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MICROSPONGE DRUG DELIVERY SYSTEM: AN OVERVIEW

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ABSTRACT

Microsponges are porous microspheres that having myriad of interconnected size ranging voids of particle from 5-150 µm. Microsponge delivery systems (MDS) that can precisely control the release rates or target drugs to a specific body site have an enormous impact on the health care system. The microsponge drug delivery technology is widely applicable to the dermatological drug delivery products.MDS expands application in oral drug delivery, bone and tissue engineering, in detecting the diseases and in RNAi silencing .The area of drug delivery technology is being rapidly and becoming highly competitive day by day.The microsponges have the ability 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.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.

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 [4,5]. 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[6]. 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[4]. 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[7].

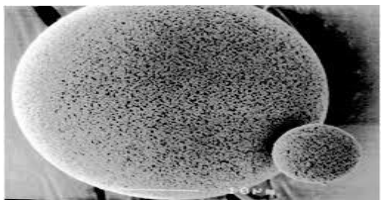

Figure 1: Microsponge technology

Advantages of microsponge delivery system [7]

1. Microsponges can times its weight absorb oil up to 6 without drying.
2. It provides continuous action up to 12 hours i.e. extended release.
3. Improved product elegancy. Lessen the irritation and better tolerance leads to improved patient compliance.
4. They have better thermal, physical and chemical stability.
5. These are non-irritating,nonmutagenic, non allergenic and nontoxic
6. MDS allows the incorporation of immiscible products.
7. They have superior formulation flexibility.
8. In contrast to other technologies like microencapsulation and liposome
9. High drug loading capacity Improve therapy.
10. Compatible with vehicle and ingredients.
11. Flexibility to develop novel product forms Stable over the range 1 -11 ph.
12. Solution Free flowing and cost effective
13. Improve thermal,physical, and chemical stability

Advantages over Conventional Formulations [7-11]:

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 compared 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. For example, by delivering the active ingredient gradually to the skin like MDS Benzoyl peroxide formulations have excellent efficacy with minimal irritation.

Characteristic of Microsponge drug delivery systems [7]

1. Microsponges are stable over the long Ph range from 1 to 11.
2. Microsponges are stable up 130^{0} c temperature.
3. Microsponges are compatible with many of ingredients and excipients.
4. Average pore of microsponge is 0.25 μ, so there no need of sterilization.
5. About 50 to 60 % drug may be entrapped in microsponges.
6. Microsponges show free flowing properties.

7. These are inert molecules without any allergy, irritation and toxicity.

Drug release mechanism of microsponge [7,12,13]: 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.

Factors Affecting Drug Release from Microsponge Delivery System

- Physical properties of Microsponge system like pore diameter, pore volume, resiliency etc. Properties of vehicle in which the microsponges are finally dispersed.
- Pressure Rubbing/ 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. Increased in skin temperature can result in an increased flow rate and hence release.
- 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.

Method of preparation of microsponge: Micro sponge's drug delivery system can be prepared in two ways, one-step process or by two-step process that is liquid-liquid suspension polymerization and quasi emulsion solvent diffusion techniques based that is based on physicochemical properties of drug to be loaded.

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[5-7]

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 35oC 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 11 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[5-7].

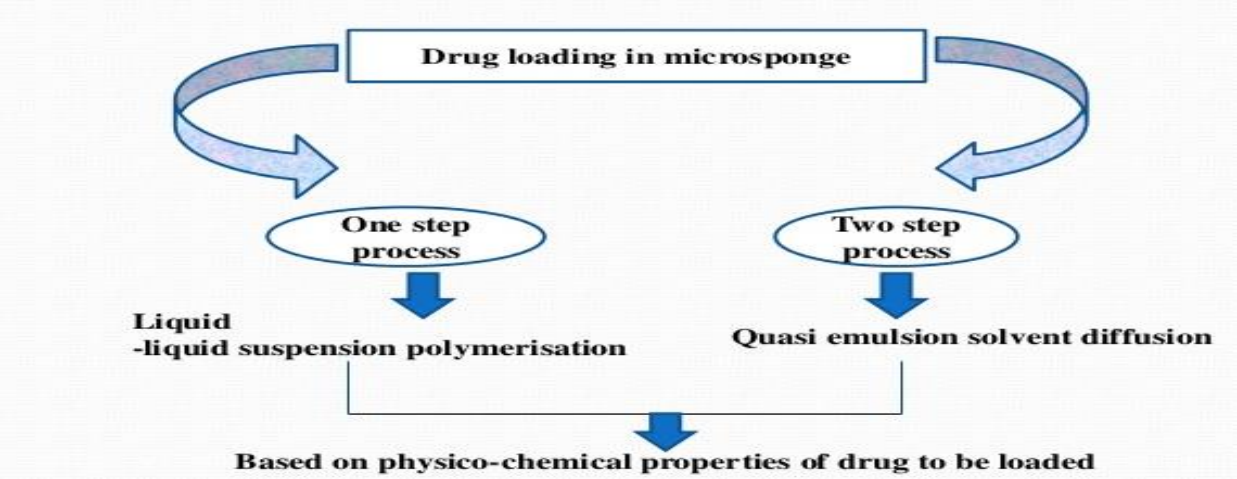

Figure 2 :Preparation of microsponge

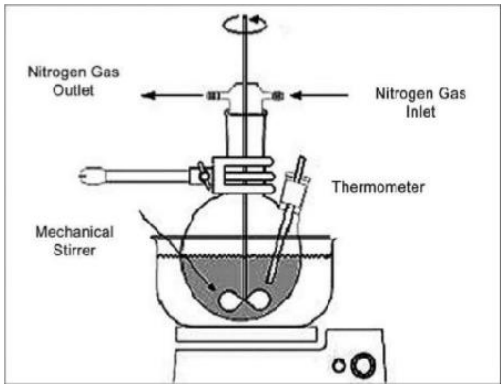

Figure 3 :Reaction vessel for microsponge preparation by Liquid-liquid suspension polymerization

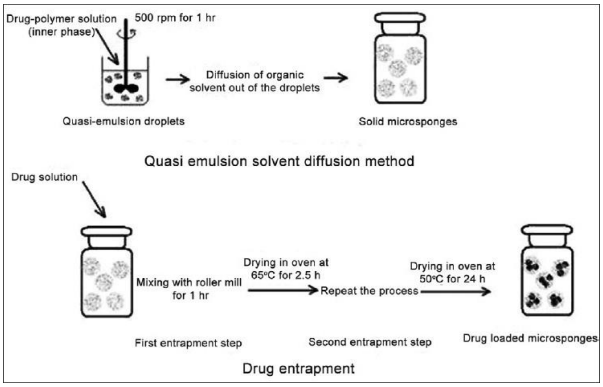

Figure 4: Quasi-emulsion solvent diffusion

Evaluation of microsponge[7,14,17]

(i) Particle size determination: - 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, 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 PMµm can impart gritty feeling and hence particles of sizes between NM and 25µm are preferred to use in final topical formulation.

(ii) Morphology and surface topography of microsponges:-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 microsponge particle can also be taken to illustrate its ultra-structure.

(iii) Determination of loading efficiency and production yield: - The loading efficiency (%) of the microsponges can be calculated according to the following equation:

Loading efficiency = Actual Drug Content in Microsponges X 100…….. (1)

Theoretical Drug Content: 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 microsponge obtained. Production Yield= Practical mass of Microsponges X 100…… (2)

Theoretical mass (Polymer+drug). (iv) Characterization of pore structure:-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. (v) Dissolution tests:-Dissolution release rate of microsponges can be studied by use of dissolution apparatus USP XXIII with a modified basket consisted of 5µm stainless steel mesh. 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.

(vi) Determination of true density:-The true density of micro particles is measured using an ultra-pycnometer under helium gas and is calculated from a mean of repeated determinations

(vii) Resiliency (viscoelastic properties):-Resiliency (visco elastic 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 [7,14-17] .

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[7] .

1. Microsponge for topical delivery: The Microsponge 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 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 [7,17].

2. Microsponge for oral delivery: In oral applications the microsponge system has been shown to increase the rate of solubilisation of poorly watersoluble 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[7],

3. 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[4-7] .

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 [7,18] .

Future Prospects: Microsponge drug delivery system holds a promising opportunity in various pharmaceutical applications in the upcoming future as it has unique properties like enhanced product performance and elegancy, extended release, improved drug release profile, reduced irritation, improved physical, chemical and thermal stability which makes it flexible to develop novel product forms. The real challenge in future is the development of the delivery system for the oral peptide delivery by varying ratio of polymers. The use of bioerodible and biodegradable polymers for the drug delivery is enabling it for the safe delivery of the active material. As these porous systems have also been studied for the drug delivery through pulmonary route which shows that these system can show effective drug release even in the scarce of the dissolution fluid thus colon is an effective site for targeting for drug release. These carriers also require to be developed for alternative drug administration routes like parenteral and pulmonary route. These particles can also be used as the cell culture media and thus can also be employed for stem cell culture and cellular regeneration in the body. Due to their elegance, these carrier systems have also found their application in cosmetics. These developments enabled researchers to utilize them variably. These novelties in formulation also open new ways for drug delivery [4].

CONCLUSION:

The microsponge delivery system is a unique technology for the controlled release of macroporous beads, loaded with active agent, offering a potential reduction in side effects, while maintaining their therapeutic efficacy. The microsponge drug delivery system offers entrapment of its ingredients and is believed to contribute toward reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility. Various studies have confirmed that microsponge systems

are non-irritating, non-mutagenic, non-allergenic, and non-toxic. Currently this technology is being used in cosmetics, over-the-counter skin care, sunscreens, and prescription products. This drug delivery technology may lead to a better understanding of the healing of several diseases. Hence, the microsponge-based drug delivery technology is become a valuable drug delivery for various therapeutic applications in the future.

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