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MICROSPONGES AS A MODIFIED DRUG DELIVERY SYSTEM

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ABSTRACT

The area of drug delivery technology is evolving rapidly and becoming highly competitive day by day. The developments in the delivery systems are being utilized to optimize the efficacy and the cost effectiveness of the therapy. Recently, microsponge delivery system (MDS) has been successively addressed for the controlled release of drugs onto the epidermis with assurance that the drug remains chiefly localized and does not enter the systemic circulation in major amounts. The Microsponges are extremely small, inert, indestructible clusters of even Tinier spherical particles of microscopic size patented polymeric delivery systems consisting of porous microspheres that can entrap a wide range of active ingredients, capable of holding four times their weight in skin secretions and can absorb skin secretions. Like a true sponge, each microspheres consist of a myriad of interconnecting voids within a non-collapsible structure with a large porous surface. The size of microsponges can be varied usually from 5-300µm in diameter.safety concern is the potential bacterial contamination of the materials entrapped in the microsponge. Because the size of the pore diameter is smaller than bacteria, ranging from 0.007 to 0.2µm, bacteria cannot penetrate into the tunnel structure of microsponges, the microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Potentially, the microsponge system can reduce significantly the irritation of effective drugs without reducing their efficacy.

KEYWORDS: Microsponge delivery system, controlled release, topical drug delivery.

INTRODUCTION

Microsponges are highly cross-linked, patented, porous, polymeric microspheres that acquire the flexibility to entrap a wide variety of active ingredients that are mostly used for prolonged topical administration and recently for oral administration.Conventional topical preparations

are supposed to work on the outer layer of the skin. On application, these preparations release their active ingredient which produces the accumulation of drug that is rapidly absorbed. The application of topical preparations suffers from many problems such as, ointments which are greasy and sticky nature, and also aesthetically unappealing, this results into lack of patient compliance. The topical preparations also have other drawbacks like uncontrolled evaporation of active ingredient, unpleasant odor and incompatibility of drugs with the vehicle. Thus, for the effective therapy these types of formulations require high amount of active ingredient because of their low efficiency of delivery system which results into irritation and allergic reactions. Therefore there exists a need of such delivery system which can overcome these problems and thus microsponge delivery system can be used in this case.Microsponges are uniform, tiny, micro-porous polymeric beads and spherical in shape. It has the interconnected voids of particle size ranges between 5-300µ[13](Figure 1). Microsponges have the network of pores which holds the active ingredient to provide the controlled release of it. Micro-sponge 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.[1] The active ingredient is released in controlled manner due to the porous surface of non-collapsible structure. The microsponge system has the high degree of cross linking which results in particle that is insoluble, inert and of sufficient strength to withstand the high shear.

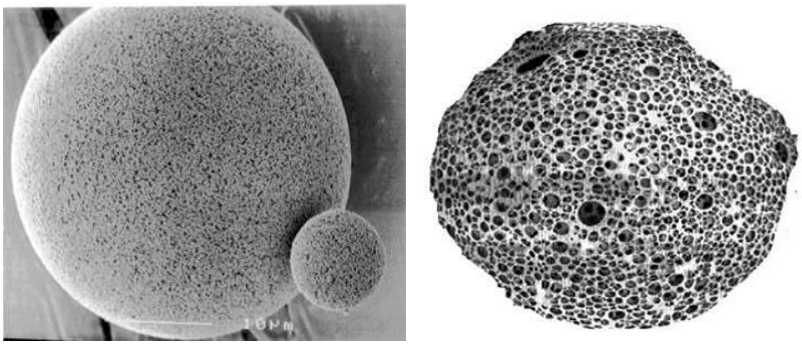

Fig.1.Microsponge: Porous nature of microsponge

The microsponge delivery system is designed to:

- deliver a pharmaceutically active ingredient efficiently at minimum dose,
- enhance the stability,
- modify drug release profile,
- reduce side effects.

Microsponges are capable of absorbing skin secretions which reduces the oiliness from skin. It has the ability to load a wide range of actives which provides the benefit of enhanced product efficiency, tolerability, mildness etc. These microsponges are further incorporated into the formulations like gels, lotions, creams, ointments, and powder.

Objectives of microsponges

- To hold active ingredients in a protected environment.
- To provide controlled delivery of oral medication to the lower gastrointestinal (GI) tract.
- To enhance the solubility of poorly water-soluble drugs by entrapping in the microsponge system pores.
- To increase the dissolution of drug.
- To reduce the irritationat site of application.

Advantages of microsponge[2]

Microsponge delivery system has three main advantages, which includes:

- **Advantages over conventional topical preparation:** Conventional topical preparation releases their active ingredient upon application and produces highly concentrated layer of drug which is rapidly absorbed. While microsponge delivery system can prevent the accumulation of active ingredient and reduces the irritation at site of application and also helps in maintaining the efficacy of drug.

- **Advantages over liposomes and microencapsulation:** Microsponge delivery system can control the release rate of actives which is not possible in case of microcapsules, where once the wall is ruptured the active ingredient will be released. Liposome formulations suffer from the problems like lower payload, formulation difficulty, limited chemical stability and microbial instability. Microsponge delivery system can help to overcome these problems.

- **Advantages over ointments:** Generally the ointments are greasy and sticky in nature, and these vehicles require the high concentration of active drug because of their low efficiency which results into irritation and allergic reactions. It also suffer from other drawbacks such as, uncontrolled evaporation of actives, unpleasant odor etc. Whereas microsponge system increases the amount of time for which the actives remains present on skin surface and reduces its transdermal penetration.

This delivery system also has other advantages[3] like

- Improved bioavailability.
- Improved product elegancy.
- Improved efficacy in treatment.
- Improved chemical, physical and thermal stability.
- Improved product aesthetic.
- Non-irritant, non-allergic and non-toxic.
- Ease of formulation.
- Extended release upto 12hrs.
- Formulation flexibility.
- Allows incorporation of immiscible product.
- Flexibility to develop novel product form.

Characteristics of microsponges[4]

- The microsponge formulations are stable at the temperature upto 130^0c.
- Liquid or semisolid formulations are stable over the pH range of 1 to 11.
- The average pore size of microsponge is 0.25µm where bacteria cannot penetrate, hence these are self-sterilizing.
- Compare to other drug delivery system these are cost effective.
- Microsponge reduces the oiliness by absorbing the skin secretions.
- Microsponges have the ability of higher payload (50-60%) with free flowing nature.
- Microsponge formulations are compatible with most vehicles and ingredients.

Formulation considerations

After entrapment of actives, the microsponge can be incorporated into dosage forms like, lotions, creams, powders, and soaps. To achieve the desired characteristic product, certain considerations are taken into account during the formulation of vehicle. These are:

- The solubility of active in the vehicle must be limited to avoid the depletion of microsponge before the application.
- Only 10-12% microsponge must be incorporated into the vehicle to avoid the cosmetic problems.
- The optimized polymer design and payload of the microsponge for active must be there for required release rate for given time period.

Criteria of the actives to be entrapped into microsponges[4]

The active ingredients which can be entrapped into microsponges must meet the following requirements,

- The active ingredient should be inert to monomer and should not increase the viscosity of formulation.
- The active ingredient should be either fully miscible in monomer or miscible by addition of small amount of water immiscible solvent.
- The active should be water immiscible or at most only slightly soluble.
- It should be stable in condition of polymerization condition, and in contact with polymerization catalyst.

Table: Commonly used Drugs, Polymers and excipients in microsponge formulation[2]

Drugs	Polymers	Excipients
Benzoyl peroxide, Dicyclomine, Fluconazole, Flurbiprofen, Ibuprofen, Ketoconazole, Ketoprofen, Paracetamol, Retinol.	Dimethacrylate, Ethyl cellulose, Eudragit RS 100, Polystyrene, Polyhydroxyethylmethacrylate.	Triethyl citrate.

Methods of preparation for microsponges[5-6]

Depending upon the physicochemical properties of the drug microsponges can be prepared by two methods,

- Liquid-liquid suspension polymerization
- Quasi-emulsion solvent diffusion

Liquid-liquid suspension polymerization

This is the one-step process.

↓

Formation of solution of the monomer along with an active ingredient in an appropriate solvent.

↓

Addition of above solution in an aqueous phase with agitation

(Aqueous phase consist the surfactants, suspending agents in order to facilitate the formation of suspension)

↓

Here, the formation of the suspension of preferred droplet size occurs.Initiation of the polymerization by addition of catalyst or by increasing temperature as well as irradiation.

The method of polymerization leads to development of reservoir type of system which opens at the surface through pores. During the polymerization, an inert liquid which is immiscible with water but completely miscible with monomer is used to form the pore network. After completion of polymerization process the liquid is removed leaving the porous microsponge which can incorporate the variety of actives and act as topical carriers.

Quasi-emulsion solvent diffusion

This is the two-step process and used when the drug is sensitive to polymerization reaction. In this method the microsponge are prepared by using different polymer amount.

This method consists of two phases:

External phase: It includes the 40mg polyvinyl alcohol in 200ml distilled water.

Internal phase: The internal phase consists of drug, ethyl alcohol, triethyl citrate and polymer. Triethyl citrate is used to facilitate the plasticity and it is added at an amount of 20% of the polymer.

Steps involved in preparation of microsponges by quasi-emulsion solvent diffusion technique:

Step1: Preparation of the internal phase by dissolving the polymer in ethyl alcohol.

Step2: Addition of drug to above solution under ultrasonication at 35^0c.

Step3: Addition of internal phase into external phase followed by continuous stirring for 60min.

Step4: Filtration of mixture to separate the microsponges.

Step5: Drying in an air heated oven at 42^0c for 12hrs and weighing to determine the production yield.

Hypothetical Mechanism of Action

The active ingredient is added to the vehicle in an entrapped form. As the microsponge particles have an open structure (they do not have a continuous membrane surrounding them), the active is free to move in and out from the particles and into the vehicle until equilibrium is reached, when the vehicle becomes saturated. Once the finished product is applied to the skin, the active that is already in the vehicle will be absorbed into the skin depleting the

vehicle, which will become unsaturated, therefore, disturbing the equilibrium. This will start a flow of the active from the microsponge particle into the vehicle, and from it to the skin, until the vehicle is either dried or absorbed. Even after that the microsponge particles retained on the surface of the stratum corneum will continue to gradually release the active to the skin, providing prolonged release over time. This proposed mechanism of action highlights the importance of formulating vehicles for use with microsponge entrapments. If the active is too soluble in the desired vehicle during compounding of the finished products, the products will not provide the desired benefits of gradual release. Instead they will behave as if the active was added to the vehicle in a free form. Therefore, while formulating microsponge entrapments, it is important to design a vehicle that has minimal solubilizing power for the actives. This principle is contrary to the conventional formulation principles usually applied to topical products. For these conventional systems it is normally recommended to maximize the solubility of the active in the vehicle. When using microsponge entrapments, some solubility of the active in the vehicle is acceptable, because the vehicle can provide the initial loading dose of the active until release from the microsponge is activated by the shift in equilibrium from the polymer into the carrier. Another way to avoid undesirable premature leaching of the active from the microsponge polymer is to formulate the product with some free and some entrapped active, so the vehicle is pre-saturated. In this case there will not be any leaching of the active from the polymer during compounding. The rate of active release will ultimately depend not only on the partition coefficient of the active ingredient between the polymer and the vehicle (or the skin), but also on some of the parameters that characterize the beads. Examples of these include surface area and primarily, mean pore diameter. Release can also be controlled through diffusion or other triggers such as moisture, pH, friction or temperature.

Mechanism of drug release through microsponges[7,16]

The release of drug through microsponges can be initiated by following triggers:

- **Solubility:** Release can be achieved by diffusion taking into consideration the partition coefficient of the actives into microsponges and outside system. Microsponges of water soluble ingredients release the drug in presence of water.

- **pH triggered system:** The modification in coating of microsponges can be used to achieve the pH based drug release.

- **Pressure:** The release of drug from microsponges can be achieved by applying the pressure or by rubbing.

- **Temperature triggered system:** The flow rate and release of the actives which are too viscous at room temperature can be increased by increasing the skin temperature.

Characterization of microsponges[8-6]

- **Particle Size Determination**

Particle size analysis of loaded and unloaded microsponges can be performed by laser light diffractometry or by any other suitable method. The values can be expressed for all formulations as mean size range. Cumulative percentage drug release from microsponges of different particle size can be plotted against time to study effect of particle size on drugrelease. 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.

- **Morphology and Surface Topography of Microsponges**

For morphology and surface topography, 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**

The loading efficiency (%) of the microsponges can be calculated according to the following equation[14]:

$$\text{Loading efficiency}(\%) = \frac{\text{DCact}}{\text{DCtheo}} \times 100 \quad \text{---------(1)}$$

DC act = Actual drug content in microsponges

DC theo. = Theoretical drug content.

The production yield of the microsponges can be determined by following equation:

$$\text{Production yield}(\%) = \frac{\text{Wpr}}{\text{Wth}} \times 100 \quad \text{---------(2)}$$

W pr = Practical mass of Microsponges

W th = Theoretical mass (Polymer + Drug).

- **Determination of true density**[19]

The true density of microparticles can be measured using an ultra-pycnometer under helium gas and can be calculated from a mean of repeated determinations.

- **Characterization of Pore Structure**[7-8]

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 isotherm 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**

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).[20]

- **Resiliency**

Resiliency (viscoelastic properties) of microsponges can be modified 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.[2]

- **Dissolution studies**

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

Marketed formulations of microsponges

Table: Marketed formulation of microsponges

Sr. No.	Brand name	Active Pharmaceutical Ingredient	Manufacturer	Uses
1	Retin-A-Micro	0.1% & 0.4%Tretinoin	Ortho-McNeil Pharmaceutical, Inc.	For topical treatment of acne vulgaris
2	Carac Cream, 0.5%	0.5% Fluorouracil	Dermik Laboratories, Inc.	For the treatment of actinic keratosis
3	Retinol cream	Retinol	Biomedic, Inc.	Reduces skin irritation
4	EpiQuin Micro	Hydroquinone and Retinol	SkinMedica, Inc	Minimizes skin irritation

CONCLUSION

Microsponges constitute a significant part by virtue of their small size and efficient carrier characteristics microsponge technology has been introduce in topical drug products to facilitate the controlled release of active drug into the skin in order to reduce systemic exposure and minimize local coetaneous reactions to active drugs, these are non-irritating, non-mutagenic, non-allergenic, and non-toxic. 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 needed to be explored.

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