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A review on Microsponges Drug Delivery System

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ABSTRACT: Microsponges are microscopic spheres with pores, known for their inert nature. These spheres typically range in size from 10 to 25 micrometers and are synthesized using the Quasi-emulsion solvent diffusion method, a specialized technique for controlled release formulations. Their unique structure allows for the controlled release of active drug ingredients, making them particularly valuable in topical drug products. By delivering drugs directly to the skin in a controlled manner, microsponges help minimize systemic exposure and reduce local skin reactions to active drugs. This review provides an overview of microsponge technology, covering its characterization, benefits, evaluation methods, and the mechanism behind its drug delivery system, including commercially available microsponge products.

Keywords: Microsponges, Quasi emulsion solvent diffusion method, porous particles

I. INTRODUCTION

The Microsponge Delivery System, a patented polymeric system, comprises porous microspheres resembling tiny sponges. These microspheres possess a multitude of interconnected voids within a non-collapsible structure, featuring a large porous surface facilitating controlled release of active ingredients. Ranging from 5 to 300 micrometers in diameter, these microsponges can contain up to 250,000 pores in a typical 25-micrometer sphere.[1]This system, characterized by highly cross-linked, porous, polymeric microspheres, effectively entraps a wide range of actives and releases them at a desired rate. Particularly beneficial for enhancing the performance of topically applied drugs, it stands out as a unique technology for controlled release of topical agents. Comprising micro-porous beads, typically 10-25 microns in diameter, loaded with active agents, its notable feature lies in its ability to adsorb or load a high degree of active materials into the particle and onto its surface. Additionally, this system may contribute to stability enhancement, reduction of side effects, and favorable modification of drug release.[2] The Microsponge Drug Delivery System offers the potential for heightened effectiveness of topically applied agents, coupled with improved safety, prolonged product shelf-life, and enhanced aesthetic characteristics, all achieved with optimal efficiency. [3-5]

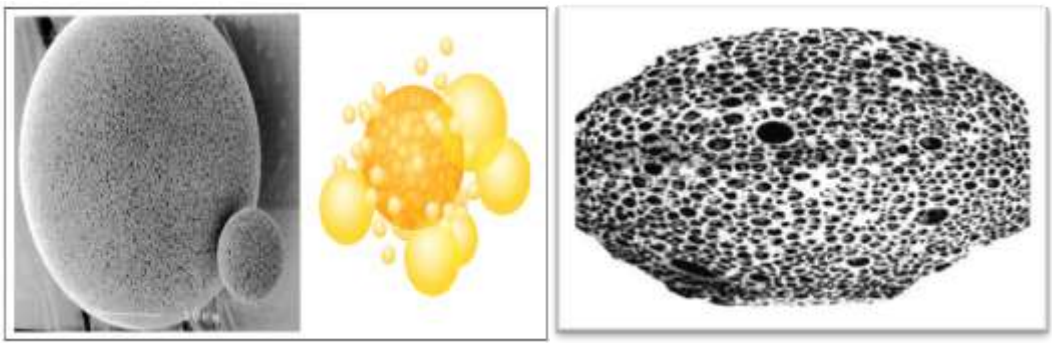

Figure 1: Microsponge

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HISTORY OF MICROSPONGE [6]

The microsponge technology was pioneered by Won in 1987, with the original patents assigned to Advanced Polymer Systems, Inc. This company extensively refined the technique, creating numerous variations applied to cosmetic, over-the-counter (OTC), and prescription pharmaceutical products alike.

CHARACTERISTICS[7]

- Microsponge formulations are stable across pH 1 to 11.
- They remain stable up to 130°C.
- Compatible with most vehicles and ingredients.
- Self-sterilizing due to 0.25µm pores.
- Offer a high payload (50-60%) and affordability.

FEATURE OF MICROSPONGES[8]

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

ADVANTAGES OF MICROSPONGES [9,10]

- Provides continuous action for up to 12 hours, ensuring extended-release.
- Enhances product elegance.
- Reduces irritation, improving patient tolerance and compliance.
- Improves treatment efficacy.
- Exhibits superior thermal, physical, and chemical stability.
- Non-irritating, non-mutagenic, non-allergenic, and non-toxic.
- Allows incorporation of immiscible products.
- Offers superior formulation flexibility.
- Compared to other technologies like microencapsulation and liposomes, microsponges boast wider chemical stability, higher payload, and easier formulation.
- Facilitates conversion of liquids into powders, simplifying material processing.
- Enables the development of novel product forms.
- Enhances drug bioavailability.
- Microsponges have the capacity to absorb oil up to six times their own weight without causing dryness.

II. RELEASE MECHANISM: [11]

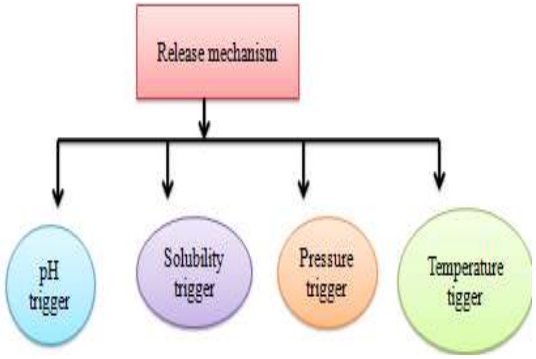

Figure 2: Programmable release from microsponge

pH - Triggered Systems:utilize modifications in the coating of microsponges to control the release of active substances based on pH levels. This approach finds diverse applications in drug delivery, offering tailored release profiles to meet specific therapeutic needs.

Solubility Triggered System:operates in such a way that when a microsponge is filled with water-soluble components, it releases these components when it comes into contact with water. The release rate of active ingredients can be expedited in the presence of an aqueous medium. Factors such as the solubility of the active in the external medium, concentration gradient, or the swelling ability of the microsponge network can all influence this release process.

Pressure Triggered Systems: When subjected to pressure or friction, the microsponge system releases the entrapped material, with the amount released dictated by the unique properties of the sponge. By adjusting the type of material used and

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various process variables, the microsponge best suited for a specific application can be optimized.

Temperature Triggered Systems: Certain active ingredients in microsponges may exhibit high density at room temperature, hindering their free flow into the skin. Increasing the skin temperature can enhance the flow rate, thereby promoting release. Thus, temperature adjustment serves as a means to regulate the release of substances from the microsponge.

III. METHOD OF PREPARATION OF MICROSPONGE DRUG DELIVERY SYSTEM:

Drug loading into microsponges can be achieved through either a single-step or a two-step process, which involves liquid-liquid suspension polymerization or quasi-emulsion solvent diffusion techniques, respectively. These methods are chosen based on the physicochemical characteristics of the drug intended for loading.

1) Liquid-liquid suspension polymerization: [12-14]

In the Liquid-liquid suspension polymerization method, porous microspheres are created through polymerization in liquid-liquid systems. The process begins by dissolving monomers and active ingredients in a solvent solution of monomers. This mixture is then dispersed into an aqueous phase containing additives such as surfactants and suspending agents. Polymerization is initiated by introducing a catalyst, increasing temperature, or using irradiation.

The steps involved in the preparation of microsponges can be summarized as follows:

- Selection of monomer or combination of monomers
- Formation of chain monomers during polymerization initiation
- Formation of ladders through cross-linking between chain monomers
- Folding of monomer ladders to form spherical particles
- Agglomeration of microspheres, leading to the formation of clusters
- Binding of clusters to form microsponges

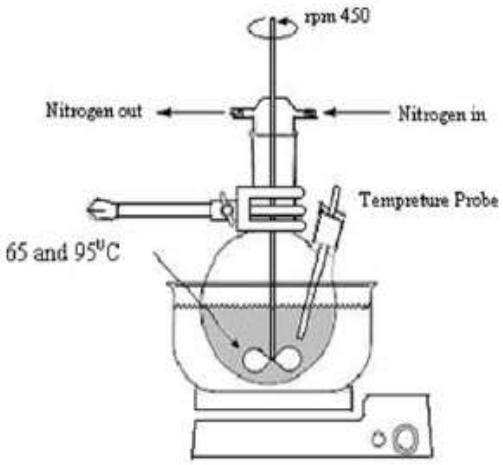

Figure 3: Method of liquid-liquid suspension polymerization

2) Quasi-emulsion solvent diffusion: [15-17]

The Quasi-emulsion solvent diffusion method is a two-step process used to prepare microsponges by employing different amounts of polymer. Initially, the inner phase is prepared by dissolving Eudragit RS 100 in ethyl alcohol, followed by the addition of the drug and dissolution under ultrasonication at 35°C. This inner phase is then poured into a polyvinyl alcohol (PVA) solution in water, serving as the outer phase. After 60 minutes of stirring, the mixture is filtered to separate the microsponges.Following this, the microsponges undergo drying in an air-heated oven set at 40°C for a duration of 12 hours, after which they are weighed to ascertain the production yield.

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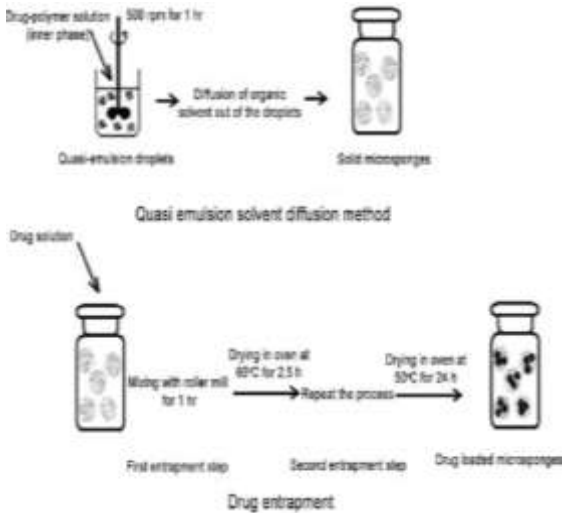

Figure 4: Method of quasi-emulsion solvent diffusion

IV. EVALUATION PARAMETERS OF MICROSPONGES

1) Particle size determination:involves utilizing techniques such as laser light diffractometry to analyze the particle size of both loaded and unloaded microsponges. The obtained values can be expressed across all formulations and size ranges. To evaluate the influence of particle size on drug release, the cumulative percentage of drug release from microsponges with different particle sizes is graphed over time. It is preferred to use particles ranging between 10 and 25 µm in the final topical formulation, as particles larger than 30 µm may cause a gritty sensation.[18]

2) Scanning electron microscope study: For examining morphology and surface topography, prepared microsponges undergo gold palladium coating under an argon atmosphere at room temperature. Subsequently, scanning electron microscopy (SEM) is employed to study the surface morphology of the microsponges. SEM images of fractured microsponge particles can also be captured to analyze their ultrastructure.[19]

3) Determination of loading efficiency and production yield: To ascertain loading efficiency and production yield, the loading efficiency (%) of the microsponges is computed utilizing the following equation:[20]

$$\text{Loading efficiency} = \frac{\text{Actual Drug Content in Microsponge} \times 100}{\text{Theortical Drug Content}}$$

4) Production yield: The production yield of the micro particles is determined by accurately measuring the initial weight of the raw materials and the final weight of the obtained microsponge.

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

5) Determination of true density: To determine the true density of Microsponges, an ultra-pycnometer is utilized under helium gas, and the value is calculated from the mean of repeated determinations.

6) Compatibility studies: The compatibility of the drug with reaction adjuncts is investigated through thin layer chromatography (TLC) and Fourier Transform Infrared spectroscopy (FT-IR). Additionally, the impact of polymerization on the crystallinity of the drug is analyzed using powder X-ray diffraction (XRD) and Differential Scanning Calorimetry (DSC).[21]

7) Polymer/monomer composition: The release of drugs from microspheres is influenced by factors such as microsphere size, drug loading, and polymer composition. The polymer composition of the Microsponge Drug Delivery System (MDS) can impact the partition coefficient of the entrapped drug between the vehicle and the microsponge system, thus directly affecting the release rate of the entrapped drug. To study the release of drugs from microsponge systems with different polymer compositions, cumulative percentage drug release can be plotted against time.[22]

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TABLE 1: LIST OF MARKETED PRODUCTS USING MICROSPONGE DRUG DELIVERY SYSTEM: [23]

Product name	Content	Manufacturer
Retin-A-Micro	0.1% and 0.04% Tretinoin, methyl methacrylate/ glycol dimethacrylate, Aqueous gel base	Biomedic, Sothys
NeoBenz®Micro	Benzoyl peroxide, methyl methacrylate/glycol	Intendis Inc. Morristown NJ07962 USA
Salicylic Peel 20	Salicylic acid 20%	Biophora
Salicylic peel 30	Salicylic acid 30%,	Biomedic

APPLICATIONS OF MICROSPONGES AS DRUG DELIVERY SYSTEM

Microsponges find extensive applications in topical and, more recently, oral administration, as well as in biopharmaceutical delivery. Various uses, both proven and under research, highlight their versatility.

1. Microsponges loaded with silver sulfadiazine were formulated using the water-in-oil-in-water Quasi-emulsion solvent diffusion method for burn wound therapy. These loaded microsponges were then incorporated into a gel base, effectively enhancing the drug's efficacy by reducing cytotoxicity towards keratinocytes and fibroblasts while maintaining antimicrobial properties. This approach demonstrates the potential of microsponges to improve the delivery of silver sulfadiazine to burn wounds while minimizing cytotoxicity towards host cells.[24]
2. Microsponges loaded with Eberconazole nitrate for antifungal purposes were synthesized using the Quasi-emulsion solvent diffusion method. These microsponges, upon dispersion in a gel, underwent an in-vivo skin deposition study, revealing a fourfold increase in retention within the stratum corneum layer compared to a commercial cream.[25]
3. Microsponges loaded with Retinoic acid for treating acne were developed and evaluated for drug release and anti-acne efficacy. The results indicated statistically significant reductions in both inflammatory and non-inflammatory lesions when tretinoin was encapsulated within the microsponge.
4. For targeting rheumatoid arthritis in the colon, controlled delivery of flurbiprofen was achieved using a commercial Microsponge® 5640 system. In vitro studies demonstrated that compression-coated colon-specific tablet formulations initiated drug release after 8 hours, aligning with the arrival time at the proximal colon. This was attributed to the enzyme addition, resulting in a modified release pattern. Conversely, colon-specific formulations prepared by pore plugging the microsponges exhibited increased drug release for 8 hours, coinciding with the enzyme addition.[26]
5. Microsponges containing stable acetazolamide were effectively prepared using the Quasi-emulsion solvent diffusion technique. Ex-vivo studies demonstrated that the in-situ gel formulation of acetazolamide microsponges could be utilized for topical ocular administration in the treatment of glaucoma, offering a method to avoid systemic side effects associated with oral acetazolamide.[27]
6. A topical gel formulation of 5-Fluorouracil (5-FU) loaded microsponges was developed for the treatment of skin cancer, aiming for enhanced skin deposition and reduced skin irritation potential. Brunauer-Emmett-Teller analysis revealed higher surface area and pore volume of the developed microsponge formulation. The optimized formulation exhibited improved thixotropic and texture properties compared to a commercial cream formulation used as a control. Moreover, an in-vivo local bioavailability study demonstrated a 5.5-fold increase in skin deposition with significantly reduced skin irritation compared to the commercial formulation. Therefore, the microsponge-based formulation presents a promising alternative for enhanced topical delivery of 5-FU compared to existing commercial formulations.[28]

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Applications of Microsponge Systems:

Microsponges have been designed with the aim of effectively delivering pharmaceutical active compounds at reduced doses, all while enhancing stability, mitigating adverse effects, and controlling the release of drugs.These porous, polymeric microspheres are primarily utilized for topical applications, although recent advancements have extended their use to oral administration.[29]

Table 2: APPLICATION OF MICROSPONGE

Active agents	Applications
Sunscreen	Improve efficacy and protection against sunburns and sun related injuries
Anti-inflammatory e.g. Hydrocortisone	Long lasting activity with reduction of skin allergic response
Anti-dandruffs e.g. Zinc pyrithione, selenium sulfide	Reduced unpleasant odor with lowered irritation with extended safety and efficacy
Anti-acne e.g. Benzoyl peroxide	Maintained efficacy with decreased skin irritation and sensitization
Anti-fungal	Sustained release of actives

Table 3: EXAMPLES OF MICROSPONGE DRUG DELIVERY WITH THEIR FORMULATIONS [30-32]

Microsponge Delivery Systems	Drug	Disease
Gels	Benzoyl peroxide Fluconazole Mupirocin Diclofenac sodium Acyclovir Hydroxyzine HCl Terbinafine HCl	Benzoyl peroxide Inflammation Antibacterial activity Inflammation Viral infections Urticaria and atopic dermatitis Anti-fungal
Lotions	Benzoyl Peroxide	Anti-Acne Treatment
Creams	Hydroquinone and Retinol	Melanoma
Tablets	Indomethacin Paracetamol Chlorpheniramine maleate Ketoprofen Fenofibrate Meloxicam	Inflammation Anti-pyretic Hay Fever Musculoskeletal Pain Gout Arthritis
Injection	Basic fibroblast growth factor	Growth factor

V. CONCLUSION

The microsponge delivery system represents a groundbreaking technology for controlled release, utilizing macroporous particles loaded with active ingredients. Notably, microsponges offer the potential to decrease side effects while maintaining therapeutic efficacy. When combined with innovative development strategies and inventive formulation techniques, the microsponge delivery system emerges as a promising solution for the Pharmaceutical and Cosmetic industries of the future. With added benefits over conventional topical dosage forms, microsponges present a novel approach for the treatment of tropical diseases, offering controlled release capabilities for topical, oral, and biopharmaceutical drug delivery. As a result, microsponges hold immense potential and offer a wide scope for the development of sustained-release topical formulations.

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