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Review Article

Microsponge A Novel New Drug Delivery System: A Review

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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. Microsponge technology offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility. In addition, numerous studies have confirmed that microsponge systems are non-irritating, non-mutagenic, non-allergenic, and non-toxic. MDS technology is being used currently in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products. One of the best feature of microsponge is it is self-sterilizing. This review is focused on method of preparation, characterization and application of microsponge.

1. 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, 2, 3]. 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[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 [5, 6].

Defining Microsponge: 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 microsponges 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 /g and 2 pore volume range from 0.1 to 0.3cm /g. This results in a large reservoir within each 3 microsponge, which can be loaded with up to its own weight of active agent [7, 8, 9]. 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 procedures and those are applied to the cosmetic as well as over-the- counter (OTC) and prescription pharmaceutical products [7, 10]. At the current time, this interesting technology has been licensed to Cardinal Health, Inc., for use in topical products. The scanning electron microscopy of the microsponge particle reveals that its internal structure as the "bag of marbles". The porosity is due to the interstitial spaces between the marbles. The interstitial pores can entrap many wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, anti-infective and anti-inflammatory agents. These entrapped microsponges may then integrated or formulated into product forms, such as creams, lotions, powders, soaps, capsules and tablets. When these products are applied the entrapped material gets delivered to the skin in a controlled time release pattern or a pre-programmed manner through the use of several different 'triggers', rubbing or pressing the Microsponge after it has been applied to the skin, elevates skin surface temperature introducing solvents for the entrapped materials such as water, alcohol or even perspiration and controlling the rate of evaporation. Active ingredients entrapped in the porous polymeric structure display altered behaviour, with respect to their release, which is restricted and prolonged [7, 11].

Potential features or characteristic of microsponge drug delivery systems:

1. Microsponges show acceptable stability over pH ranging from 1 to 11 and at high temperatures (up to130°C).
2. Microsponges exhibit good compatibility with various vehicles and ingredients.
3. Microsponges have high entrapment efficiency up to 50 to 60%.
4. Microsponges are characterized by free flowing properties.
5. 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.
6. Microsponges are non-allergenic, non-irritating, non-mutagenic and non-toxic.
7. Microsponges can absorb oil up to 6 times their weight without drying [12, 13, 14, 15].

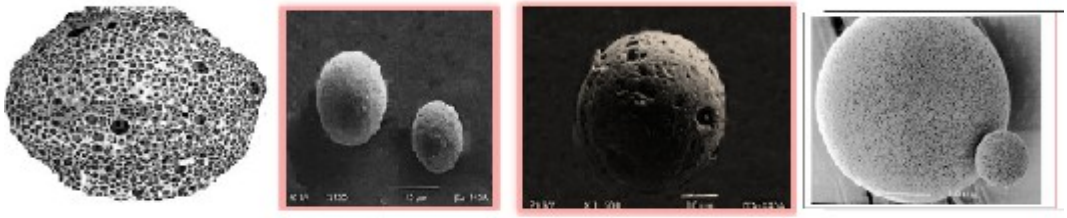
Benefit of microsponge drug delivery system:

1. Enhanced product performance.
2. Extended release.
3. Reduced irritation and hence improved patient Compliance.
4. Improved product elegancy.
5. Improved oil control as it can absorb oil up to 6 times its weight without drying.
6. Improved formulation flexibility.
7. Improved thermal, physical, and chemical stability.
8. Flexibility to develop novel product forms.
9. Microsponge systems are non-irritating, non-mutagenic, non-allergenic and non-toxic [4, 16].

Characteristics of actives moieties that is entrapped into microsponges:

1. Active ingredients that are entrapped in microsponge can then be incorporated into many products such as creams, gels, powders, lotions and soaps.
2. Certain considerations are taken into account while, formulating the vehicle in order to achieve desired product characteristics:
3. 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.
4. It should be inert to monomers and should not increase the viscosity of the mixture during formulation.
5. It should be water immiscible or nearly only slightly soluble.
6. It should not collapse spherical structure of the microsponges.
7. It should be stable in contact with polymerization catalyst and also in conditions of polymerization.
8. The solubility of actives in the vehicle must be limited.
9. If not, the vehicles will deplete the microsponges before the application.
10. Not more than 10 to 12% w/w microsponges must be incorporated into the vehicle in order to avoid cosmetic problems.
11. Payload and polymer design of the microsponges for the active must be optimized for required release rate for given period of time [17, 18]

Structure of microsponge:



Drug enclosed in microsponge drug delivery system [19-23]:

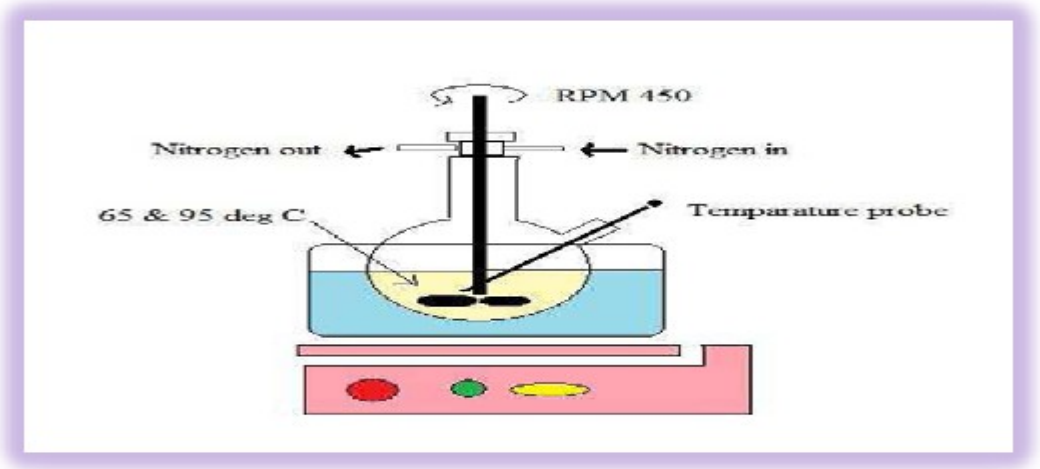
- Ketoprofen
- Benzyl peroxide
- Retinol
- Fluconazole
- Ibuprofen
- Tretinoin
- Trolamine

2. 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 physico-chemical properties of drug to be loaded.

1. 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 [1, 24-26].



2. 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^{o}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 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. [17, 27].

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 [7, 28].

Accelerated or Triggered by following mechanism [29, 30]:

(i)Pressure triggered systems

Microsponge releases the entrapped material when pressurized/rubbed.

(ii)Temperature triggered systems

It is possible to modulate the release of substances from the microsponge by modulation of temperature. That is viscous sunscreens were show a higher release when exposed to higher temperatures.

(iii)pH triggered systems

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

(iv)Solubility triggered system

Microsponges loaded with water-soluble ingredients will release the ingredient in the presence of water. Perspiration can trigger the release rate of active ingredients [29, 30].

Advantages over Conventional Formulations: 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 [31-34].

Advantages over Microencapsulation and Liposomes: The MDS has advantages over other technologies like microencapsulation and liposomes. Microcapsules cannot usually control the release rate of actives. Once the Wall is ruptured. The actives contained within microcapsules will be released. Liposomes suffer from lower payload, difficult formulation, limited chemical stability and microbial instability. While microsponge system in contrast to the above systems are stable over range of pH 1 to 11, temperature up to 130 ^{0}C ; compatible with most vehicles and ingredients; self-sterilizing as average pore size is 0.25 µm where bacteria cannot penetrate; higher payload (50 to 60%), still free flowing and can be cost effective [31-34].

Evaluation of Microsponge:

(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 [35-41].

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 [42].

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 [41-49].

2. 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[41-49].

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 [41-49].

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 [50].

3. Conclusion

The microsponge delivery 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. 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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