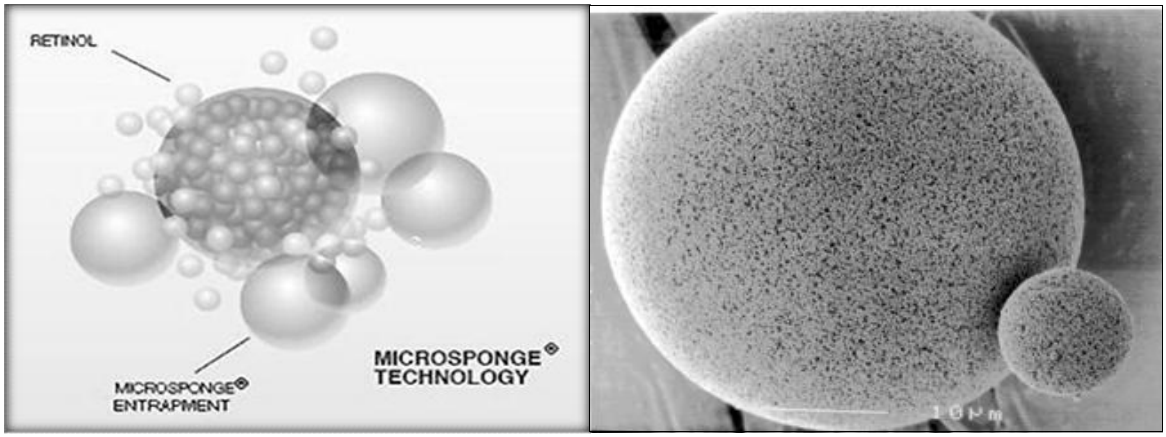

Figure 1:View of Microsponge[3].

CHARACTERISTICS OF MICROSPONGES:

1. Microsponge formulations are stable over range of pH 1 to 11.
2. Microsponge formulations are stable at the temperature up to 130°C.
3. Microsponge formulations are compatible with most vehicles and ingredients.
4. Microsponge formulations are self-sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.
5. Microsponge formulations have higher payload (50 to 60%), still free flowing and can be cost effective [4].

Advantages of Microsponge Delivery System:

1. Microsponges can absorb oil up to 6 times its weight without drying.
2. It provides continuous action up to 12 hours i.e. extended release.
3. Improved product elegancy.
4. Lessen the irritation and better tolerance leads to improved patient compliance.
5. It can also improve efficacy in treatment.
6. They have better thermal, physical and chemical stability.
7. These are non-irritating, non-mutagenic, non-allergenic and non-toxic.
8. MDS allows the incorporation of immiscible products[5],[6].

CHARACTERISTICS OF MATERIALS THAT IS ENTRAPPED IN MICROSPONGES:

1. It should be either fully miscible in monomer or capable of being made miscible by addition of small amount of a water immiscible solvent.
2. It should be water immiscible or at most only slightly soluble.

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3. It should be inert to monomers hence it can react with other excipients in formulation
4. 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.
5. The spherical structure of microsponges should not collapse.
6. Polymer design and payload of the microsponges for the active must be optimized for required release rate for given time period.
7. It should be stable in contact with polymerization catalyst and conditions polymerization [7].

Characterization of microsponges:

1. **Scanning electron microscopy:** 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 microsponges particle can also be taken to illustrate its ultra-structure[8].
2. **Determination of loading efficiency:** The loading efficiency (%) of the microsponges can be calculated according to the following equation: The production yield of the microparticles can be determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponge obtained. The loading efficiency (%) of the microsponges can be calculated according to the following equation[9].

$$Loading\ Efficiency = \frac{Actual\ drug\ content\ in\ microsponge}{Theortical\ drug\ content} \times 100$$

3. **Production yield:** The production yield of the microsponges can be determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponge obtained.
4.

$$Production\ Yield\ (PY) = \frac{Parical\ mass\ of\ microsponge}{Theortical\ \ mass\ (Polymer\ +\ Drug)} \times 100$$

5. **Size analysis of microsponges:** The mean diameter of 100 dried microsponges was determined by optical microscopy (Metzer, India). The optical microscope was fitted with a stage micrometer by which the size of microsponges could be determined. Particle size analysis of loaded and unloaded microsponges can be performed by laser light diffractometry or any other suitable method. The values can be expressed for all formulations as mean particle size range. Cumulative percentage drug release from microsponges of different particle size will be plotted against time to study effect of particle size on drug release. Particles larger than 30µm can impart gritty feeling and hence particles of sizes between 10 and 25µm are preferred to use in final topical formulation.
6. **Determination of True Density**: The true density of microparticles is measured using an ultrapycnometer under helium gas and is calculated from a mean of repeated determinations.
7. **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

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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[10],[11].

8. **Compatibility Studies:** Compatibility of drug with reaction adjuncts can be studied by thin layer chromatography (TLC) and Fourier Transform Infra-red spectroscopy (FT-IR). Effect of polymerization on crystallinity of the drug can be studied by powder X-ray diffraction (XRD) and Differential Scanning Colorimetry (DSC)[11].
9. **Resiliency:** Resiliency (viscoelastic properties) of microsponges can be modified to produce beadlets that is softer or firmer according to the needs of the final formulation. Increased cross-linking tends to slow down the rate of release. Hence resiliency of microsponges will be studied and optimized as per the requirement by considering release as a function of cross-linking with time[10].
10. **Dissolution Studies:** Dissolution profile of microsponges can be studied by use of dissolution apparatus (USP XXIII) with a modified basket consisted of 5µm stainless steel mesh. Speed of the rotation is 150 rpm. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. Samples from the dissolution medium can be analyzed by suitable analytical method at various intervals[12].
11. **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:

$$Q = k_1 t^n \text{ OR } Q = \log k_1 + n \log t \quad \text{.....Eq.1}$$

Where, Q is the amount of the released at 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.1, which may be considered a simple, Higuchi type equation;

$$Q = k_{2t}^{0.5} + C \quad \text{.....Eq.2}$$

Above Eq. for release data dependent on the square root of time, would give a straight line release profile, with k_2 presented as a root time dissolution rate constant and C as a constant[13].

12. **Mechanism of Drug Release:** By proper manipulation of the aforementioned programmable parameters, microsponge can be designed to release given amount of active ingredients over time in response to one or more external triggers[4].
13. **Temperature Change**: At room temperature, few entrapped active ingredients can be too viscous to flow suddenly from microsponges onto the skin. With increase in skin temperature, flow rate is also increased and therefore release is also enhanced[14].
14. **Pressure**: Rubbing or pressure applied can release the active ingredient from microsponges onto skin [15].

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15. **Solubility**: Microsponges loaded with water miscible ingredients like antiseptics and antiperspirants will release the ingredient in the presence of water. The release can also be activated by diffusion but taking into consideration, the partition coefficient of the ingredient between the microsponges and the external system [16].

PREPARATION OF MICROSPONGES:

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

i. 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) [17]. The polymerization is then initiated by adding catalyst or by increasing temperature or irradiation. The various steps in the preparation of microsponges are summarized as:

Step 1: Selection of monomer or combination of monomers.
Step 2: Dispersed in the aqueous phase, which consist of additives.
Step 3: Adding catalyst or by increasing temperature or irradiation.
Step 4: Formation of chain monomers as polymerization begins of ladders as
aresult of cross linking between chain monomers.
Step 5: Folding of monomer ladder to form spherical particles.
Step 6: Binding of spherical particles bunches to form microsponges.

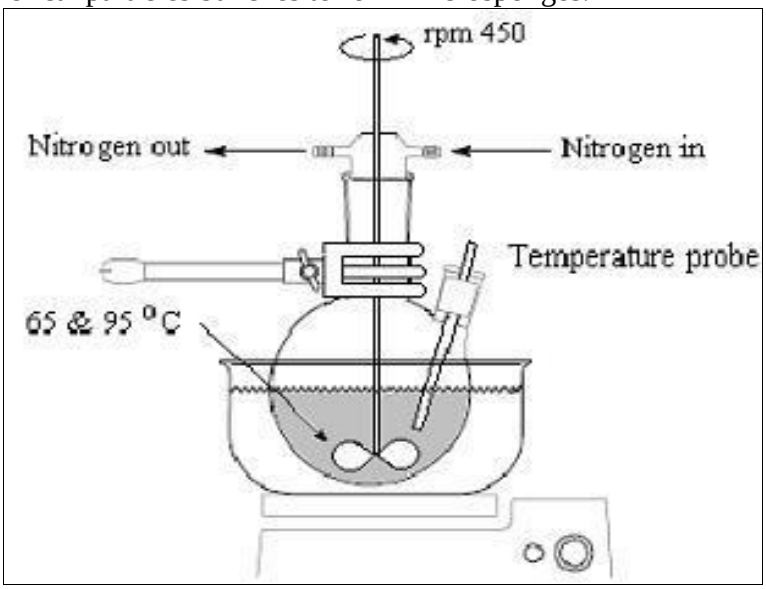

Fig 2: Reaction vessel for microsponge preparation by liquid-liquid suspension polymerization.

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 the polymerization to form the pore net-work. After the

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polymerization the liquid is removed leaving the porous microspheres, i.e., microsponges. Impregnating them within preformed microsponges then incorporates the functional substances. Some-times solvent may be used for faster and efficient in-corporation of the active substances. The micro-sponges act as topical carriers for variety of function-al substances, e.g. anti-acne, anti-inflammatory, anti-purities, anti-fungal, rubefacients, etc.

ii. Quasi-emulsion solvent diffusion :

This method consists of two steps. In first step inner phase was prepared by dissolving the polymer in solvent. Then dissolvedthe activeingredient in inner phase under sonication at 35-40°C. Then outer phase prepared by dissolving another polymer in aqueous solvent such as water under room temperature. Then pour the inner phase into the outer external phase. After emulsification, the mixture was continuously stirred for 2 hours. Then the mixture was filtered to separate the micro-sponges. The product was washed and dried by vacuum oven at 40°C for 24 hours [18].

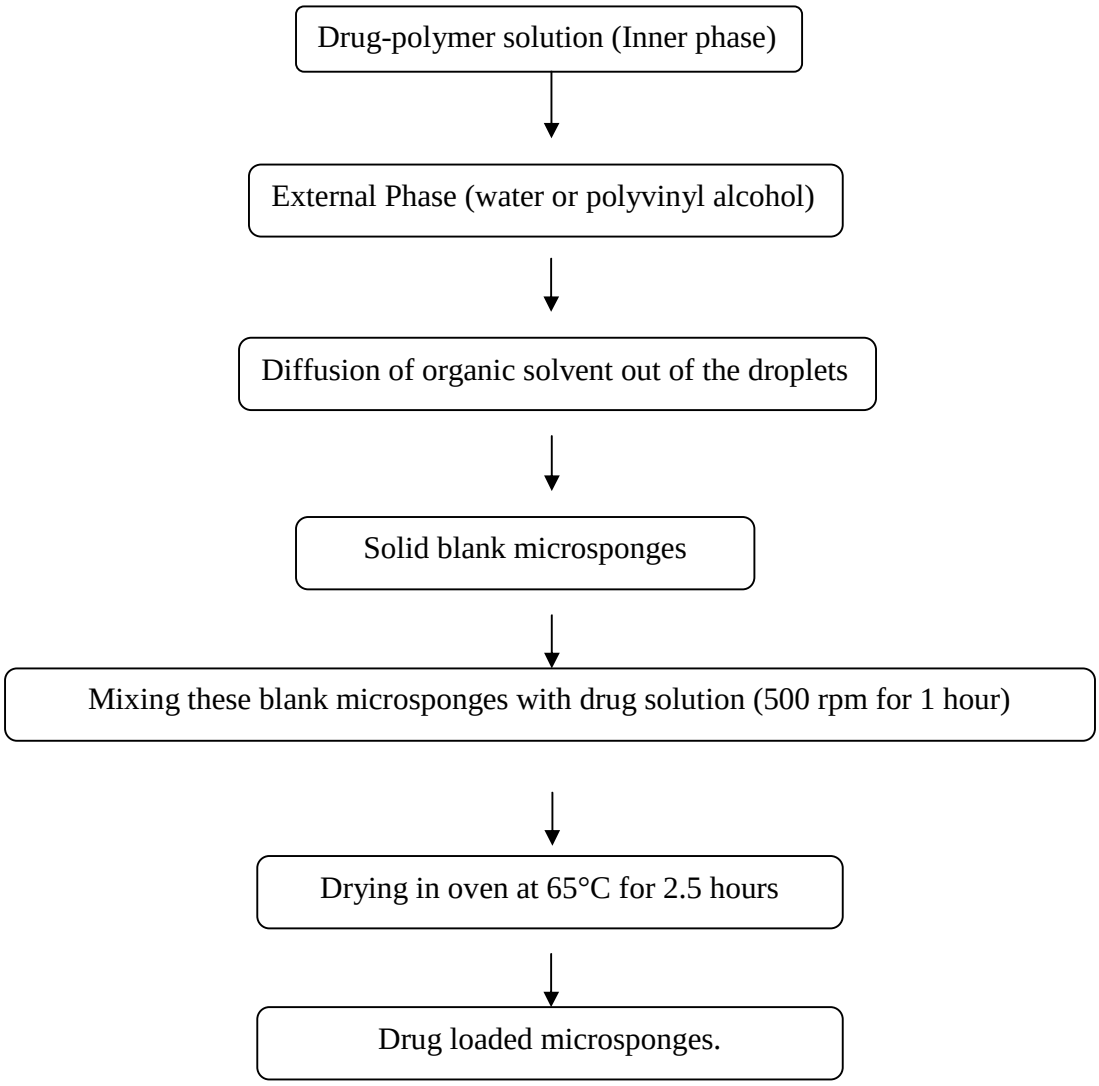

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Table no. 1: List of Marketed Products using MDS [21]

Product name	Content	Uses	Manufacturer
NeoBenz®Micro,	Benzoyl peroxide, methyl methacrylate/glycol	Antibacterial properties and is classified as keratolytic.	Intendis Inc. Morristown NJ07962 USA
Retin-A-Micro	0.1% and 0.04% Tretinoin, methyl methacrylate/ glycol dimethacrylate, Aqueous gel base.	Diminishment of fine lines and wrinkles, a noticeable improvement in the skin discolorations due to aging, and enhanced skin smoothness.	Biomedic, Sothys
Retinol cream, Retinol 15 Night cream	Retinol, Vitamin A	For the treatment of actinic keratosis (AK), a common pre-cancerous skin condition caused by over-exposure to the sun.	Dermik Laboratories, Inc. Berwyn , PA 19312 USA
Carac Cream	0.5% Fluorouracil, 0.35% methyl methacrylate / glycol dimethacrylate cross-polymer and dimethicone.	Visibly diminishes appearance of fine lines, wrinkles & skin discolorations associated with aging.	Avon
Line Eliminator Dual Retinol Facial Treatment	Vitamin A	Improve fine lines, pigmentation, and acne concerns.	Biophora
Salicylic Peel 20	Salicylic acid 20%,	Improve fine lines, pigmentation and acne concerns.	Biophora
Salicylic peel 30	Salicylic acid 30%,	Freeing the skin of all dead cells while doing no damage to the skin.	Biomedic
Dermalogica Oil Control Lotion	Niacinamide, Zinc Gluconate, Yeast Extract, Caffeine, Biotin,SalicylicAcid,EnantiaChlorantha Bark Extract.	To reduce oily shine on skin's surface.	John and Ginger Dermalogica Skin Care Products
Ultra Guard	Dimethicone	To protect a baby's skin from diaper rash, hypoallergenic and skin protectants.	Scott Paper Company

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Application of microsponges:-

1. The microsponge as topical delivery - Potentially, the Microsponge system can reduce significantly the irritation of effective drugs without reducing their efficacy. Further these porous microspheres with active ingredients can be incorporated in to formulations such as creams, lotions and powders.
2. Oral drug delivery using microsponge technology-In oral drug delivery the microsponge system increase the rate of solubilization of poorly water soluble drugs by entrapping them in the microsponge system's pores.
3. Microsponge technology used in bone tissue engineering.
4. Cardiovascular engineering using microsponge technology.
5. Reconstruction of vascular wall using microsponge technology[19],[20].

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