

Available online on 15.06.2019 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

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Review Article

Novel Strategy: Microsponges for Topical Drug Delivery

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ABSTRACT

Microsponge delivery system is a unique and effective technology for the controlled release of topical agents. It is highly cross-linked porous, polymeric microspheres that can entrap wide range of active agents and in response to trigger or stimuli and release them onto the skin over a time. It consists of micro-porous beads, typically 5-300µm in diameter that acquire the flexibility to entrap a wide variety of active ingredients such as fragrances, sunscreens, emollients, anti-fungal, anti-infective, and anti-inflammatory agents etc., that are mostly used to prolong the topical administration of the drug. Recently it was investigated that microsponges also used for oral drug delivery system. The topical agent formulation with microsponge delivery system can be prepared in many different forms, such as cream, gel, or lotion. When the formulation is applied to the skin, the MDS releases its active ingredients on a time and in response to other stimuli (rubbing, temperature, pH etc.). They reduce side effects, enhance stability and modify drug release. Because of the size of the microsponges they cannot pass through the stratum corneum, so they remain on the skin surface and slowly releasing the active ingredients over a period. Slow rate of release from MDS reduce the irritancy associated with the topical agents. Slow and gradual release pattern of MDS prevents excessive build-up of the active agents in the epidermis and dermis. Therefore, these particles, remains on the surface of the skin and its fine lines delivering the active over prolonged time.

Keywords: Microsponge Delivery System, Quasi- emulsion solvent diffusion.**Article Info:** Received 01 May 2019; Review Completed 09 June 2019; Accepted 10 June 2019; Available online 15 June 2019**Cite this article as:**Monika, Dua JS, Prasad DN, Hans M, Sharma R, Kumari S, Novel Strategy: Microsponges for Topical Drug Delivery, Journal of Drug Delivery and Therapeutics. 2019; 9(3-s):1025-1031 <http://dx.doi.org/10.22270/jddt.v9i3-s.2935>***Address for Correspondence:**

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INTRODUCTION

Microsponge is Novel technology, which provides extended release of pharmaceutical active ingredients^{1, 2} and mostly used for topical formulations. In 1987, Won was developed the microsponge technology and the original patents were authorized by Advanced Polymer System, Inc.³. Now a day the major challenge to the pharmaceutical industry is to control the delivery rate of active pharmaceutical ingredient to a pre-determined site. So to improve efficacy, patient compliance and modify drug release researcher focused on designing of different controlled release drug delivery systems. Microsponge having a myriad of interconnected voids of particle size ranging from 5-150 µm.⁴ The main purpose of Microsponge drug delivery system is to achieve desired concentration of the drug in blood in which is therapeutically more effective and non-toxic for long period of time in the recent study. A typical 25 µm sphere can have up to 250000 pores and have an internal pore structure equivalent to 10 feet in length and this results in a large reservoir type system within each microsponge, which can be loaded with up to its own weight of the active agent. The

microsponge particles are too large to be absorbed into the skin^{5, 6}.

Microsponges have the capacity to entrap a wide range of active ingredients such as emollients, fragrances, essential oils, anti-fungal and anti-infective etc. are used as a topical carrier system^{7, 8}. Various methods for preparation of microsponge drug delivery systems studied⁹.

POTENTIAL FEATURES OF MICROSPONGE DRUG DELIVERY SYSTEM^{9, 10}:

1. Stable over a pH range of 1 to 11.
2. Stable up to 130°C temperature.
3. Free flowing and cost effective.
4. Higher pay load (50-60%).
5. Compatible with the many of the vehicles and ingredients.
6. Self sterilizing as their average pore size is 0.25micrometer where bacteria cannot penetrate.

7. Can absorb oil up to 6 times their weight without drying.
8. Reveal good compatibility with various vehicles and ingredients.

BENEFITS OF MICROSPONGE TECHNOLOGY¹¹:

- Enhanced product performance.
- Extended release.
- Improved thermal, physical, and chemical stability.
- Reduced irritation and hence improved patient compliance.
- Improved product elegance.
- Flexibility to develop novel product forms.
- Microsponge systems are non-irritating, non-mutagenic, non-toxic and non-allergenic.
- Allows incorporation of immiscible substances.
- Improved formulation flexibility.

CHARACTERISTICS OF THE MATERIALS ENTRAPPED IN MICROSPONGES^{12, 13}:

Soluble ingredients or liquids can be entrapped in the particles. Actives that can be entrapped in microsponges must meet following requirements:

- It should be slightly soluble or water immiscible.
- It should be either fully miscible in monomer or capable of being made miscible in monomer by addition of small amount of a water immiscible solvent.
- It should be inert to monomers.
- It should be stable in contact with polymerization catalyst and conditions of polymerization
- To avoid cosmetic problems the solubility of actives in the vehicle must be limited; 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.

MECHANISM OF ACTION^{14, 15}:

The active ingredients are added to the vehicle in an entrapped form



The active is free to move in and out from particles and into the vehicle as they have an open structure and the vehicle becomes saturated at equilibrium state



Once the product is applied to the skin, the active will be absorbed into the skin, depleting the vehicle, which becomes unsaturated, thus disturbing the equilibrium.



A flow of microsponge particle to vehicle and from vehicle to skin, until the vehicle is either absorbed or dried.

RELEASE MECHANISM^{16, 17, 18}:

A variety of triggers can cause further release of the substances from the microsponges. These triggers include pressure, solubility and change in temperature^{16, 17}.

Pressure:

Physical rubbing of the product against the skin exerts pressure and increases the release of the active ingredients from the beads, pores closets to the surface of the skin. Pressure thereby increases the amount of entrapped active material on the skin, enhancing the amount of entrapped active substance available.

Temperature:

Substances that are viscous at room temperature are unable to leave the microsponge spontaneously, can become less viscous when warmed to skin temperature, allowing them to flow onto the skin.

Solubility:

The solubility of the entrapped ingredient can be used to regulate its diffusion from the microsponge. For e.g. Microsponge loaded with water miscible ingredients will release the ingredient in the presence of water. This release from microsponge may be achieved based on the ability of

the external medium to dissolve the active, the concentration gradient or the capability to swell the microspore network. .

pH:

Triggering the pH-based release of the active from microsponge can be achieved by modifying the coating on the microsponge.

Drugs explored in the microsponge delivery system¹⁹⁻²²:

Paracetamol	Miconazole
Benzoyl peroxide	Curcumin
Ketoprofen	Tretinoin
Fluconazole	Itraconazole
Hydroquinone	Mupirocin
Acyclovir sodium	Ibuprofen
Retinol	Prednisolone
Erythromycin	Indomethacin

Polymers used for the preparation of microsponges:

Eudragit RS 100 and RL 100	Ethylcellulose
Polystyrene	Acrylic polymer
PHEMA	Carbopol 934

PREPARATION OF MICROSPONGES^{23, 24, 25, 26;}

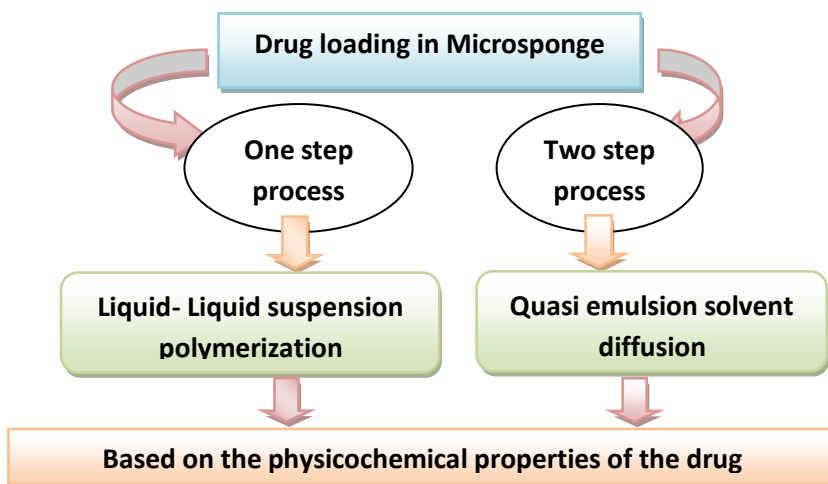


Fig. 1: One step and Two step preparation of Microsponge

Drug loading in microsponges can take place in two ways, by one-step or two-step process; based on physicochemical 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 neither hinders the polymerization nor become activated and stable to free radicals, is entrapped with one-step process.

Liquid-Liquid Suspension Polymerization^{25, 26;}

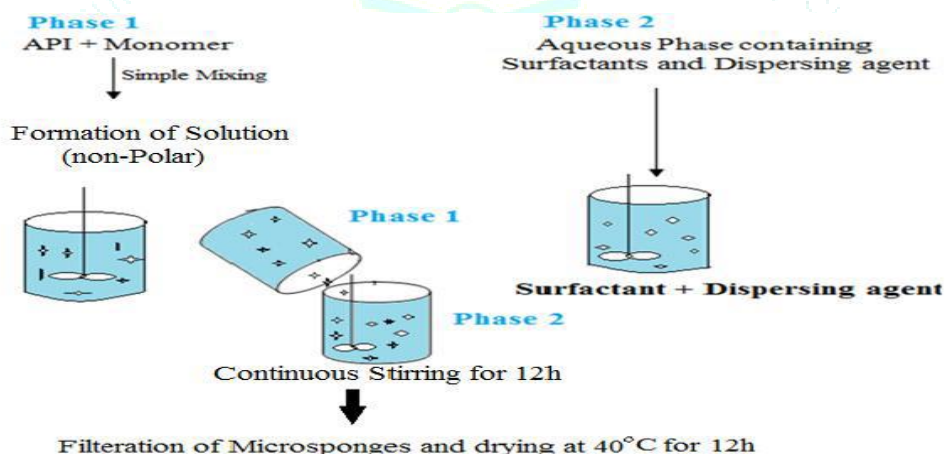


Fig.2: Formation of Suspension for the Preparation of Liquid Liquid Suspension Polymerization²⁴

The porous Microsponges are prepared by liquid-liquid suspension polymerization method. Polymerization of methyl methacrylate or styrene is carried out in round bottom flask. The polymerization process leads to formation of a reservoir type system, which opens at the surface through pores.

solution of monomer and then dispersed in the aqueous phase containing additives such as surfactant and suspending agents, which are used or help in formation of suspension. Once suspension with discrete droplets of the desired size is established, polymerization is achieved by activating monomers either by catalysis or by increased temperature irradiation.

In their preparation, monomers are first dissolved along with non-polar active ingredients in a suitable solvent

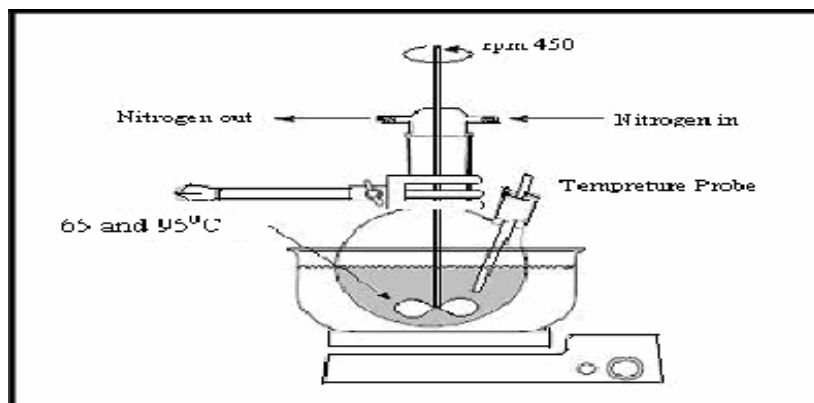


Fig.3: Reaction vessel for microsphere preparation by liquid-liquid suspension method²⁵

1.6.2 Quasi-emulsion Solvent Diffusion^{27, 28:}

Microsponges are prepared by quasi-emulsion solvent diffusion method using the different polymer quantities.

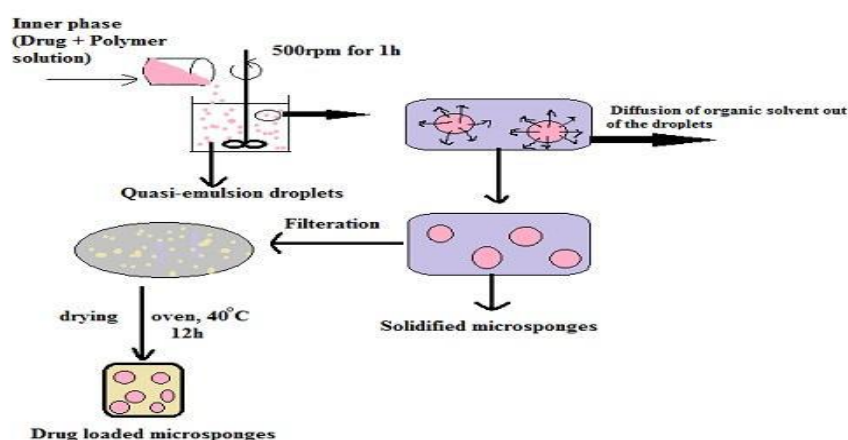


Fig.4: Preparation of microsponges by quasi-emulsion solvent diffusion method²⁵

In this method external phase and internal phase were used. The internal phase is organic phase containing drug, ethyl alcohol/acetone (good solvent), polymer and triethyl citrate (TEC)/Trichloromethane/Dichloromethane (bridging liquid), which was added at an amount of 20% of the polymer in order to facilitate the plasticity. The external phase mostly consists of distilled water and polyvinyl alcohol (PVA). The polymer along with the active, plasticizer and

diffusible substance (porogen) is poured into an external phase, which consists of a polyvinyl alcohol as stabilizer. After emulsification, the system is continuously stirred for 2 hours and maintained at a high temperature if required. Then the mixture is filtered to separate the porous microsponges. The product is washed and dried in vacuum oven at 40°C for 12 hours as shown in figure: 4.

Table 1: Optimum values for microsponges formulation

Sr.no	Specification	Optimum value
1	Drug and polymer ratio	1:1,1:2,1:3, 2:1& 3:1
2	Amount of drug (mg)	100-300
3	Polyvinylalcohol (mg)	100
4	Inner phase solvent (ml)	Ethyl alcohol
5	Amount of inner phase solvent	10
6	Amount of water in outer phase (ml)	100
7	Temperature of inner phase	25°C
8	Type of process	Magnetic stirrer and bath sonicator
9	magnetic stirrer speed	1000 rpm

EVALUATION METHODOLOGY OF MICROSPONGE^{28-30:}

Particle size evaluation:

The particle size distribution is evaluated using optical microscope or electron microscope. Particle size determination of Microsponge can be performed by laser

light diffractometry or other suitable method. The values (d 50) can be expressed for all formulations as mean size ranges. Particle size greater than 30 µm can give gritty feeling and hence particles sizes between 10 and 25 µm are used in the final formulation.

Morphology and surface topography:

In the morphological study of microsp sponge topography various techniques are used such as the photon correlation spectroscopy (Pcs), Transmission electron spectroscopy (TEM), scanning electron microscopy (SEM).

Determination of loading efficiency:

The loading efficiency (%) of the microsponges can be calculated as follows:-

$$\text{Loading efficiency} = \frac{\text{Actual Drug Content in Microsponge}}{\text{Theoretical Drug Content}} \times 100$$

Determination of production yield:

The production yield of the microsponges can be determined by:

$$\text{Production Yield} = \frac{\text{Practical weight of Microsponges}}{\text{Theoretical weight (polymer+drug)}} \times 100$$

Determination of true density:

The true density of the microsp sponge can be measured using an ultra-pycnometer in the presence of helium gas and is calculated from a mean of repeated determinations.

Compatibility study:

It can be studied by thin layer chromatography (TLC) and Fourier Transform Infra-red spectroscopy (FT-IR). Effect of polymerization on the crystallinity of drug can be studied by powder X-ray diffraction (XRD) and differential scanning calorimetric.

Release evaluation:

Release of microsponges can be controlled through diffusion or other triggering mechanism such as moisture, pH, friction, temperature. This release mechanism used to enhance product aesthetics.

Resiliency:

For the production of bullets a particle that is softer or firmer according to the needs of the final formulation

viscoelastic properties of the microsp sponge can be modified. Increased cross-linking tends to decrease the rate of release.

Stability study:

Gel formulation is subject to stability testing as per ICH norms. Gel fill in clean, lacquered, collapsible aluminium tubes, and various replicates kept at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ relative humidity in a Chamber. Gel assessed for change in appearance, pH and *in vitro* release profile at an interval of 30, 60 and 90 days.

APPLICATIONS OF MICROSPONGES^{30,31}:

Few applications of microsp sponge drug delivery system are as follows:

Microsponges in oral care cosmetics:

The Microsp sponge system provides the controlled delivery of oral medications to the lower gastrointestinal tract, where upon exposure to specific enzymes it will be released in the colon. It has been shown that microsp sponge system enhances the solubilization of poorly soluble drugs by entrapping these drugs in their pores. Itraconazole prepared with Eudragit RS100 by using quasi emulsion solvent diffusion method for controlled oral delivery and subsequently tablet of microsp sponge was prepared by the direct compression method results show that compressibility was improved in the physical mixture of the drug and the polymer due to the plastic deformation of sponge like microsphere structure³¹.

Long lasting coloured cosmetics:

It is a new application for microsponges. Colours entrapped in microsponges may be used in a variety of coloured cosmetic products such as lipsticks or rouge to make them long lasting.

Going the natural way using a functional active:

Although natural actives are important consumer attractants, now focus has shifted on using multifunctional natural ingredients.

Table 2: Applications of Microsponges³²:

S.No	Application	Advantages
1.	Anti-acne: Eg: Benzyl Peroxide	Maintained efficacy with decreased skin irritation and sensitization.
2.	Anti-inflammatory: Eg: Hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatoses.
3.	Sunscreens:	Improved protection against sunburns with long lasting product efficacy and sun related injuries even at elevated concentration and with reduced irritancy and sensitization
4.	Anti-dandruffs: Eg: zinc pyrithione, selenium sulphide.	Extended safety and efficacy with reduced unpleasant odour with lowered irritation.
5.	Anti-fungals:	Sustained release of active ingredients.
6.	Skin depigmenting: Eg: Hydroquinone	Improved stabilization against oxidation with improved efficacy and aesthetic agents appeal.

Microsponges for Topical Delivery:

Microsp sponge consists of a myriad of interconnecting voids within a non-collapsible structure that can accept a wide variety of substances. The outer surface of microsp sponge is typically porous, allowing the controlled flow of substances into and out of the sphere. Several primary characteristics, or parameters, of the microsp sponge system can be defined during the production phase to obtain spheres that are tailored to

specific product applications and vehicle compatibility. Benzoyl peroxide (BPO) is used for the treatment of acne and athlete's foot is commonly used in topical formulations. Controlled release of the microsp sponge delivery system of BPO to the skin could reduce the side effect.

Microsp sponge used for bone and tissue engineering:

Bone like compounds were obtained by the mixing

prepolymerized powder of polymethyl methacrylate monomer with two aqueous dispersion of tricalcium phosphate grains and calcium deficient hydroxyapatite powders. The final compound appeared to be porous and developed as microsp sponge.

MARKETED FORMULATION USING MDS^{32, 33}:

It includes Ethical Dermatological Products (APS defined ethical dermatological products are prescriptional and non-prescriptional drugs that are promoted primarily through the medical profession for the prevention and treatment of skin problems or diseases). Several ethical dermatological products approved by US FDA as over the counter (OTC) and personal care products are sold in the United States.

Tretinoin Acne Medication:

In 1997, the FDA approved the first ethical pharmaceutical product which is based on the patented microsp sponge technology. Retin-A-Micro™, Which has been licensed to Ortho-McNeil Pharmaceutical Corporation. However, skin irritation among sensitive individuals can limit patient compliance with the prescribed therapy. The company believes its patented approach to reduce the potentially irritating side effects of tretinoin.

5-Fluorouracil:

It is an effective chemotherapeutic agent for the treatment of keratosis, hardened skin condition caused by excessive exposure to sunlight. However, due to significant side effects, patient compliance with the treatment regimen is poor.

Cosmeceutical Product Retinol:

Retinol is a highly pure form of vitamin A which has demonstrated a remarkable ability for maintaining the youthful appearance of skin. It becomes unstable when mixed with other ingredients. Stabilized retinol in a formulation which is cosmetically elegant and which has a low potential for skin irritation is successfully developed and marketed.

CONCLUSION

The microsp sponge delivery system is a technology of controlled release system in which active pharmaceutical ingredient is loaded in the macro porous beads and initiates reduction in side effects with improved therapeutic efficacy. Microsp sponge can be effectively incorporated into topical drug delivery system like gel, cream etc. for retention of dosage form on skin. It is also use for oral delivery of drugs using bio erodible polymers, especially for colon specific delivery. The microsp sponge drug delivery system is believed to reduce side effects, improved stability, increased elegance, enhanced formulation flexibility and also offers entrapment of its ingredients. Microsp sponge systems are non-irritating, non-mutagenic, non-allergenic, and nontoxic. This technology is being used currently in cosmetics, over-the-counter skin care, sunscreens, and prescription products. This kind of drug delivery technology may lead to a better understanding of the healing of several diseases.

ACKNOWLEDGEMENT

I myself Monika wants to firstly thank Almighty God and my parents for their immense support during the research work. I would like to put my gratitude to the co-authors who helped a lot during this research work. Special thanks to our Head of Pharmaceutics Department, Dr. Jagdeep Singh Dua

who helped a lot with the understanding of concepts which arises during research work.

CONFLICT OF INTEREST

A special thanks as a token of helping hands was given to co-authors. But during the submission of this manuscript, not any kind of financial or personal help was taken. During the review article work, it was kept in mind that nobody intentions are disturbed. Thus after the publication of this review article, not any kind of conflict of interest will be seen at any step. As this review article work is of my keep interest, hard work and efforts.

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