

## A Review on Novel Drug Delivery System: Microsponges

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*Received: 12<sup>th</sup> May, 17; Revised 28<sup>th</sup> Sept, 17, Accepted: 14<sup>th</sup> Nov, 17; Available Online: 25<sup>th</sup> Dec, 2017*

### ABSTRACT

Recent research on idealizing drug delivery system which is progressing at a prodigious rate and aims at development of drug delivery system (DDS), with maximum therapeutic advantages of drug delivery, thus resulting in safe and effective management of disease. More and more developments in delivery systems are being integrated to optimize the efficacy and cost effectiveness of the therapy. New classes of pharmaceuticals, biopharmaceuticals are fueling the rapid evolution of drug delivery technology. 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. Microsponge consists of microporous beads loaded with active agent. 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.) that are used mostly for topical and recently for oral administration. Microsponges are porous, polymeric microspheres that are mostly used for prolonged topical administration. 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. Microsponges are prepared by several methods utilizing emulsion system or by suspension polymerization in a liquid-liquid system. The most common emulsion system used is oil-in-water (o/w), with the microsponges being produced by the emulsion solvent diffusion (ESD) method. Microsponge delivery system (MDS) can provide increased efficacy for topically active agents with enhanced safety, extended product stability, enhanced formulation flexibility, reduced side effects and improved aesthetic properties in an efficient and novel manner. In addition these are non-irritating, non-mutagenic, non-allergenic, and nontoxic. The present review introduces microsponge technology in great detail.

**Keywords:** Controlled Release, topical drug delivery, microsponge technology, programmable release, microsponges.

### INTRODUCTION

A Microsponge Delivery System (MDS) is patented, highly cross-linked, porous, polymeric microspheres that can entrap wide range of actives and then release them onto the skin over a time and in response to trigger. This system was employed for the improvement of performance of topically applied drugs. It is a unique technology for the controlled release of topical agents and consists of micro porous beads, typically 10-25 microns in diameter, loaded with active agent. When 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. (Shown in fig 1 and 2)<sup>5</sup>

Microsponge technology offers:

Enhanced product performance

Extended release

Reduced irritation and hence improved patient compliance

Improved product elegance

Improved formulation flexibility

Improved thermal, physical, and chemical stability

Flexibility to develop novel product forms

Microsponge systems are non-irritating, non-mutagenic, non-allergenic and non-toxic

*Topical Delivery Systems (TDS)*

The purpose of topical dosage form is to conveniently deliver drugs across a localized area of the skin. To develop an ideal dosage form one must take into account the flux of drug across skin, retention of the dosage form and the patient acceptability of the formulation. The problem of formulating a drug is complex because of the wide diversity of drug solubility in vehicle components and the vast range in cutaneous fluxes. When it comes to the delivery of a drug to a specific site, topical formulations are probably among the most challenging products to develop. An effective topical formulation needs to provide a stable chemical environment in order to accommodate multiple compounds that may have different, if not incompatible, physicochemical characteristics. Once applied, a topical formulation must interact with the skin environment, which can influence the rate of the release of the compound in order to achieve adequate skin absorption. The excipients themselves will exert additional physical effects on the skin, such as drying, occluding, or

moisturizing. These insights have resulted in new delivery systems that are capable of enhancing the efficacy, tolerability, and cosmetic acceptability of topical formulations<sup>9</sup>.

#### *Liposomes*

Liposomes are the most widely known cosmetic delivery systems. These are artificial spherical submicroscopic vesicles with diameter between 25 and 5000 nm. Vesicles are composed inevitably of amphiphilic molecules. Their centre consists of an aqueous cavity, which is encapsulated by one or more bimolecular phospholipid sheets, each separated from each other by aqueous layers. The polar head group forms the interface at both the external and internal surfaces of liposomal bilayers. The phosphatidyl moiety consists of two fatty acids, which are ester bridged to glycerol phosphate. The chain length of fatty acids (mainly C14, C16 and C18) and the degree of unsaturation (one or two bonds) may vary. The polar head group may be zwitter ionic, negatively or positively charged.

The intensity of the mechanical mixing needed to form liposomes from lipid bilayer sheets determines the dimensions and number of vesicle bilayers. Such liposomes are multilamellar, small unilamellar and large unilamellar vesicles. The type of head group and fatty acid nature of phospholipids determine physical stability of liposomes. Natural lecithins (egg or soyabean lecithin) or synthetic lecithin (di-palmitoyl lecithin) are mostly used. The most common lecithin is mixture of phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine and phosphatidic acid. Depending on the nature of components which form their envelope, whole series of name other than liposome have been given to the commercial products<sup>7</sup>.

#### *Ultrasomes*

Ultrasomes are specialized liposomes encapsulating an endonuclease enzyme extracted from *Micrococcus luteus*; the enzyme recognizes the sun damage to the skin and initiates removal of damaged DNA.

#### *Photosomes*

Photosomes are incorporated in sun-care product to protect the sun-exposed skin by releasing a photo-reactivating enzyme extracted from a marine plant, *Anacystis nidulans*. Photosomes on light activation reverse the cell DNA damage, reducing immune suppression and cancer induction.

#### *AOCS liposome*

Asymmetric oxygen carrier system (AOCS) liposomes are designed to carry oxygen into the skin. These vesicles are composed of perfluorocarbon core surrounded by a monolayer of phospholipids, followed by a bilayer system. Perfluorocarbons are excellent carriers of oxygen and so this system is used to transport molecular oxygen into the skin.[15]

Advantages of Microsponges over other Formulations

#### *Characteristics of the Materials Entrapped in Microsponges*

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 as well as capable of being made miscible by addition of small amount of a water immiscible solvent.

It should be inert to monomers and should not increase the viscosity of the mixture during formulation.

It should be water immiscible or nearly only slightly soluble.

It should not collapse spherical structure of the microsponges.

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

Microsponges consisting of non-collapsible structures with porous surface through which active ingredients are released in a controlled manner. Depending upon the size the total pore length may range up to 10 ft and pore volume up to 1 ml/g. Microsponges are porous microspheres having interconnected voids of particle size range 5-300µm. These microsponges have the capacity to entrap a wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens and anti-infective, etc. are used as a topical carrier system. MDS technology is being used currently in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products. Microsponge delivery system can be incorporated into conventional dosage forms such as creams, lotions, gels, ointments, powders<sup>6</sup>.

#### *Preparation of microsponges*

Drug loading in microsponges can take place in two ways, by one-step or two-step process; based on physico-chemical properties of drug to be loaded. If the drug is typically an inert non-polar material, it will create the porous structure which is called as porogen. Porogen drug, which neither hinders the polymerization nor become activated by it and stable to free radicals is entrapped with one-step process<sup>18</sup>.

#### *Liquid-Liquid Suspension Polymerization*

Microsponges are prepared by suspension polymerization process in liquid-liquid systems (one-step process). Firstly, the monomers are dissolved along with active ingredients (non-polar drug) in an appropriate solvent solution of monomer, which are then dispersed in the aqueous phase with agitation. Aqueous phase typically consists of additives such as surfactants and dispersants (suspending agents) etc. in order to facilitate the formation of suspension. Once the suspension is established with distinct droplets of the preferred size then, polymerization is initiated by the addition of catalyst or by increasing temperature as well as irradiation. The polymerization method leads to the development of a reservoir type of system that opens at the surface through pores. The general assembly of reaction vessel is presented in.

During the polymerization, an inert liquid immiscible with water but completely miscible with monomer is used to form the pore network in some cases. Once the polymerization process is complete, the liquid is removed leaving the microsponges which permeate within preformed microsponges then, incorporates the variety of active substances (like anti fungal, rubefacients, anti-acne, anti-inflammatory etc.) and act as a topical carriers.

Table 1: *Advantages of Microsponges.*

Microsponge	Other formulations
Microsponge formulations are self sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate. The size of the microsponges ranges from 5-300µm in diameter	Liposomes are artificial spherical submicroscopic vesicles with diameter between 25 and 5000 nm.
Microsponges are biologically safe and offer unique advantage of programmable release.	Microcapsules cannot usually control the release rate of actives. Once the wall is ruptured, the actives contained within microcapsules will be released.
Microsponges system in contrast to the above system has several advantages like stable over a ph range of 1-11 and upto temperature of 130 °c, stable thermally, physically and chemically, have higher payload up to 50 to 60%	Liposomes suffer from lower payload, difficult formulation, limited chemical stability and microbial instability,
Microsponge system 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.	Ointments are often aesthetically unappealing, greasiness; stickiness etc. That often results into lack of patient compliance.
Microsponges are compatible with the majority of vehicles and ingredients.	Liposomes neosomes and other formulation are not compatible with the majority of vehicles and ingredients.

In some cases, solvent can be used for efficient and faster inclusion of the functional substances.

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

Step 1: Selection of monomer as well as combination of monomers.

Step 2: Formation of chain monomers as polymerization starts.

Step 3: Formations of ladders as a result of cross-linking between chain monomers.

Step 4: Folding of monomer ladder to form spherical particles.

Step 5: Agglomeration of microspheres leads to the production of bunches of microspheres.

Step 6: Binding of bunches to produce microsponges.

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.

#### *Quasi-Emulsion Solvent Diffusion*

When the drug is sensitive to the polymerization conditions, two-step process is used. Microsponges are prepared by a quasi-emulsion solvent diffusion method using the different polymer quantities.

In the emulsion solvent diffusion the affinity between the drug and the good solvent is stronger than that of the good solvent and the poor solvent. The drug is dissolved in the good solvent, and the solution is dispersed into the poor solvent, producing emulsion (quasi) droplets, even though the pure solvents are miscible. The good solvent diffuses gradually out of the emulsion droplets into the surrounding poor solvent phase, and the poor solvent diffuses into the droplets by which the drug crystallizes inside the droplets.

This is a two-step process wherein the polymer along with the active, plasticizer and diffusible substance (porogen) is poured into an external aqueous phase, which typically consists of a stabilizer such as polyvinyl

alcohol. After stirred for 2 h and maintained at a high temperature if required. Diffusion of the porogen into the external medium results in a highly porous microparticle called 'Microsponge'. Then the mixture is filtered to separate the microsponges. The product is washed and dried in vacuum oven at 50°C for 24 h.

#### *Release mechanisms from microsponges*

MDS consists of a multitude of porous microspheres that contain a complex network of interconnecting voids with a non-collapsible structure. Depending on several modifiable factors, the rate of release of the active ingredients can be determined before they are entrapped in the microspheres. These modifiable factors include the pore diameter, the extent of cross-linking of the polymers, the difference in concentration of the active ingredient between the microspheres, and the vehicle in which these spheres reside. The topical agent formulation with the MDS can be prepared in many different forms, such as a gel, cream, or lotion. Once the formulation is topically applied to the desired area of the skin, the active ingredients diffuse out of the spheres into the vehicle and then onto the skin. Microsponges can be designed to release given amount of active ingredients over time in response to one or more external triggers.

#### *Pressure*

Rubbing or 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. Increase in skin temperature can result in an increased flow rate and hence an increase in release. So it is possible to modulate the release of substances from the microsphere by modulation of temperature. For example, viscous sunscreens were found to show a higher release from microsponges when exposed to higher temperatures; thus a sunscreen would be released from a microsphere only upon exposure to the heat from the sun.

#### *pH*

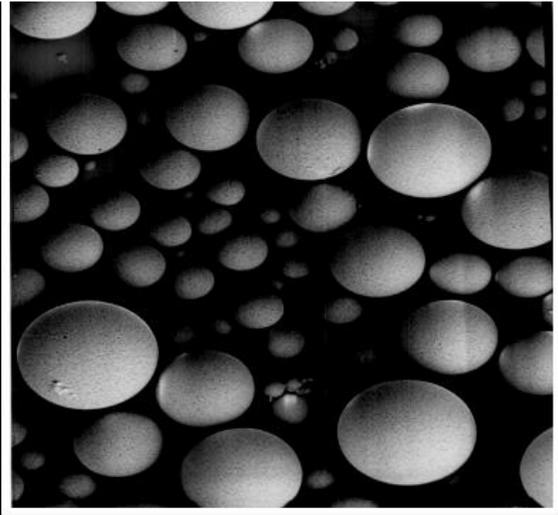


Figure 1: Microsponge System (Porous Microspheres).

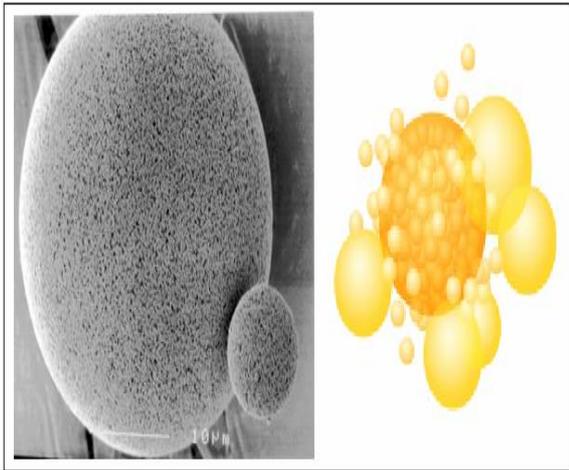


Figure 2: Microsponge Technology.

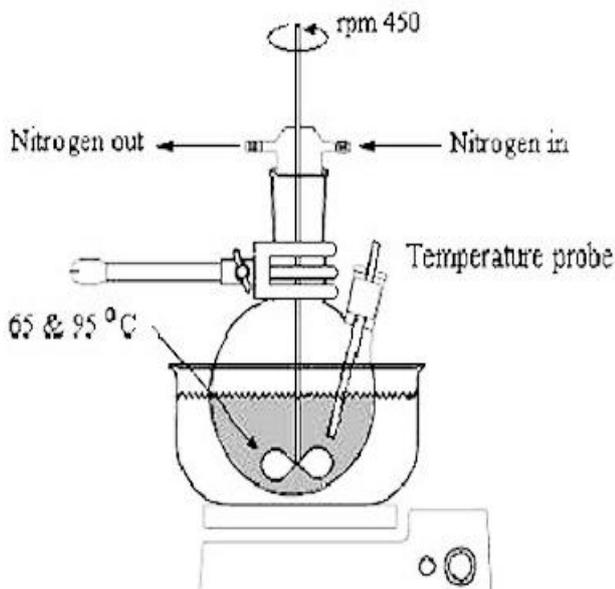


Figure 3: Reaction vessel for microsponge preparation by liquid-liquid suspension polymerization.

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.

#### *Solubility*

Microsponges loaded with water-soluble ingredients like antiperspirants and antiseptics will release the ingredient in the presence of water. Thus release may be achieved based on the ability of the external medium to dissolve the active ingredient, the concentration gradient varies or the ability to swell the microsponge network. The release can also be activated by diffusion, taking into consideration the partition coefficient of the ingredient between the microsponges and the outside system.

Safety studies of microsponges can be established by

Eye irritation studies in rabbits.

Skin irritation studies in rabbits.

Mutagenicity in bacteria.

Oral toxicity studies in rats.

Allergenicity in guinea pigs.

#### *Evaluation Parameters*

##### *Particle size and size distribution*

Particle size and size distribution are evaluated using either an optical microscope or an electron microscope. This is an extremely crucial step, as the size of the particles greatly affects the texture of the formulation and its stability. Free-flowing powders with fine aesthetic attributes are possible to obtain by controlling the size of particles during polymerization. Particle size analysis of loaded and unloaded Microsponges can be performed by laser light diffractometry or any other suitable method. The values ( $d_{50}$ ) can be expressed for all formulations as mean 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.

##### *Morphology and Surface topography of SPM*

For morphology and surface topography, various techniques have been used like photon correlation spectroscopy (PCS), Scanning electron microscopy (SEM), transmission electron microscopy (TEM) etc. SEM is used widely for which prepared Microsponges are coated with gold-palladium under an argon atmosphere at room temperature and then the surface morphology of the Microsponges is studied.

##### *Determination of loading efficiency and production yield*

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 SPM obtained.

##### *Determination of true density*

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

##### *Pore structure*

Porosity parameters of microsponges are essential in monitoring the intensity and the duration of active ingredient effect. Average pore diameters, shape and morphology of the pores can be determined by using

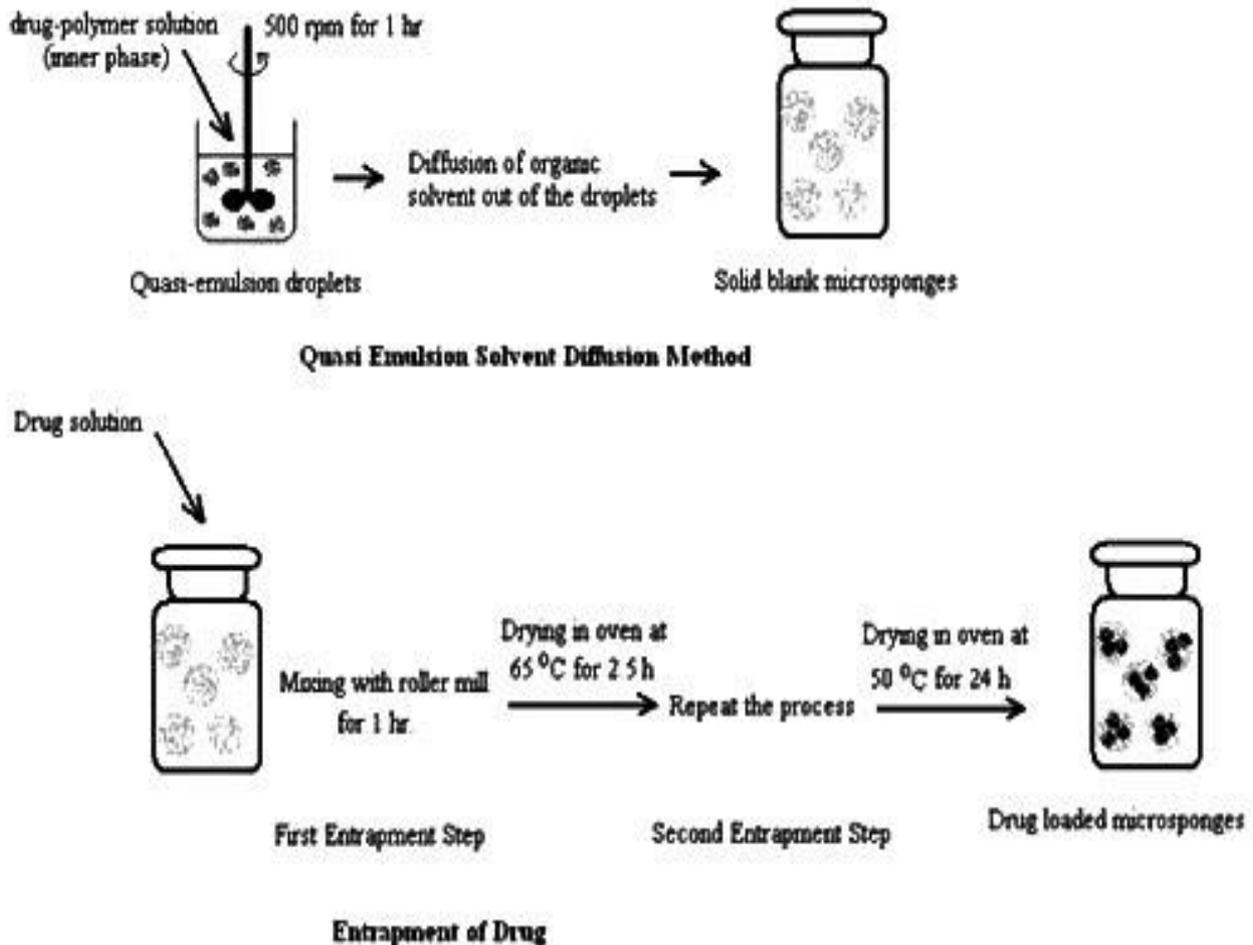


Figure 4: Method of quasi-emulsion solvent diffusion emulsification, the system is continuously.

mercury intrusion porosimetry technique. The effect of pore diameter and volume on the rate of drug release from microsponges can also be studied using the same technique.

#### Compatibility studies

The drug-excipients compatibility studies are carried out in order to ensure that there is no inadvertent reaction between the two when formulated into a dosage form. These studies are commonly carried out by recording the differential scanning calorimetry (DSC) of the chemicals viz., API and excipients individually and also together and checking for any addition or deletion of any peaks or troughs. For DSC approximately 5 mg samples can be accurately weighed into aluminium pans and sealed and can be run at a heating rate of 150C/min over a temperature range 25–430oC in atmosphere of nitrogen. Infrared (IR) spectroscopy can also reveal the incompatibilities between the chemical moieties. Compatibility of drug with reaction adjuncts can also be studied by thin layer chromatography (TLC) and FT-IR Effect of polymerization on crystallinity of the drug can be studied by powder X-ray diffraction (XRD) and Differential Scanning Colorimetry (DSC).

#### Polymer/ Monomer composition

Factors such as particle size, drug loading, and polymer composition govern the drug release from Microsponges.

Polymer composition of the Microsponges Drug Delivery system can affect partition coefficient of the entrapped drug between the vehicle and the Microsponges system and hence have direct influence on the release rate of entrapped drug.

#### 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 crosslinking tends to slow down the rate of release. Hence resiliency of Microsponges is studied and optimized as per the requirement by considering release as a function of crosslinking with time.

#### 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.

$$Q = k_1 t^n \text{ or } \log Q = \log k_1 + n \log t \dots \dots \text{Equation (1)}$$

Where Q is the amount of the released at time (h), n is a diffusion exponent which indicates the release mechanism, and k<sub>1</sub> 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 k<sub>1</sub> were calculated for comparison

purposes, the data was also subjected to Equation (2), which may be considered a simple, Higuchi type equation.

$Q = k_2 t^{0.5} + C$  ..... Equation (2)

Equation (2), 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<sup>12</sup>.

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