INTERNATIONAL JOURNAL OF DRUG DISCOVERY AND HERBAL RESEARCH (IJDDHR)
ISSN: 2231-6078
12(1):April-June : (2022), 46-50

Review Article

Microsponges Technology: Novel Approach for Topical Drug Delivery

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Abstract
Microsponges are polymeric delivery systems they made up of porous microspheres. They are small, round, sponge-like globular particles with a large porous surface. Microscopic scanning of fine needle-like particles showed that the internal structure was a "marble bag". Microsponges have high entrapment up to 50 to 60%, Stable in the pH range from 1 to 11, Stable up to 130°C temperature. Microsponges show many advantages over other technologies and delivery system like microsponges give better control of drug release than microcapsules and compare to liposomes microsponges have better chemical stability, higher load and easier formulation. Microsponges can be prepared by Liquid-Liquid Suspension Polymerization or Quasi-emulsion solvent diffusion method. Particle size determination, Scanning Electron Microscope study, loading efficiency, compatibility studies are used to characterize the microsponges. Drug can be released by sustained or timed release mechanism or by release on command such as temperature release, pH release. Microsponges are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to reduce side effects, enhance stability and modify drug release.

Keyword : Microsponges, Polymer, Nanoparticles

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 favorable 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. The outer surface is typically porous, allowing a sustained flow of substances out of the sphere. Microsponges are porous, polymeric microspheres that are used mostly for topical use and have recently been used for oral administration. 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.

Ideal Properties of MDS

1. The structure of the Microsponges should not collapse i.e., it should maintain its structure integrity.
2. It should have slightly soluble property in water.
3. It should be stable when in contact with the polymerization catalyst and under condition of polymerization.
4. It should not react with monomer used in the formulation.
5. MDS should not increase the viscosity of the mixture during formulation.
6. Microsponges having particle size of 10-25 µm in diameter.

Advantage of the MDS

1. MDS has stability over the wide range of pH from 1 to11.
2. MDS can withstand at high temperature up to 130 °C.
3. Loading efficiency of MDS is up to 60%.
4. MDS act as good adsorbent over the skin.
5. It will bypass first pass hepatic metabolism.
6. It will resist attack by moisture.
7. It will not undergo any unwanted reaction.
8. It can resist moderate oxidation & reduction.
9. MDS processes relatively longer half-life.

Characteristics Of Microsponge Based Delivery Systems

When a microsponge is applied topically, the release of bioactive compound to the skin is done with excellent efficacy and minimal irritation in response to stimuli such as temperature, rubbing or the pH effect. Microsponges have several characteristic features, e.g. they are stable over pH 1 to 11 range. Such formulations are thermostable and can withstand up to 130°C temperature. The presence of porous structure (pore size approx. 0.25µm) creates a self-sterilizing feature which prevents penetration of the bacteria. The particle spherical form provides a free-flowing property, improved compressibility and enhanced loading performance.[23]

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Evaluation of Microsponges:

1) **Particle size determination**: Particle size analysis of loaded and unloaded microsponges can be performed using laser light diffraction or other suitable methods. The value (d50) can be expressed as the average of the measured value over all formulations. To investigate the effect of particle size on drug release, the percentage of cumulative drug release from microsponges with different particle sizes is plotted against time. Particles larger than 30 µm can have a gritty appearance, so particles between 10 and 25 µm are used in final topical formulation.

2) **Scanning electron microscopy**: The processed microsponges can be plated with palladium-gold under argon atmosphere at normal room temperature and then the surface morphology of the microsponges can be confirmed using a Scanning Electron Microscope (SEM). SEM of damaged microsponge particles can also be used to describe the ultra-structure.

3) **Determination of loading efficiency**: The loading efficiency (%) of microsponges can be calculated according to the below equation:

Loading efficiency= $\frac{Actual\ drug\ \ content\ in\ \ microsponge}{Theoretical\ drug\ \ content} * 100$

4) **Determination of production yield**: 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 = $\frac{Practical\ \ mass\ \ \ of\ \ microsponge}{Theoretical\ mass\ (drug+polymer)} * 100$

5) **Determination of true density**: The true density of microsponges can be measured using an ultra-pycnometer under helium gas and is calculated from a mean of repeated determinations.

6) **Compatibility studies**: Compatibility of drug with reaction adjuncts can be studied by thin layer Fourier Transform Infrared spectroscopy (FT-IR) and chromatography (TLC). X-ray diffraction (XRD) and Differential Scanning Calorimetry (DSC) methods are used to investigate the effect of polymerization on crystallinity of the drug.

7) **Polymer/monomer composition**: Factors such as microsphere size, drug loading, and polymer composition govern the drug release from microspheres. Polymer composition of the microsponges drug delivery system can affect partition coefficient of the entrapped drug between the vehicle and the microsponge system and hence have direct influence on the release rate of entrapped drug. Plotting cumulative percent drug release against time can be used to investigate drug release from microsponge structures with various polymer compositions.

Drug Release Mechanisms:

These programmable parameters can be effectively controlled to create microsponge delivery systems that release functional substances over time in response to one or more external stimuli. The release mechanisms of this system are mainly as follows:

1) Sustained or Timed Release: In the development of sustained-release microsponges, various physical and chemical parameters of the entrained active ingredients, such as volatility, viscosity and solubility will be investigated, while for polymer microsponges pore diameter, volume, and resiliency of the polymer

microsponges are evaluated to give required sustained release effects.

2) Release on Command: Microsponges can be designed to release the given amounts of active ingredients over time in response to external stimuli.

a) Pressure Release: Microsponge system releases active ingredient when it is pressed or squeezed, this replenishes the quantity of entrapped active ingredient onto the skin. The amount of material released can also depend on the release of the sponge and the stability of the microsponges.

b) Temperature Release: The release of the active ingredients from the microsponges can be activated depending on the temperature. Active ingredients that linger a little at room temperature can be so thick that they cannot suddenly transfer from the microsponge to the skin. As the temperature of the skin rises, the flow rate is increased and thus release is also enhanced.

c) pH Release: An easier release of the pH-based active agent can be achieved by changing the coating of the microsponge.

d) Solubility: A microsponges filled with water-soluble substances such as antiseptics and antiperspirants releases substances in the presence of water. The discharge can also be activated by diffusion, taking into account the distribution coefficient of the material between the microsponge and the external system.

Preparation Methods of Microsponges

The process to be used to prepare microsponges mainly depends on the drug's physicochemical properties and its solubility characteristics with the polymer(s) used for encapsulation. Microsponges can be prepared by following two techniques based on the physicochemical properties of the drug that will be loaded.

Liquid–Liquid Suspension Polymerization:

In this step, the monomers are dissolved in an appropriate solvent along with the active ingredients and then surfactant, suspending agents, etc. is added as aqueous phase. Polymerization is triggered by introducing a catalyst or the temperature is raised. The polymerization process continues the formation of the spherical structure along with reservoir type of system. Finally the solvent is removed with spherical structures to obtain porous microsphere. When the medication is prone to polymerisation conditions, the two-step procedure should be utilized. Accordingly, the preparation of microsponges by this method involves following steps that are shown as flow chart in (Figure 2).

1. Selection of monomer or different monomers in combination. [4]
2. Polymerization will cause monomer chain formation.
3. Cross-linking between the monomeric chains will form ladders.
4. Spherical particles will be formed by folding the ladder.
5. Bunches of microspheres will be formed due to microsphere aggregation.
6. Bunches will further give rise to the formation of Microsponges.

Quasi-emulsion solvent diffusion

This technique involves two phases - internal organic phase and external aqueous phase. Internal phase generally consists of volatile solvents like ethanol, acetone or dichloromethane, while the external phase consists of aqueous PVA (polyvinyl alcohol) solution or water. Dichloromethane (20%) or TEC (Triethyl citrate) offers plasticity to the formulation. First, the internal organic phase polymer is dissolved in ethyl alcohol and drug is dissolved in this solution by ultrasonication at room temperature while the external phase consists of PVA solution in water. The solution is stirred and filtered for further use. The internal phase is mixed in external phase on mechanical stirrer dropwise. On continuous stirring, the Quasi emulsion droplets are formed which on further evaporation of organic solvent produces the solid microsponge cages. The obtained microsponge mixture is filtered to separate the microsponges and washing is done to obtain microsponges. Separated and washed microsponge is dried in a vacuum oven for 12hr at 40°C[4]

Table No 01: List of Marketed Products Using Microsponge Drug Delivery System

Product Name	Pharmaceutical Uses	Manufacturer
Aramis Fragrances	Soothes and cools the skin surface	Aramis Inc.
Benzoyl peroxide	Anti –Acne	Dermik Laboratories, Inc.
Murad Moisturing Cream	Moisturizer	Murad Inc
Neutrogena oil free Acne Face wash	Anti-Acne	Jhonson and Jhonson
Oil free matte block SPF 20	Sunscreen	Dermalogica
Retinol Cream	Maintain Healthy skin	Biomedic
Sports cream	Anti –Inflammatory	Embil Pharmaceutical Co.Ltd.
EpiQuin Micro	Hyper Pigmentation	Skin Medica Inc.
Micro Peel Plus /Acne Peel	Anti-wrinkles,softer and smooth skin	Biomedic

Applications of Microsponges as Drug Delivery Systems

Microsponges are often used for topical delivery as anti-fungal, anti-inflammatory, antizits, anti-ulcer, in the therapy of Acitinic keratoses and may be included in a variety of products such as creams, gel, lotion. The microsponge technique is also used in the engineering of bone as well as cardiac tissue. Microsponge technique is used to minimize skin irritation or inflammation and sensitization in the sunscreen [24, 25]. The detailed applications of microsponges are listed as under and some are listed in

Topical Application

Microsponges have been researched for delivery of dental, topical, and biopharmaceutical products (Figure 5). The formulator is accessible with a broad variety of alternatives for medication and cosmetic product production. Besides supplying active ingredients at small concentrations to the target site, microsponges exhibits improved efficacy, decreased side effects and adjusted product release. For example, Paeonol microsponges provides a safer solution to managing skin diseases than plain paeonol cream due to improved bioavailability, leading to decreased residence time of the product on the face. Furthermore, adverse effects are minimized as fewer formulation passes into bloodstream circulation. Similarly, Microsponges for acne therapy are effective in managing acne lesions and oiliness in patients receiving acne vulgaris treatment.[26]

Oral appilcation

The Microsponges compression property is remarkable since it varies from traditional microcapsules or solid powder mixtures owing to its matrix or sponge-like composition. The compressibility properties of microsponges are better than those of a physical drug mixture because of their sponge-like structure. A microsponge"s spongy feature contributes to plastic particle deformation; creating mechanically solid tablets. The rate of solubilization of bioactive compounds that are poorly water-soluble rises after being trapped in microsponges pores. In addition, the microsponges offer a safe environment and regulated medication release. It can be taken up by colonic macrophages due to its smaller size (< 200 µm), and localized drug action occurs at the desired site; therefore, microsponges is used for colon targeting. Similarly, Curcumin Microsponges with a gastro-retentive as floating microsponges offer improved site-specific absorption to combat gastric cancer. In vitro permeation of this curcumin microsponge across the matrix of gastric mucin gel shows the significant potential to transmit the medication through mucin and enter the intended site of gastric cancer as illustrated in

Occular Application

Many forms of anatomical and physiological barriers (e.g. various layers of cornea, retina, and sclera including both blood aqueous and blood retinal barriers and other barriers) that present

challenges to the delivery of a drug alone or in dosage form to the posterior of the eye.[27] Topical administration as an aqueous solution helps in the occular delivery of water-soluble drugs, whereas water-insoluble drugs can be administered topically as ointments or aqueous suspensions [28].

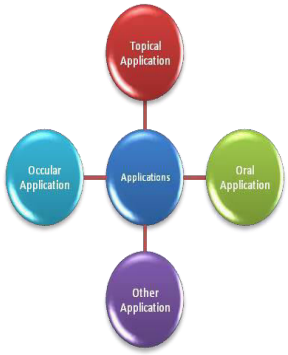
Other Applications Microsponges have developed as an innovative drug delivery method with applications that involve not only topical and oral distribution, but also production of siRNA and fibroblast growth factors. i. siRNA Delivery: In the field of modern therapeutics and pharmaceutical science, the delivery of siRNA by such a method can be used as transporting more than half a million copies of siRNA to a cell can be facilitated by taking one single RNAi-Microsponges. The Microsponges shows a high RNA load (15–21 wt %) that provides protection from degradation (Figure 8)[30,31]

ii. Fibroblast Growth Factor In processing Poly(DL-lactic-co-glycolic acid), a thin biodegradable hybrid mesh, three-dimensional culture of human skin fibroblasts has been successfully tested. In the opening of a PLGA knitted mesh, the preparation consisted of web-like collagen microsponges [32]. In addition, a type 1 collagen was intended to act as a reservoir of the basic fibroblast growth factor (bFGF). When the microsponge was introduced by intramuscular injection into a mouse model, dose-dependent angiogenic activity occurred via sponge matrix biodegradation. An increase in blood flow in the murine ischemic limb was detected, which was not accomplished by bolusinjection of bFGF .[33]

Fig 1Applications of Microsponges

Recent Advancements In Microsponge Drug Delivery System

In Microsponge technologies, pharmaceutical companies are



taking a step forward.Some of the marketed preparations and patented technologies (Table 2 and Table 3) [34-40]. Nowadays they are engaged in nanosponges, nanoferrosponges, and porous microbeads by changing the process. Such preparations are better and more durable than the microsponges.

Nanosponges: Nanosponges are the nanoformulations that are used in the delivery of topical drugs, particularly passive targeting of cosmetic agents. These are useful for skin absorption and extended retention within skin layer. These nanosponges have been developed by modifying the method of diffusion of the Solvent through either change in agitation, the amount of polymer and the emulsifier. Some researcher also showed that nanosponges are good carrier for the delivery of active ingredient which is available in gaseous form. These nanosponges carriers are also responsible for targeting cancerous cells.

Nao-ferrosponges: Nano-ferrosponges are nano targeting devices made up of ferric ions that can be triggered with the help of magnets. The magnet enforces the carrier to stimulate the deeper tissues and supply the drug at the specific target location. Such nano-ferrosponges were primed with polymers by co-precipitation of magnetic liquid. The prepared Nano-ferrosponges have high swelling index, excellent elasticity, hydrophilicity, and response to magnetism.

Porous Microbeads: Improved porous microsphere properties generate microbeads that have a wide number of pores. Technologies for polymerisation and cross-linking are used for the production of stable porous microbeads. These microbeads are used for the delivery of drugs to topical, buccal, and oral systems.

Conclusion

MDS holds significant potential in both pharmaceutical as well as cosmetic industries because of its release technique is novel and its ease of administration with fewer side effects, more research works are carried out to optimize its efficacy for the therapy. It is a unique technology for the sustained release of topical agents which act locally. It is originally developed for topical delivery of drug like anti-acne, antiinflammatory, anti-fungal, anti-dandruffs, antipruritics, and rubefacients. Microsponges delivery system that can release its active ingredient on stimuli. Therefore, a microsponge has got a lot of potential in drug delivery technology today.

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Neutrogena oil free Acne Face wash	Anti-Acne	Jhonson and Jhonson
Oil free matte block SPF 20	Sunscreen	Dermalogica
Retinol Cream	Maintain Healthy skin	Biomedic
Sports cream	Anti –Inflammatory	Embil Pharmaceutical Co.Ltd.
EpiQuin Micro	Hyper Pigmentation	Skin Medica Inc.
Micro Peel Plus /Acne Peel	Anti-wrinkles,softer and smooth skin	Biomedic

Fig No:2 Quasi-emulsion solvent diffusion method