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A brief review of microsponges: An update

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Abstract

Microsponges are porous microspheres and biologically inert. Particle size of microsponges was 10-25µm. microsponges were prepared by Quasi emulsion solvent diffusion method. It is a unique technique for controlled release formulation. Particles size determination by Scanning Electron microscopy (SEM) and Fournier transmission infrared spectroscopy (FTIR). Microsponges are characterized by particle size determination, entrapment efficacy, true density, % drug content and % yield, dissolution studies, Resiliency, compatibility studies and *in-vitro* studies.

Keywords: Microsponges, Quasi emulsion solvent diffusion method, FTIR and SEM

Introduction

Controlled drug delivery system can be major advance towards solving problems concerning the targeting of a drug to a specific organ or a tissue and controlling the rate of drug delivery to the target site. The development of oral drug delivery system has been a challenge to formulation due to their inability to restrain and localize the system as targeted areas of the gastrointestinal tract. Oral sustain release and controlled release product provide an advantage over conventional doses form by optimizing Biopharmaceutics, pharmacokinetic and pharmacodynamic properties of drug in such a way that its reduce dosing frequency to an extent that once daily dose is sufficient for therapeutic management through uniform plasma concentration providing maximum utility of drug with reduction local and systemic side-effect and cure. Controlled release system is to deliver constant supply of active ingredient, zero order rates by continuously releasing for a certain period of time an amount of drug equivalent to the eliminated by the body^[1].

Microsponges

Microsponges delivery system is patented polymeric system consist of porous microspheres. Micro sponges were originally developed for topical delivery of drugs. Micro sponges were macro porous beads typically 10-25 microns in diameter, loaded with active agents. Micro sponges are porous polymeric microspheres that was mostly used for prolonged typical administration. Micro sponges are porous microspheres having interred connected voids of particle size range 5-300 µm. They are uniform, spherical polymer particles. Microspheres are designed to deliver a pharmaceutical active ingredient efficiently at minimum dose and also to enhance stability reduce side-effect and modify drug release profile^[2].

History of Microsponge^[3]

The microsponge technology was developed by Won in 1987 and the original patents were assigned to Advanced Polymer Systems, Inc. This Company developed a large number of variations of the technique and applied those to cosmetic as well as OTC and prescription pharmaceutical products.

Hypothetical Mechanism of Microsponge^[3]

The active ingredient is added to the vehicle in an entrapped form. As the microsponge particles have an open structure (i.e., 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 microsphere 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 microsphere 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 microsphere 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 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 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 microsphere 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.

Characteristics ^[4]

- Monomers and polymer are inert without increase the viscosity.
- Immiscible in water or slightly soluble
- To avoid cosmetics problems incorporating not more than 10-12% w/w microspheres.
- Rate of release was controlled by diffusion or moisture, pH and temperature.
- Weight without drying
- Extended release
- Improved product elegance

Important feature of Microspheres ^[4]

- Stable at pH1-11
- Stable at up to 130 °C temperature
- Compatible with most of vehicles
- Higher loading capacity 50-60%
- Cost effective
- Free flowing

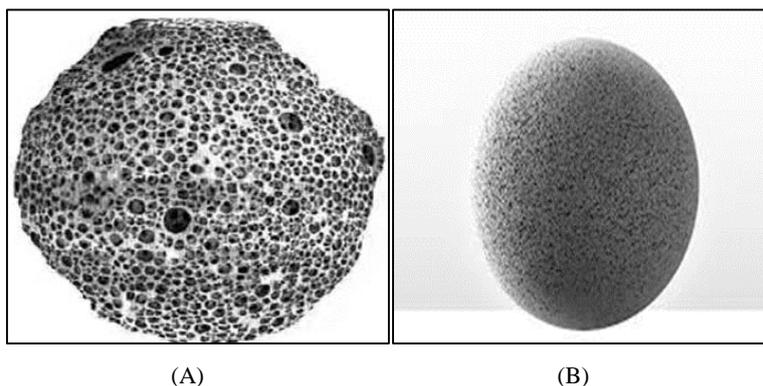


Fig 1: (A) Highly Porous structure of microspheres (B) Microspheres

Advantages of microspheres ^[5]

- These formulations are stable over range of pH1-11
- These formulations are stable at room temperature up to 130 °C
- These formulations are compatible with most vehicles' and ingredients.
- These are stabilizing as their average pore size is 0.25 μm where bacteria cannot penetrate.
- These formulations are free flowing and cost effective.
- These are non-irritating, non-mutagenic and non-toxic.

Release mechanism ^[6]

Pressure triggered systems: Microspheres system releases the entrapped material when pressurized/rubbed; the amount released depends upon various characteristics of the sponge. By varying the type of material and different process variables, the microsphere best suited for a given application may be optimized. When compared with mineral oil containing microcapsules, mineral oil containing

Temperature-triggered systems: Some entrapped active

ingredients can be too viscous at room temperature to flow spontaneously from microsphere onto the skin. Increased in skin temperature can result in an increased flow rate and hence 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 microsphere when exposed to higher temperatures; thus a sunscreen would be released from a microsphere only upon exposure to the heat from the sun.

pH triggered system: 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.

Solubility triggered systems: Presence of an aqueous medium such as perspiration can trigger the release rate of active ingredients. Ingredients such as antiseptics, deodorants and antiperspirants may be formulated in such types of systems. Release may be achieved based on the ability of the external medium to dissolve the active, the concentration gradient or the ability to swell the microsphere network.

Table 1: Application of microspunge system ^[7]

S. No	Active agents	Application
1	Anti-inflammatory e.g. Hydrocortisone	Long lasting activity with lessening of skin allergic response and dermatoses.
2	Anti-dandruffs e.g. zinc pyrithione, selenium sulfide	Reduced unpleasant odor with reduced irritation with extended efficacy and safety.
3	Skin depig-menting agents e.g. hydroquinone	Improved stabilization against oxidation with improved efficacy and aesthetic appeal.
4	Anti-Fungal	Sustained release of actives.
5	Anti-acene	Maintained efficacy with reduced skin irritation and sensitization
6	Anti-Pruritics	Extended and improved activity
7	Rubefaciens	Sustained activity with reduced irritancy, greasiness and odor.

Method of Preparation of Microspunge Drug Delivery System ^[8]**1) Liquid –liquid suspension polymerization**

Immiscible monomers and active ingredient are dissolved in suitable solvent monomers.



Dispersed in aqueous phases which consist of additives like surfactant, suspending agent



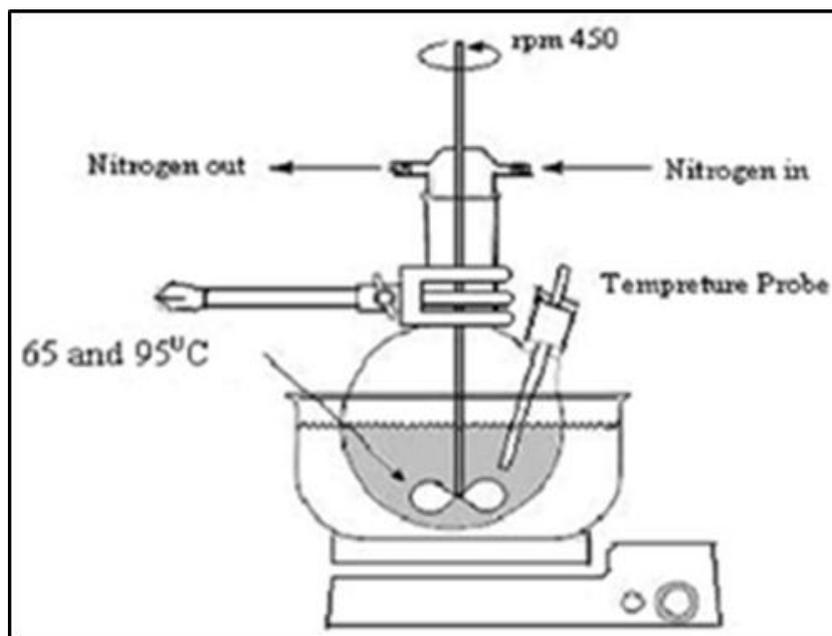
Polymerization is activated by increasing temperature or irradiation or by adding catalyst.



Polymerization process is continues the formation of spherical structure.



After the process solvent is removed and formed spherical porous microsponges.

**Fig 2:** liquid-liquid suspension polymerization**2) Quasi-emulsion solvent diffusion method ^[8]**

Polymer like Eudragit RS 100 was dissolved in Dichloro methane (inner phase).



Then the drug is added in solution and dissolved in Ultrasonication at 35 °C.



Inner phase was poured into PVA solution in water (outer phase).



Continuously stirring 3-4 hour and after that filtered.



Dried in oven at 40 °C and microspunge was formed.

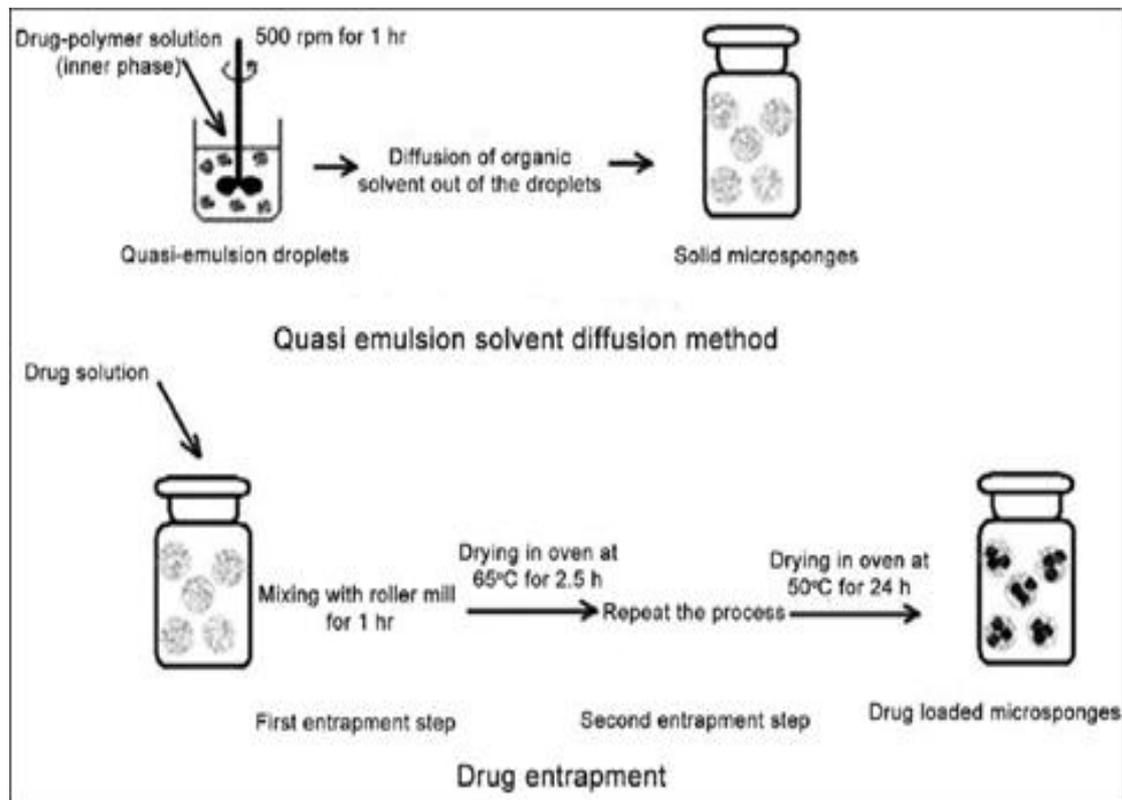


Fig. 3 Quasi emulsion solvent diffusion method

Evaluation Parameters of Microsponges ^[9]

- Particle size (Microscopy)
- Morphology and Surface topography
- Characterization of pore structure
- Loading efficiency and production yield
- Characterization of pore structure
- Compatibility studies
- Resiliency
- Drug release study

a. Particle Size Determination ^[9]

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 30 μ m can impart gritty feeling and hence particles of sizes between 10 and 25 μ m are preferred to use in final topical formulation.

b. Morphology and Surface Topography of Microsponges ^[10]

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 microsp sponge particle can also be taken to illustrate its ultra structure.

c. Determination of Loading Efficiency and Production Yield ^[11]

The loading efficiency (%) of the Microsponges can be calculated according to the following equation:

$$\text{loading efficeacy} = \frac{\text{cutual drug content in microsp sponge}}{\text{Theoretical drug content}} \times 100$$

The production yield of the micro particles can be determined by calculating accurately the initial weight of the raw materials and the last weight of the microsp sponge obtained.

$$\text{Production Yield} = \frac{\text{Practical Mass of Microsponges}}{\text{Theoretical Mass (Polymer + Drug)}} \times 100$$

d. Determination of True Density ^[11]

The true density of micro particles is measured using an ultracycnometer under helium gas and is calculated from a mean of repeated determinations.

e. Characterization of Pore Structure ^[12]

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 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.

f. Compatibility Studies ^[13]

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). For DSC approximately 5mg samples can be accurately weighed into aluminum pans and sealed and can be run at a heating rate of 15 $^{\circ}$ C/min over a temperature range 25–430 $^{\circ}$ C in atmosphere of nitrogen.

g. Polymer/Monomer Composition ^[14]

Factors such as microsphere size, drug loading, and polymer composition govern the drug release from microsponges. Polymer composition of the MDS can affect partition coefficient of the entrapped drug between the vehicle and the microsphere system and hence have direct influence on the release rate of entrapped drug. Release of drug from microsphere systems of different polymer compositions can be studied by plotting cumulative % drug release against time. Release rate and total amount of drug released from the system composed of methyl methacrylate/ethylene glycol dimethacrylate is slower than styrene/divinyl benzene system.

h. Resiliency ^[15]

Resiliency (viscoelastic properties) of microsponges can be modified to produce beads 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.

i. Dissolution Studies ^[16]

Dissolution profile of microsponges can be studied by use of

dissolution apparatus 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.

j. In-vitro diffusion studies ^[16]

The *in vitro* diffusion studies of prepared microsphere gel were carried out in Keshary– Chien diffusion cell using through a cellophane membrane. 100 ml of phosphate buffer was used as receptor compartment, and then 500 mg of gel containing 10 mg of drug was spread uniformly on the membrane. The donor compartment was kept in contact with a receptor compartment and the temperature was maintained at 37±0.50. The solution on the receptor side were stirred by externally driven Teflon coated magnetic bars at predetermined time intervals, pipette out 5 ml of solution from the receptor compartment and immediately replaced with the fresh 5 ml phosphate buffer. The drug concentration on the receptor fluid was determined spectro-photometrically against appropriate blank. The experiment was carried out in triplicate.

Table 2: List of marketed products using microsphere drug delivery system ^[17]

S. no	Product name	Advantages
1	Retin-A-Micro	0.1% and 0.04% tretinoin entrapped in MDS for topical treatment of acne vulgaris. This formulation uses patented methyl methacrylate/ glycol dimethacrylate cross-polymer porous microspheres (Microsphere System) to enable inclusion of the active ingredient, tretinoin, in an aqueous gel.
2	Carac Cream, 0.5%	Carac Cream contains 0.5% fluorouracil, with 0.35% being incorporated into a patented porous microsphere (Microsphere) composed of methyl methacrylate / glycol dimethacrylate cross-polymer and dimethicone. Carac is a once-a-day topical prescription product for the treatment of actinic keratoses
3	Line Eliminator Dual Retinol Facial Treatment	Lightweight cream with a retinol in MDS delivers both immediate and time released wrinkle-fighting action.
4	Retinol cream	The retinol molecule is kept in the microsphere system to protect the potency of the vitamin A by reducing the possibility of irritation
5	Retinol 15 Night cream	A nighttime treatment cream with Microsphere technology using a stabilized formula of pure (visible diminishment of fine lines and wrinkles.
6	EpiQuin Micro	The Microsphere system entrapping hydroquinone and retinol release drug into the skin gradually throughout the day (minimize skin irritation).
7	Sportscream RS and XS	Topical analgesic-anti-inflammatory and counterirritant actives in a Microsphere Delivery System for the management of musculoskeletal conditions.

Microsphere for topical delivery ^[18]

The Microsphere systems are based on microscopic, polymer-based microspheres 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. A single Microsphere is as tiny as a particle of talcum powder, measuring less than one-thousandth of an inch in diameter. Like a true sponge, each microsphere consists of a myriad of interconnecting voids within a non-collapsible structure that can accept a wide variety of substances. The outer surface is typically porous, allowing the controlled flow of substances into and out of the sphere. Several primary characteristics, or parameters, of the Microsphere system can be defined during the production phase to obtain spheres that are tailored to specific product applications and vehicle compatibility. Microsphere systems are made of biologically inert polymers. Extensive safety studies have demonstrated that the polymers are non-irritating, non-mutagenic, non-allergenic, non-toxic and non-biodegradable. As a result, the human body cannot

convert them into other substances or break them down. Although they are microscopic in size, these systems are too large to pass through the stratum corneum when incorporated into topical products. Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne, with skin irritation as a common side effect. It has been shown that controlled release of BPO from a delivery system to the skin could reduce the side effect while reducing percutaneous absorption. Therefore, microsphere delivery of Benzoyl peroxide was developed using an emulsion solvent diffusion method by adding an organic internal phase containing benzoyl peroxide, ethyl cellulose and dichloromethane into a stirred aqueous phase containing polyvinyl alcohol and by suspension polymerization of styrene and divinyl benzene. The prepared microspheres were dispersed in gel base and microsphere gels are evaluated for anti-bacterial and skin irritancy. The entrapped system released the drug at slower rate than the system containing free BPO. Topical delivery system with reduced irritancy was successfully developed

Microsponge for oral delivery

In oral applications, the microsponge system has been shown to increase the rate of solubilization of poorly water-soluble drugs by entrapping such drugs in the microsponge system's pores. As these pores are very small, the drug is in effect reduced to microscopic. Particles and the significant increase in the surface area thus greatly increase the rate of solubilization. Controlled oral delivery of ibuprofen microsponges is achieved with an acrylic polymer, Eudragit RS, by changing their intraparticle density. Sustained release formulation of chlorpheniramine maleate, using powder-coated microsponges, is prepared by the dry impact blending method, for oral drug delivery. Controlled oral delivery of Ketoprofen prepared by quasi-emulsion solvent diffusion method with Eudragit RS 100 and afterwards tablets of microsponges were prepared by the direct compression method. Results indicated that compressibility was much improved in the physical mixture of the drug and polymer; due to the plastic deformation of the sponge-like microsponge structure, producing mechanically strong tablets. Colon-specific, controlled delivery of flurbiprofen was conducted by using a commercial Microsponge 5640 system. In vitro studies exhibited that compression-coated colon-specific tablet formulations started to release the drug at the eighth hour, corresponding to the proximal colon arrival time, due to addition of the enzyme, following a modified release pattern, while the drug release from the colon-specific formulations prepared by pore plugging the microsponges showed an increase at the eighth hour, which was the point of time when the enzyme addition was made ^[19].

Microsponge for Bone and Tissue Engineering

Bone-substitute compounds were obtained by mixing pre polymerized powders of polymethyl-methacrylate and liquid methyl methacrylate monomer with two aqueous dispersions of tricalcium phosphate grains and calcium deficient hydroxyl apatite powders. The final composites appeared to be porous and acted as microsponges. Basic fibroblast growth factor incorporated in a collagen sponge sheet was sustained released in the mouse sub-cutis according to the biodegradation of the sponge matrix, and exhibited local angiogenic activity in a dose-dependent manner. The injection of collagen microsponges incorporating basic fibroblast growth factor induced a significant increase in the blood flow, in the murine ischemic hind limb, which could never have been attained by the bolus injection of basic fibroblast growth factor. These results suggest the significance and therapeutic utility of the type I collagen as a reservoir of basic fibroblast growth factor ^[19].

Conclusion

Microsponges drug delivery system is very emerging pharmaceutical application for controlled release system, it reduces irritancy, reduces toxicity and compatible with most of ingredient and vehicles. SEM and FTIR study was carried out. Microsponges are a valuable drug delivery matrix substance for various therapeutic applications in the future. Now a day it was used in tissue engineering, oral delivery system and especially for colon specific delivery.

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