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MICROSPONGE - A NOVEL DRUG DELIVERY SYSTEM: AN OVERVIEW

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Abstract:

Microsponge is recent novel technique for control release and target specific drug delivery system. Therefore many scientist or researcher attracted towards the microsponge drug delivery system. Also 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. More and more developments in delivery systems are being integrated to optimize the efficacy and cost-effectiveness of the therapy. Microsponges are porous microspheres having myriad of interconnected size ranging voids of particle from 5-150 µm. 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. 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. These porous microspheres with active ingredients can be incorporated in to formulations such as creams, lotions and powders. Microsponges consisting of noncollapsible structures with porous surface through active ingredients are released in a controlled manner. Release of drug into the skin is initiated by a variety of triggers, including rubbing and higher than ambient skin temperature.

Keywords: *Microsponge, porous microspheres, Microsponge drug delivery system, SEM.*

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INTRODUCTION:

Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge-like spherical particles with a large porous surface. Moreover, they may enhance stability, reduce side effects and modify drug release favorably. Microsponge technology has many favourable characteristics, which make it a versatile drug delivery vehicle. 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. MDS can provide increased efficacy for topically active agents with enhanced safety, extended product stability and improved aesthetic properties in an efficient manner [1].

To control the delivery rate of active agents to a predetermined site in the human body has been one of the biggest challenges faced by Pharmaceutical scientists. Several predictable and reliable systems have been developed for systemic delivery of drugs under the heading of transdermal delivery system (TDS) using the skin as portal of entry. It has improved the efficacy and safety of many drugs that may be better administered through skin. But TDS is not practicable for delivery of materials whose final target is skin itself. Controlled release of drugs onto the epidermis with assurance that the drug remains primarily localized and does not enter the systemic circulation in significant amounts is a challenging area of research [2].

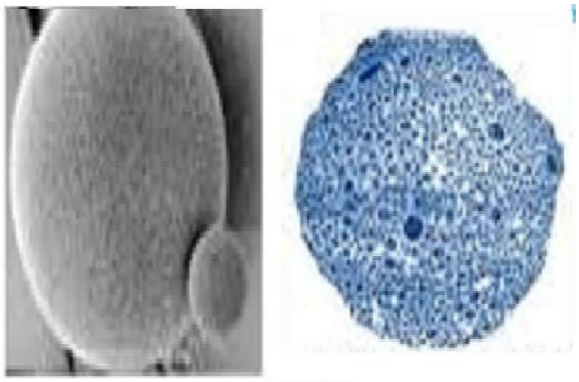


Figure 1: Typical views of Microsponge

Microsponges consist of non-collapsible structures with porous surface through which active ingredients are released in controlled manner. Depending upon the size, the total pore length may range up to 10 ft. and pore volume up to 1 ml/g. When applied to the skin, the microsponge drug delivery system (MDS) releases its active ingredient on a time mode and also in response to other stimuli such as rubbing, temperature, and pH Microsponges have the capacity to adsorb or load a high degree of active materials into the particle or onto its surface. Its large capacity for entrapment of actives up to 3 times its weight differentiates microsponges from other types of dermatological delivery systems. Mostly microsponge is use for transdermal drug delivery system [4].

DEFINING MICROSPONGES

The Microsponge Delivery System (MDS) is a patented polymeric system consisting of porous microspheres. They are tiny sponge like spherical particles that consist of a myriad of interconnecting voids within a non-collapsible structure with a large porous surface through which active ingredient are released in a controlled manner. The size of the microsponge's ranges from 5-300µm in diameter and a typical 25µm sphere can have up to 250000 pores and an internal pore structure equivalent to 10 feet in length, providing a total pore volume of about 1ml/g for extensive drug retention. The surface can be varied from 20 to 500 m^2/g and pore volume range from 0.1 to 0.3cm^3/g. This results in a large reservoir within each microsponge, which can be loaded with up to its own weight of active agent [4,5].

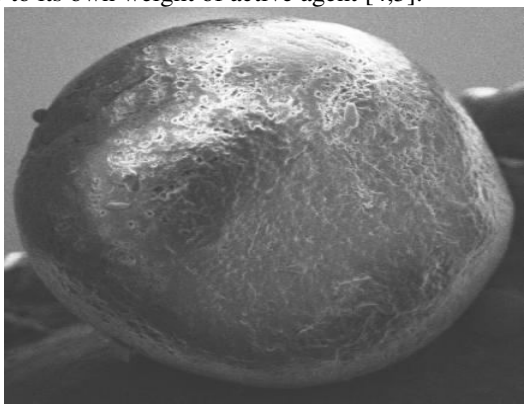


Figure 2: Microsponge

POTENTIAL FEATURES OR CHARACTERISTICS OF MICROSPONGE DRUG DELIVERY SYSTEMS [6,7]

- Microsponges show acceptable stability over pH ranging from 1 to 11 and at high temperatures (up to130°C).
- Microsponges exhibit good compatibility with various vehicles and ingredients.
- Microsponges have high entrapment efficiency up to 50 to 60%.
- Microsponges are characterized by free flowing properties.

- The average pore size of microsponges is small (0.25 µm) in a way to prevent the penetration of bacteria, thus they do not need sterilization or addition of preservatives.
- Microsponges are non-allergenic, non-irritating, non-mutagenic and non-toxic.
- Microsponges can absorb oil up to 6 times their weight without drying.

BENEFITS OF MICROSPONGE DRUG DELIVERY SYSTEM [8,9]:

- Enhanced product performance.
- Extended release.
- Reduced irritation and hence improved patient compliance.
- Improved product elegancy.
- Improved oil control as it can absorb oil up to 6 times its weight without drying.
- 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.

DRUGS ENCLOSED IN MICROSPONGE DRUG DELIVERY SYSTEM [10]

- Ketoprofen
- Benzyl peroxide
- Retinol
- Fluconazole
- Ibuprofen
- Tretinoin
- Trolamine

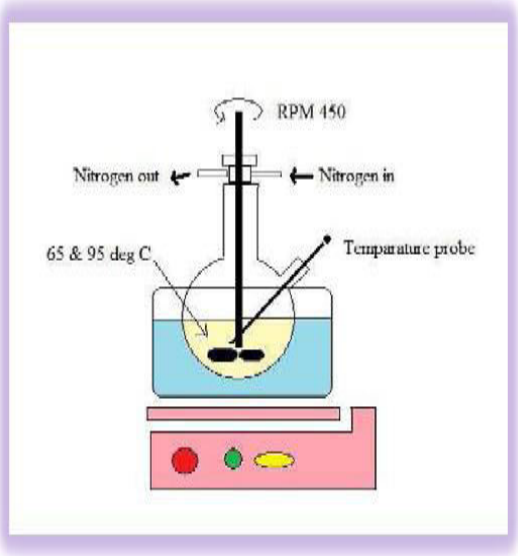
METHODS OF PREPARATION OF MICROSPONGES

The selection of a particular encapsulation method is primarily determined by the solubility characteristics of the drug and polymer. A popular method for the encapsulation of water-insoluble drugs within water insoluble polymers is the diffusion solvent method. This method can be both readily performed in the laboratory but has scale up potential such that large volumes of water can be handled. When finally developing a microencapsulation procedure then finally selected method should ideally produce [11,12]

- High yields of microparticles and free of extensive agglomeration
- Higher encapsulation of the core material,
- A reproducible release profile from batch to batch, and
- An ability to modify in vitro release rates by varying process parameters in order to prepare microparticles with the desired in vivo release characteristics.

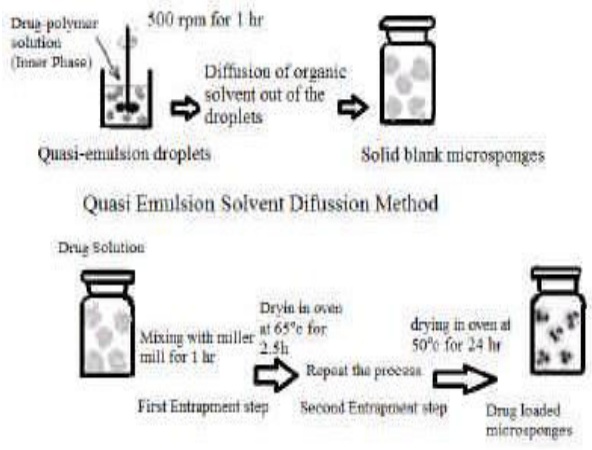
Liquid-liquid suspension polymerization

The porous microspheres are prepared by suspension polymerization method in liquid-liquid systems. In this method the monomers which are immiscible are first dissolved along with active ingredients in a suitable solvent monomer and are then dispersed in the aqueous phases which consist of additives like surfactant, suspending agents to facilitate formation of suspension. The polymerization is then activated by increasing temperature or irradiation or by addition of catalyst. The polymerization process continues the formation of a reservoir type of system with spherical structure. After the polymerization process the solvent is removed leaving the spherical structured porous microspheres, i.e., microsponges.



Quasi-emulsion solvent diffusion

Porous microspheres (microsponges) were also prepared by a quasi-emulsion solvent diffusion method (two-step process) using an internal phase containing polymer such as eudragit which is dissolved in ethyl alcohol. Then, the drug is slowly added to the polymer solution and dissolved under ultra-sonication at 35°C and plasticizer such as triethylcitrate (TEC) was added in order to aid the plasticity. The inner phase is then poured into external phase containing polyvinyl alcohol and distilled water with continuous stirring for 2 hours. Then, the mixture was filtered to separate the microsponges. The product (microsponges) was washed and dried in an air- heated oven at 40°C for 12 hr [13,14].



DRUG RELEASE MECHANISM OF MICROSPONGE

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 [15-17].

EVALUATION TESTS

Particle size and size distribution [18]

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 be1 performed by laser light diffractometry or any other suitable method. The values (d50) 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.(eg.gel)

Determination of pH [19]

The pH of the microsponges enriched gel was determined using a calibrated pH meter. The readings were taken for average of 3 samples**.**

Determination of true density [20]

The true density of microparticles is measured using an ultrapycnometer under helium gas and is calculated from a mean of repeated determinations.

Surface topography of microsponge (SPM) [21]

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.

Scanning Electron Microscopy(SEM) [22]

The morphology and size of microsponges were observed by scanning electron microscopy. Prepared microsponges were coated with gold and studied by scanning electron microscopy (Phenoworld) under vacuum at room temperature.

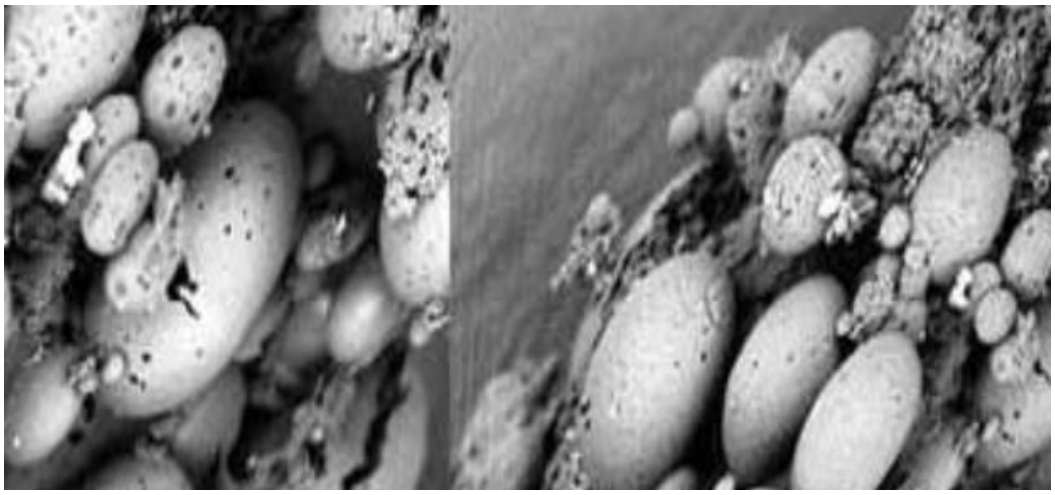


Figure 2: (A and B) SEM photography of microsponges.

Determination of Loading Efficiency [23]

The drug content in the microsponges was determined by High Performance Liquid Chromatography (HPLC) method. A sample of drug containing microsponges(10 mg) was dissolved in 100 ml of methanol. The drug content was calculated from the calibration curve and expressed as loading efficiency.

Loading efficiency=Actual drug content in microsponge/Theoritical drug content x100

Determination of Production Yield [24]

The production yield of the microsponges was determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponges obtained.

Production Yield (PY)=Practical mass of microsponge/Theoritical mass(drug+polymer) x100

Dissolution Test [25]

Dissolution release rate of microsponges can be studied by use of dissolution apparatus with a modified basket consisted of 5µm stainless steel mesh. The speed of the rotation is 150 rpm. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. At various intervals the samples from the dissolution medium was analysed by suitable analytical methods.

Thermoanalytical Methods [26]

Thermal analysis using differential scanning calorimetry (DSC) is carried out for the pure drug, polymer and the drug-polymer physical mixture to confirm compatibility. DSC is also performed for the microsponge formulations to ensure that the formulation process does not change the nature of the drug. Samples (approximately 2 mg) are placed in aluminum pans, sealed and operated at a heating rate of 20°C/min over a temperature range 40 to 430°C. The thermograms obtained by DSC for the physical mixtures, as well as microsponges, should be observed for broadening, shifting and appearance of new peaks or disappearance of certain peaks. The peak corresponding to the melting of the drug should be preserved in all thermograms.

Resiliency [27]

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 cross-linking tends to slow down the rate of release.

Compatibility Studies [28]

Compatibility of drug with reaction adjuncts can be studied by thin layer chromatography (TLC) and Fourier Transform Infra-red 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 approximately5mg samples can be accurately weighed into aluminum pans and sealed and can be run at a heating rate of15ºC/min over a temperature range 25–430ºC in atmosphere of nitrogen.

APPLICATIONS OF MICROSPONGES

Microsponge delivery systems are used to enhance the safety, effectiveness and aesthetic quality of topical prescription, over-the-counter and personal care products. Microsponges can be used in variety of applications. It is used mostly for topical and recently for oral administration. Several patents have reported that it can be used as an excipient due to its high

loading capacity and sustained release ability. It offers the formulator a range of alternatives to develop drug and cosmetic products. Microsponges are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects and modify drug release. Over-the-counter products that incorporate microsponge drug delivery system include numerous moisturizers, specialized rejuvenated products, and sunscreens [29-33].

Microsponge for topical delivery

The Microsponge systems are based on microscopic, polymer-based microspheres that can bind, suspend or entrapa wide variety of substances and then be incorporated into a formulated product, such as a gel, cream, liquid or powder. A single Microsponge 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 Microsponge system can be defined during the production phase to obtain spheres that are tailored to specific product applications and vehicle compatibility.

Microsponge 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, microsponge 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 microsponges were dispersed in gel base and microsponge 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 solubilisation 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 increases the rate of solubilisation. 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.

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 hydroxyapatite powders. The final composites appeared to be porous and acted as microsponges. Basic fibroblast growth factor (bFGF) 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 bFGF 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

bFGF. These results suggest the significance and therapeutic utility of the type I collagen as a reservoir of bFGF .

RECENT ADVANCES IN MICROSPONGE DRUG DELIVERY SYSTEM

Various advances were made by modifying the methods to form Nan sponges, nanoferrosponges and porous micro beads. β - CD nanosponges were also developed that can be used for hydrophobic as well as hydrophilic drugs, in contrast to polymeric micro or nanosponges. These advanced systems were studied for oral administration of dexamethasone, Flurbiprofen, doxorubicin hydrochloride, itraconazole and serum albumin as model drug. These nanosponges were developed by cross- linking the β CD molecule by reacting the β-CD with biphenyl carbonate. Some researchers also observed the nanosponges as good carrier for the delivery of gases. Researchers also observed that incorporating a cytotoxic in a nanosponge carrier system can increase the potency of the drug suggesting that these carriers can be potentially used for targeting the cancerous cells [34].

CONCLUSION:

The microsponge delivery technology of controlled release system in which active pharmaceutical ingredient is loaded in the macro porous beads and they initiates reduction in side effects with improved therapeutic efficacy. Microsponge can be effectively incorporated into topical drug delivery system for retention of dosage form on skin, and also use for oral delivery of drugs using bio erodible polymers, especially for colon specific delivery and controlled release drug delivery system thus improving patient compliance by providing site specific drug delivery system and prolonging dosage intervals. 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. Hence, the microsponge-based drug delivery technology is likely to become a valuable drug delivery matrix substance for various therapeutic applications in the future.

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