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Microsponge: A Prominent Strategy to Accelerate Performance of Topical Formulation



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ABSTRACT

Microsponges are polymeric delivery systems which composed of porous microspheres. They have large porous surface with tiny sponge-like spherical particles. 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. The outer surface is typically porous, allows a sustained release of substance through sphere & preferred for topical use. This system can prevent excessive accumulation of ingredients within the epidermis and the dermis. No efficient vehicles have been developed for controlled and localized delivery of drugs into the stratum corneum and underlying skin layers and not beyond the epidermis. Releasing of active ingredients from conventional topical formulations over an extended period of time is quite difficult. The system was employed for the improvement of performance of topically applied drugs. Microsponge system allows for a high accumulation of drug in the skin, with relatively low permeation flux as compared to the conventional dosage form. Microsponges are designed to deliver a pharmaceutically active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects, and modify drug release that make it versatile drug delivery system.



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INTRODUCTION

Topical application has been used for centuries, predominantly in the treatment of localized skin diseases. Local treatment requires only that, the drug permeate the outer layers of the skin to treat the diseased state, with the hope that this occurs with little or no systemic accumulation. It is rare that the industry produces a new chemical entity specific for dermal or transdermal use and often, therefore, its inherent physicochemical properties are not ideally suited to uptake into and through the skin. This means that considerable effort has to be expended on the appropriate design of a formulation or a device to deliver enough of the medicine such that there is sufficient present at its site of action.¹

The main interests in the application of compounds to the skin are:

- (a) For local effects in dermatology (e.g., corticosteroids for dermatitis);
- (b) For transport through the skin for systemic effects (e.g., nicotine patches for smoking cessation);
- (c) For surface effects (e.g., sunscreens, cosmetics, and anti-infective); and
- (d) To target deeper tissues (e.g., non-steroidal anti-inflammatory agents such as NSAIDs for muscle inflammation)²

The skin acts as a boundary which separates the external environment from the internal organs. The epidermis acts as a barrier between the varied conditions of the external surroundings and the controlled internal environment of the living tissues and body fluids. The skin provides physical protection of internal organs and acts as a sensory organ. It controls body temperature and water loss, and functions as a regulatory barrier which controls the movement of substances into and out of the body.³

The skin has gained increasing favors as a target site for drug delivery as it avoids problems associated with oral drug administration, namely pH and to some extent, enzyme-driven drug degradation and hepatic first-pass metabolism.¹ Cutaneous drug administration is not however without its problems. The drug is subjected to the skin's own first-pass metabolic effect. In addition to this, percutaneous absorption is subject to significant variability owing to differences

in age, race, sex, site of administration, species, presence or absence of disease and the skin's reservoir capacity for a specific drug.²

There are numerous diseases which affect different regions of the skin. Any drug used will be required to reach the site of the disease in order to exert its pharmacological activity. Unless it is a local effect on the surface only, the drug must either pass through the stratum corneum (SC) or go through hair follicles or sweat glands to reach its target site. Once in the skin, a lipid-soluble drug will tend to accumulate in lipophilic regions while more water-soluble drugs will tend to enter the blood capillaries and are removed from the skin.² Transport of drugs through the skin is complex since many factors influence their permeation. To simplify the situation somewhat and also to formulate dosage forms which deliver drug to the skin, it is necessary to consider the skin structure and its properties.¹

MICROSPONGE DELIVERY SYSTEM:^{4, 5, 6, 7}

The Microsponge delivery system comprised of polymeric bead having network of pores with an active ingredient held within was developed to provide controlled release of the active ingredient whose final target is skin itself.⁷ The system was employed for the improvement of performance of topically applied drugs. This system can prevent excessive accumulation of ingredients within the epidermis and the dermis.⁴ The Microsponge systems are based on microscopic, polymer-based porous microspheres typically 10-25 microns in diameter that can bind, suspend or entrap a wide variety of substances and then be incorporated into a formulated product, such as a gel, cream, liquid or powder.⁵ When microsponge delivery system applied to the skin, the release of drug can be controlled by diffusion or other variety of triggers, including rubbing, moisture, pH, friction, or ambient skin temperature.⁶ The outer surface is typically porous, allowing the controlled flow of substances into and out of the sphere. Furthermore, although they are microscopic in size, these systems are too large to pass through the stratum corneum when incorporated into topical products.⁴

1.6.1 Characteristics of Microsponges:^{8,9}

- Microsponge formulations are stable over range of pH 1 to 11;
- Microsponge formulations are stable at the temperature up to 130°C;
- 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.
- The size of the microsponge can be varied usually from 5 to 300µm in Diameter

1.6.2 Advantages of Microsponges:^{10,11,12}

- Microsponges can absorb oil up to 6 times its weight without drying
- It provides continuous action up to 12 hours i.e. extended release
- Improved product elegance and efficacy
- Lesser the irritation and better tolerance leads to improved patient compliance
- They have better thermal, physical and chemical stability
- These are non-irritating, non-mutagenic, non-allergenic and non-toxic
- MDS allows the incorporation of immiscible products
- They have superior formulation flexibility
- Liquids can be converted into powders improving material processing

Advantages over conventional formulations:^{7,11,12}

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. When compare to 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.

Advantages over microencapsulation: ^{7,11}

The MDS has advantages over other technologies like microencapsulation. Microcapsules cannot usually control the release rate of actives. Once the wall is ruptured the actives contained within microcapsules will be released.

Advantages over liposomes: ^{7,10}

Liposomes suffer from lower payload, difficult formulation, limited chemical stability and microbial instability. While microspunge system in contrast to the above systems are stable over range of pH 1 to 11, temperature up to 130°C; compatible with most vehicles and ingredients; self-sterilizing as average pore size is 0.25µm where bacteria cannot penetrate; higher payload (50 to 60%), still free flowing and can be cost effective.

1.6.3 Characteristics of materials that are entrapped in microsponges: ^{13,14}

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

1.6.4 Methods of Preparation of Microsponges⁷

Based on physicochemical properties of drug to be loaded, drug loading in microsponges can be affected in two ways, one-step process or by two-step process; If the drug is typically an inert non-polar material, it will create porous structure. Such drug 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.⁵⁴

A] Liquid-liquid suspension polymerization^{7,15}

Microsponges are conveniently prepared by liquid-liquid suspension polymerization. Polymerization of styrene or methyl methacrylate is carried out in round bottom flask. A solution of drug is made in the monomer, to which aqueous phase, usually containing surfactant and dispersant to promote suspension is added. Polymerization is affected, once suspension with the discrete droplets of the desired size is established by activating the monomers either by catalysis or increased temperature. When the drug is sensitive to the polymerization conditions, two-step process is used. The polymerization is performed using substitute porogen and is replaced by the functional substance under mild experimental conditions.

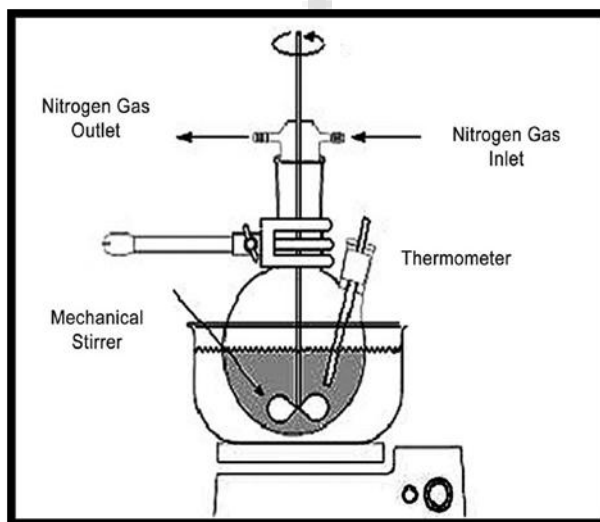


Figure 1: Reaction vessel for suspension polymerization

Various steps in the preparation of microsponges are summarized as:^{10,12}

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

B] Quasi-emulsion solvent diffusion: ^{4, 16, 17}

The microsponges can also be prepared by quasi-emulsion solvent diffusion method using the different polymer amounts. To prepare the inner phase, Eudragit RS 100 or ethyl cellulose (Polymer) was dissolved in ethyl alcohol, dichloromethane, acetone or any other suitable organic solvent (Internal phase). Then, drug can be then added to solution and dissolved under ultrasonication at 35°C. The inner phase was poured into the Polyvinyl Alcohol solution in water (outer phase). The inner phase diffuses into the outer phase; following 2 hrs of stirring, the mixture is filtered to separate the microsponges. The microsponges are dried in an air heated oven at 40°C for 12 h and weighed to determine production yield (PY).

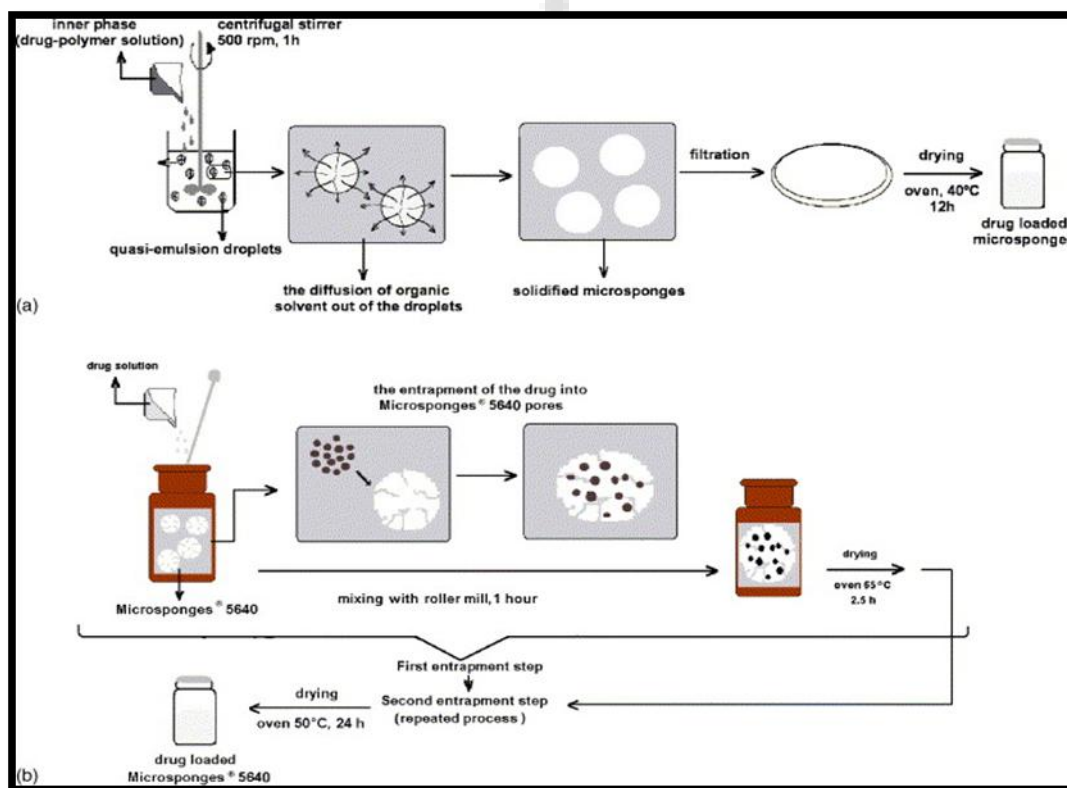


Figure 2: Preparation of Microsponges by Quasi-emulsion solvent diffusion method

1.6.5 Release Modulation

In general, microsponges retard the release of the drug. Various groups have studied the release of actives from such systems. Some studies have shown an improved rate of release by increasing the active/polymer ratio and lowering the polymer wall thickness; however, these

results are not supported by another set of studies.⁶ Thus, there seem to be many other factors affecting the release of the drug from the microsponges. Another important parameter that governs the release seems to be the pore diameter however, another study has shown that even the overall porosity (including the pore diameter and the number of pores) also affects the drug release. The microsphere particles have an open structure and the active is free to move in and out from the particles and into the vehicle until equilibrium is reached. 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 microsphere particle into the vehicle and from it to the skin until the vehicle is either dried or absorbed. Even after that, the microsphere particles retained on the surface of stratum corneum will continue to gradually release the active to the skin, providing prolonged release over time. If the active is too soluble in the desired vehicle during compounding of 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 microsphere entrapments, it is important to design a vehicle that has minimal solubilizing power for the actives.^{11, 18} when using microsphere 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 microsphere. Another way to avoid undesirable premature leaching of the active from the microsphere polymer is to formulate the product with some free and some entrapped active, so the vehicle is presaturated. In this case, there will not be any leaching of the active form of 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.⁶

Programmable release^{6, 7, 19}

By proper manipulation of the aforementioned programmable parameters, microsponges can be designed to release given amount of active ingredients over time in response to one or more external triggers.

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

2. Temperature change: Some entrapped actives can be too viscous at room temperature to flow spontaneously from microsponges onto the skin. Increased skin temperature can result in an increased flow rate and hence release.

3. Solubility: 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.

4. pH-triggered systems: Triggering the pH-based release of the active can be achieved by modifying the coating on the microsphere. This has many applications in drug delivery.

Formulation consideration⁷

Actives entrapped in Microsphere drug delivery system 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 order to achieve desired product characteristics.

- a) The solubility of actives in the vehicle must be limited. Otherwise, the vehicle will deplete the microspheres before the application.
- b) To avoid cosmetic problems; not more than 10 to 12% w/w microspheres must be incorporated into the vehicle.
- c) Polymer design and payload of the microspheres for the active must be optimized for required release rate for given time period.⁷

1.6.6 Applications of Microsphere Systems:^{8,9,18}

Microspheres 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. Microspheres are designed to deliver a pharmaceutically active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects and modify drug release.

Table 1: Application of Microsponges⁵

Active agents	Applications
Sunscreens	Long lasting product efficacy, with improved protection against sunburns and sun related injuries even at elevated concentration and with reduced irritancy and sensitization.
Anti-acne e.g Benzyl peroxide	Maintained efficacy with decreased skin irritation and sensitization.
Anti-inflammatory e.g. Hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatitis.
Anti-fungal	Sustained release of actives.
Anti-dandruff e.g. zinc pyrithione, selenium sulfide	Reduced unpleasant odor with lowered irritation with extended safety and 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 odor.

CONCLUSION

Microsponge drug delivery system is a versatile technology for controlled release of drug from microsponge loaded with active ingredient that contributes reduction in side effect and maintains therapeutic efficacy. Microsponge delivery is prominent strategy to accelerate performance of topical drug as it provides improved stability, increased elegance and enhanced formulation flexibility. Thus overall beneficial effect of Microsponge such as ease of production, enhanced product performance, elegance, physical stability of drug, extended-release and reduced irritancy confirm the microsponge has great potential as novel approach in the topical drug delivery system.

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