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Microsponge Technology: A Promising Approach for Targeted Topical Drug Delivery

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ABSTRACT

In recent years, pharmaceutical companies have focused on controlled-release dosage forms, including solid, semi-solid, and topical preparations, due to their improved efficacy and better patient acceptance. However, transdermal drug delivery systems face challenges for compounds intended for skin application. Traditional topical treatments often have drawbacks such as unpleasant odors, greasiness, and skin irritation. In some cases, topical treatments do not achieve sufficient systemic circulation concentrations. The advent of microsponges has addressed these challenges in the field of pharmaceutical research. Microsponges, with particle sizes ranging from 10 to 25 microns, offer significant entrapment and controlled release of multiple components in a single system. These polymeric delivery systems consist of sponge-like spherical particles with porous surfaces that release drugs in response to external stimuli such as pH, temperature, or friction. Topical and oral drug delivery is possible with micro-sponges. This review explores the potential of microsponges for various applications, including oral, topical, and antifungal therapies, and highlights their advantages, limitations, and release mechanisms. It also discusses recent advancements and prospects in this field. Microsponge technology holds promise for the development of safer and more effective medications, including its use in cosmetics, skincare, sunscreens, and prescription products. The review also covers the essential aspects of microsponges, including particle size, entrapment efficacy, drug content, dissolution tests, and compatibility studies.

Keywords: Microsponges, Microsphere, Novel drug delivery, Oral, Transdermal

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Introduction

In recent years, the field of drug delivery has seen significant innovation, with an increasing focus on developing technologies that offer high therapeutic efficacy and patient acceptance. As the demand for effective drug delivery systems grows, there is a rapid evolution in this field [1]. The healthcare system stands to benefit from advanced delivery mechanisms that can precisely regulate the release of medications and target specific areas within the body [2]. Drug delivery systems are increasingly being used to improve the effectiveness and cost-efficiency of treatments. Traditional methods fall short when it comes to delivering therapies like peptides, proteins, and DNA-based treatments [3].

Traditional topical medications usually act on the outer layers of the skin, releasing their active ingredients upon application. This leads to a highly concentrated layer that is quickly absorbed, but this method can cause issues like greasiness and stickiness, which can negatively impact patient adherence. Moreover, these conventional

treatments often require repeated application due to their short duration of action, leading to overmedication for brief periods, followed by long durations of treatment [4].

The rapid advancements in drug delivery technology have paved the way for new systems that modify the release rate and target medications to specific areas of the body, improving both therapeutic effectiveness and patient acceptance. The challenge for pharmaceutical companies lies in controlling the release rate of active ingredients to targeted regions. Microsponge technology has emerged as a solution to these challenges, offering a controlled and long-lasting release of drugs, minimizing irritation, and maintaining effectiveness [5].

The micro-sponge delivery system (MDS) is a porous, interconnected polymer system made up of microspheres with pores that can entrap a wide range of active pharmaceutical ingredients. These ingredients are then delivered to the skin layers over time in response to a stimulus. The diameter of these microspheres typically ranges from 10 to 25 microns. The flexibility of microsponge polymers allows for the incorporation of various active ingredients while enhancing product potency, safety, stability, and effectiveness in skin treatments [6].

While transdermal delivery systems (TDS) have improved the efficacy and safety of many drugs, they are not suitable for delivering materials intended to remain within the skin itself. Therefore, a technology that extends the duration of active ingredients at the skin's surface while reducing transdermal absorption is necessary [7, 8]. Microsponge systems, with their highly porous and spherical polymer structure, provide this solution. These systems minimize adverse effects, improve safety, and significantly enhance drug delivery. The MDS is a patented system of solid-phase porous microspheres that can entrain a wide variety of substances before being incorporated into various products, such as gels, creams, liquids, or powders [9].

Microsponges are an efficient way to deliver active pharmaceutical ingredients to targeted regions at lower concentrations, which reduces systemic degradation. These devices can be used as local carriers for various active compounds, including emollients, fragrances, flavoring oils, sunscreens, and anti-infectives, and are found in skincare products, lotions, and powder formulations [10-12]. The MDS offers a promising solution to boost the efficacy of topical treatments while enhancing their safety, stability, and cosmetic qualities [5].

The microsponges range in size from 5 to 300 µm in diameter, containing up to 250,000 pores per sphere. Designed to deliver pharmaceutically active substances efficiently at low doses, microsponges help minimize side effects, improve stability, and modify the drug release profile. Each microspong has a substantial reservoir capable of holding up to its weight in active ingredients [13, 14]. These non-folding structures with porous surfaces allow for the gradual release of active compounds. The average porous length of the microsponges may extend up to approximately 10 feet, with the pore volume equivalent to about 1 millimeter per gram. When applied to the skin, the MDS releases its active components gradually, responding to external stimuli like rubbing, temperature, and pH [12].

This microspong technique was invented by Won in 1987, and the original patents were granted to Advanced Polymer Systems, Inc. [15]. The company introduced several aspects of the technology, which were used in beauty products, over-the-counter (OTC) items, and prescription medications. Cardinal Healthcare, Inc. received permission to apply this technology to the skin. Scanning electron microscopy (SEM) reveals the microspong's structure, resembling a "bag of marbles," with intercellular gaps that provide the porosity. These gaps absorb a variety of substances, including sunscreens, fragrances, emollients, essential oils, and anti-infective agents [16]. Microsponges typically range from 5 to 300 µm in diameter, with the size depending on fluidity. A 25-micron sphere often contains up to 250,000 pores and 10-foot-long interior micropores, giving it a pore volume of about 1 ml/g. This large reservoir allows the microsponges to carry substantial amounts of active agents. Since microsponges are intended to be retained by the epidermis, they must be applied topically, making them safe. Bacteria with pore diameters ranging from 0.007 to 0.2 µm cannot pass through the microspong's structural frame due to the small pore size [6, 12, 17].

Microsponges can store significant amounts of active ingredients both on and within the particle's surface. They stand out from other dermatological delivery systems due to their capacity to trap actives up to three times their weight. The appeal of this technology lies in its ability to release active substances slowly over time, unlike traditional topical formulations, which can lead to rapid absorption of the active compounds and potential overmedication. Traditional skincare products typically focus on the surface layer of the skin, and their active ingredients, though effective, are quickly absorbed, sometimes resulting in unwanted side effects like redness. The microspong system aims to slow down the release of active ingredients, potentially reducing adverse effects while maintaining therapeutic efficacy [12].

This review explores the potential of microsponges for various applications, including oral, topical, and antifungal treatments, highlighting their benefits, limitations, and release mechanisms. It also discusses recent advancements and prospects in this area.

Results and Discussion

Advantages of micro-sponge drug delivery systems

- Microsponges are capable of absorbing up to six times their weight in oil, eliminating the drying process typically required.
- They offer sustained-release properties, ensuring active ingredients remain effective for up to 12 hours.
- These systems improve formulation purity, ensuring that the final product remains stable, potent, and safe.
- By reducing discomfort and enhancing tolerance, microsponges promote better patient adherence and overall therapeutic effectiveness.
- Microsponges are stable across a range of temperatures and environments, showing thermal, physical, and chemical resilience [18].
- They are non-toxic, non-allergenic, non-irritating, and do not cause mutations.
- Micro-sponge systems allow for the incorporation of immiscible substances, expanding formulation options.
- Compared to methods like microencapsulation or liposomes, MDS offers a wider range of chemical stability, higher dosages, and easier formulation [18].
- Liquids can be efficiently converted into powders, optimizing material processing.
- MDS can be used to develop more diverse and innovative product forms [19].
- This technology is also beneficial in enhancing the bioavailability of drugs.

Key features of micro-sponge drug delivery systems

- Micro-sponge formulations are stable within a broad pH range of 1 to 11 [20].
- They maintain stability up to temperatures as high as 130 °C [21].
- Micro-sponge preparations are compatible with various mediums and ingredients [22].
- With particles measuring 0.25 μm, the microsponges prevent microorganisms from passing through, ensuring a self-disinfecting feature [23].
- The technology shows a high rate of success in development (50–60%), making it a cost-effective approach [24].

Characteristics of active compounds encapsulated in micro-sponges

- Active ingredients trapped within microsponges can be incorporated into a variety of formulations, including creams, gels, lotions, powders, and soft soaps [25].
- During the production process, several factors are considered to meet the required quality standards.
- Active compounds should either be highly soluble within the polymer or able to become fully soluble with minimal addition of a water-resistant solution [26].
- The active ingredients should be inert, ensuring they do not affect the consistency of the final product.
- The ingredients must be insoluble in water or easily mixed with it.
- The microsponges should retain their spherical shape without collapsing.
- The structure should be stable even when exposed to polymerization catalysts and conditions.
- Active ingredients should have limited solubility in the preparation medium.
- The design and content of the microsponges should be optimized to ensure a controlled and effective release rate over time [27].

Advantages over other formulations

Microsponges offer distinct advantages compared to other widely available formulations:

1. *Conventional topical formulations:* Traditional topical treatments target the surface layer of the skin, releasing all active ingredients upon application. These formulations result in a concentrated layer of active ingredients that are quickly absorbed, leading to an excess of components in the epidermis and dermis. This rapid absorption can cause irritation and discomfort. In contrast, the micro-sponge delivery system (MDS) can

reduce these adverse effects. For example, microsponges containing benzoyl peroxide allow for gradual release, ensuring high efficacy while minimizing irritation by gently spreading the active ingredient on the skin [5].

2. *Microencapsulation and liposomes:* Microencapsulation and liposomes also offer controlled drug delivery, but with limitations. Microcapsules do not regulate the release rate of the active substance; once the capsule's wall ruptures, the contents are released all at once. Liposomes, while effective, are smaller in size, complex to prepare, chemically unstable, and prone to microbial degradation [5]. In comparison, microsponges offer more control over the release and greater stability.
3. *Ointments:* Ointments, known for their greasy, viscous nature, are not always cosmetically appealing, and patients often find them difficult to use. They require large amounts of active ingredients to be effective, which can lead to irritation and sensitization. Additionally, ointments often have unpleasant odors, cause excessive evaporation of active ingredients, and may suffer from drug-vehicle incompatibility. Microsponges, however, help prolong the presence of active ingredients on the skin's surface, enhancing the efficacy of the treatment while minimizing discomfort.

Preparation of microsponges

The preparation of microsponges depends on the physical and chemical properties of the active ingredients involved. Drugs can be incorporated into the microsponges through a process involving a porogen, which forms the porous structure. A porogen is a single-phase drug that neither prevents nor promotes polymerization, and it is free of free radicals [28]. This method allows for controlled drug encapsulation and release, ensuring the stability and effectiveness of the active components in the formulation.

Liquid-liquid suspension polymerization

The method of preparation of microsponges by liquid-liquid suspension polymerization is presented in **Figure 1**.

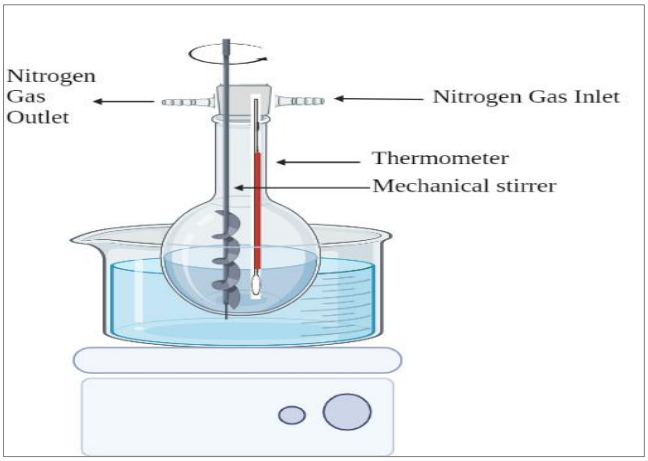

Figure 1. Method of preparation of microsponges by liquid-liquid suspension polymerization

Preparation of microsponges

Microsponges are created using different techniques, the most common of which are suspension polymerization and quasi-emulsion solvent diffusion.

1. Suspension polymerization: In this process, insoluble polymers are dissolved in a monomer solution that includes nonpolar active ingredients [29]. This mixture is then added to an aqueous phase with surfactants or suspending agents to stabilize the suspension. The polymerization is triggered by temperature changes, radiation, or catalysts. Commonly, styrene or methyl methacrylate are used in the process, which occurs in a round-bottom flask [30, 31]. The nonpolar drug solution is mixed into the monomer phase, and dispersion agents help maintain the suspension. The polymerization results in the formation of microsponges, with the active substance incorporated into the polymer during or after the polymerization process.

The process can involve replacing a porogen (a substance that forms the pores in the microsponges) during polymerization. The porogen is replaced by the active substance, leading to the creation of reservoir-type structures. After polymerization, the liquid is removed, finalizing the microsponges' structure [11, 32, 33].

2. Quasi-emulsion solvent diffusion: The quasi-emulsion solvent diffusion method creates microsponges through a two-step process [10]. Initially, a drug is mixed with a polymer solution in an ideal solvent. This solution is then dispersed into a less ideal solvent, causing emulsification, where the drug crystallizes inside the particles. The affinity of the drug for the soluble solution ensures it diffuses into the poor solvent, forming emulsified particles [34].

The second step involves mixing the polymer and drug solution into an external aqueous phase, containing plasticizers and porogens. The mixture is stirred for several hours to ensure proper dispersion. The microsponges are then filtered, washed, and dried in an oven at 50 °C to remove residual solvents and finalize the product [35-37].

These techniques result in microsponges with controlled drug release, allowing for more stable and prolonged therapeutic effects. The processes are designed to optimize the incorporation of active ingredients into the polymer matrix, ensuring sustained release and minimizing potential side effects **(Figure 2)**.

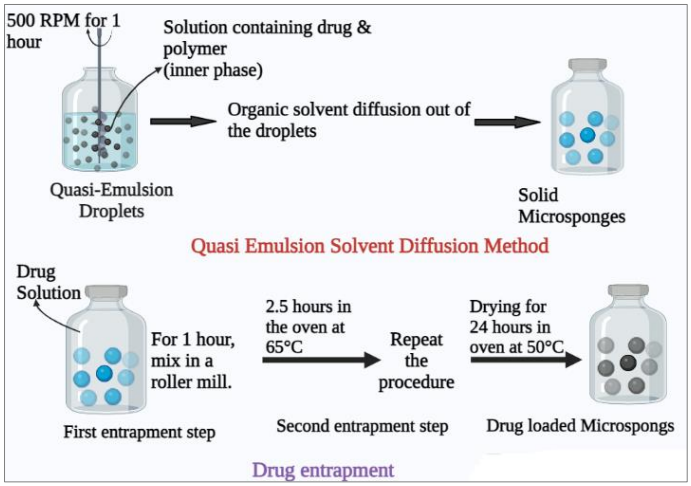

Figure 2. Method of preparation of microsponges by quasi-emulsion solvent diffusion method

Water-in-oil-in-water (W/O/W) emulsion solvent diffusion

This innovative method forms biodegradable porous microspheres by creating a double emulsion. The process begins by dispersing emulsifying agents like span, polyethyleneimine, and stearyl amine into an organic polymeric solution. The water phase is emulsified into the oil phase, resulting in a water-in-oil (W/O) emulsion. This is then added to an aqueous phase with polyvinyl alcohol (PVA), resulting in a W/O/W emulsion. This technique is useful for encapsulating both aqueous and oil-soluble drugs, as well as thermosensitive substances like proteins [38]. Xanthan gum has also been used by researchers to stabilize the W/O emulsion [5].

Porogen addition

In this variation, the W/O/W emulsion incorporates a porogen, such as hydrogen peroxide (H2O2) or sodium bicarbonate (NaHCO3), into the interior water phase. The porogen is dispersed in the polymeric solution, and the mixture is transferred into an aqueous phase containing PVA. The emulsion is then activated with a catalyst, and after evaporation of the organic solvents, the microparticles are formed. The inclusion of hydrogen peroxide produces evenly distributed pores ranging from 5 to 20 micrometers in size [39].

Oil-in-oil emulsion solvent diffusion

This method contrasts with W/O/W emulsions by using an oil-in-oil (O/O) system. The internal phase is a volatile organic solvent, such as dichloromethane, while the external phase consists of fixed oil and dichloromethane mixed with sorbitan trioleate. The internal phase is gradually added dropwise into the external phase while stirring continuously, allowing the organic solvent to evaporate. This technique has been successfully employed to create hydroxyzine HCl-loaded microsponges using acetone and liquid paraffin as solvents [40, 41].

Lyophilization

Lyophilization is commonly used to transform microspheres into porous forms. The microspheres are initially incubated in a chitosan hydrochloride solution and then freeze-dried. The rapid evaporation during lyophilization creates pores within the microspheres. While this method is efficient, it can result in damaged or collapsed micro-particles due to the quick removal of solvents [42].

Vibrating orifice aerosol generator (VOAG) method

This technique was first used to synthesize lipid-bilayered mesoporous silica particles. In the VOAG method, porous particles are formed through the evaporation-driven surfactant templating process in microdroplets. A tetraethylorthosilicate stock solution is mixed with a surfactant-containing solvent to form monodisperse droplets. These droplets are used to create microspheres, which are then encapsulated in liposomes for targeted delivery of active substances to specific areas of the body [43].

Ultrasound-assisted production

This method is used to create nanosponges with β-cyclodextrin (beta-CD) as the monomer and diphenyl carbonate as the cross-linking agent. The mixture undergoes sonication and heating to control the microparticle size. After cooling, the mixture is crushed into coarse particles, which are washed with distilled water and ethanol. Although effective in producing cross-linked β-CD microparticles with a porous structure, this method may leave residual cross-linking agents, which can be harmful **(Figure 3)** [44].

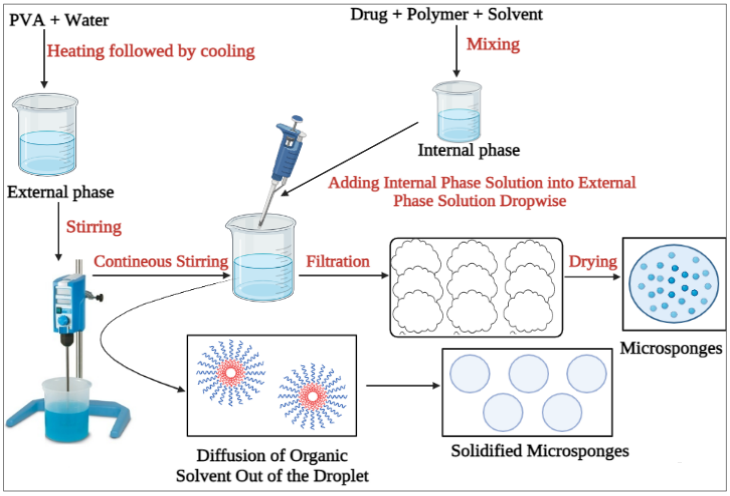

Figure 3. Ultrasound-assisted microsponge method

Electrodynamic atomization method

Pancholi *et al*. [39] introduced the electrodynamic atomization method to create porous chitosan microspheres. The process begins by sonicating a chitosan solution to generate bubbles. This bubble suspension is then collected into a syringe and transferred through a steel capillary using a syringe pump. The atomization process occurs electro-hydrodynamically. The capillary diameter is chosen to ensure that the bubbles in the suspension are retained during passage. The applied voltage in the solution is determined solely by the chitosan content. Except for the highest concentration, which proved difficult to electrospray, the combination of flow rate and voltage typically leads to a stable cone-jet mode. For cross-linking, a 4% w/v NaOH aqueous solution is used to solidify the chitosan microspheres [45].

While various methods for fabricating microsponges exist, each comes with its own set of advantages and limitations, summarized in **Table 1**.

Micro-sponge safety testing methods

Several tests can be performed to ensure the safety of micro-sponges, including:

- Eye irritation: Conducted in rabbits to assess the potential for irritation.
- Skin irritation: Tested in rabbits to determine any adverse skin reactions.
- Bacterial mutagenicity: To evaluate whether the micro-sponges have any mutagenic effects.

- Oral toxicity: Tested on rats to examine potential toxic effects when ingested.
- Allergenicity: Assessed in guinea pigs to check for allergic reactions [46].

Table 1. Advantages and disadvantages in preparation of microsponges

Method	Advantages	Disadvantages
Liquid-liquid suspension polymerization	Can easily convert between one-step and two-step drug entrapment methods.	Residues of undissolved monomers and solvents may remain. The structure may not be uniform. Reactions with monomers take a long time. Requires a two-step process for heat-sensitive drugs with low drug loading.
Quasi-emulsion solvent diffusion	No trapping of monomers. Minimal solvent residue. High drug loading. Medication remains isolated from the environment. Stirring can easily control microspore size.	Cannot be used for water-soluble drugs. Monomer reaction takes time. Requires a volatile, water-soluble solvent that can dissolve the drug.
W/O/W emulsion solvent diffusion	Effective for loading water-soluble drugs and entrapping proteins/peptides.	Uses water-insoluble surfactants, which may leave residues in microspores.
Addition of porogen	Produces well-dispersed and interconnected pores in the structure.	The structure may be disturbed during the process.
O/O emulsion solvent diffusion	No surfactant residues were detected in the microspores.	Requires extensive rinsing to remove organic solvent residues.
Lyophilization	Simple, fast, and reproducible results.	Microparticles may break or shrink during the process.
VOAG method	Produces microspores suitable for targeted drug delivery.	Requires gastric reflux for effective use.
Ultrasound-assisted production	No solvent residues. Predictable results.	Results in irregular structure. Requires the use of potentially hazardous cross-linking agents.
Electrohydrodynamic atomization	Easy to produce results.	Pharmaceutical composition may bond to the monomer. Controlling particle and pore size requires expertise.

Polymers and formulation aid in microsponges

Various polymers such as Eudragit RS-100, Eudragit RSPO, Eudragit, poly lactide-co-glycolic acid, polylactic acid, polyvinyl benzene, and polyhydroxybutyrate have been explored for the development of oral microsponges. Among these, Eudragit RS-100 is the most commonly used polymer due to its versatility, allowing researchers to utilize it in diverse applications. Eudragit RSPO is known for its ability to control drug release and improve drug solubility by forming a solid dispersion-like structure, making it ideal for developing colon-targeted microsponges. These microsponges are stable at lower pH levels but release their contents at the higher pH of the colon [47-49].

Polylactide-co-glycolic acid and polylactic acid have been studied for delivering proteins and peptides. The hydrophobic nature of these polymers prevents the molecules from interacting with the liquid vehicle, which allows the microsponges to float. This characteristic makes these polymers suitable for creating floating microsponges [48-50].

The use of a variety of polymers in microsponges highlights the adaptability of the preparation process to meet specific needs. Researchers have also utilized triethyl citrate as a plasticizer in the combination of polymers and active compounds to stabilize the microsponges' structure. Additionally, when using the quasi-emulsion solvent diffusion method to prepare microsponges, an emulsifier is essential to maintain the viscosity of the liquid medium. Studies have shown that cellulose ethers and polyvinyl alcohol (PVA) can serve as emulsifiers, with PVA being the preferred choice [48, 51, 52].

Drug release mechanism

The mechanism of drug release involves the movement of the active ingredient through the droplets and medium until equilibrium is achieved. As the medium becomes saturated, microsponges release their contents through their free structure (as they are not enclosed by a continuous membrane). The active substance will diffuse through the medium and into the skin layers as the vehicle dries and disperses the active compound. Once the formulation is applied to the skin, the active ingredient in the liquid medium is gradually released through the skin layers,

reducing the liquid medium and disrupting the equilibrium. The microsponges that remain on the stratum corneum surface provide controlled, long-term drug release [51-54].

This proposed mechanism emphasizes the importance of developing effective vehicles for microsponges that ensure sustained release of the entrapped drugs. Micro-sponge-based topical formulations can take the form of gels, creams, or lotions. When applied to the skin, the active ingredients are released from the microsponges into the surrounding medium and then absorbed by the skin. The release rate of the active compounds can be controlled by various stimuli, such as pressure, temperature, or solubility, as depicted in **Figure 4**.

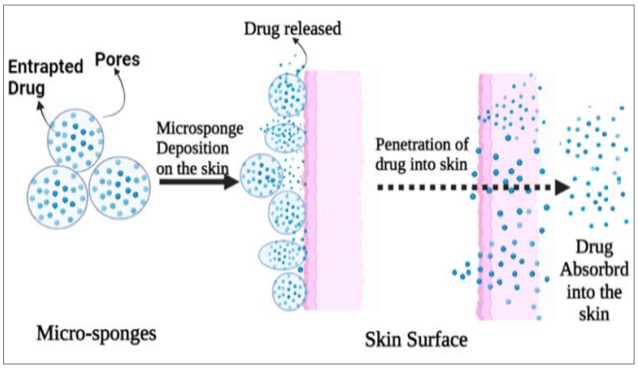

Figure 4. Mechanism of drug release

Temperature change

Microsponges containing encapsulated active compounds exhibit slightly viscous behavior and begin to flow through the microsponges onto the skin at room temperature (20-25 °C). As the skin's temperature rises, the flow rate increases, leading to a higher release rate of the active ingredient.

Pressure

When pressure is applied to the microsponges, such as through rubbing or direct application, the active substance can be released onto the skin.

Solubility

Microsponges containing water-soluble compounds, like disinfectants and deodorants, will release their active ingredients when they come into contact with water. Diffusion also plays a key role in drug release, and the partition coefficient of each component between the microsponges and the external environment should be considered to optimize the release process [32, 50].

Factors affecting drug release from micro-sponge delivery systems

- Physicochemical properties: The pore diameter, pore volume, and overall robustness of the microsponges, as well as the properties of the vehicle used, influence drug release.
- Pressure and rubbing: The application of pressure or rubbing can facilitate the release of active compounds from the microsponges onto the skin layer.
- Temperature: Encapsulated active ingredients within microsponges can be too viscous to flow freely at room temperature. However, with an increase in temperature (e.g., body heat), the flow rate and subsequent release rate can rise [29].
- Solubility: Water-soluble microsponges, such as those containing deodorants and disinfectants, can release their active compounds upon contact with water. The diffusion process is also influenced by the partition coefficients of the ingredients between the microsponges and the surrounding environment.

Limitations of microsponges drug delivery

Organic solvents, commonly used as porogens in the preparation of microsponges, pose environmental hazards and fire risks. Residual monomers can sometimes remain in the microsponges, which may be toxic and harmful to health.

Evaluation tests for microsponges

- Particle size and size determination: Adjusting the particle size during polymerization can yield free-flowing powders with desirable properties. The particle size of both loaded and unloaded microsponges can be determined using methods such as Laser Light Diffractometry. The D50 value represents the average particle size across various formulations. The release behavior of drugs from microsponges can be plotted against particle size to evaluate its impact on drug release. Typically, particles larger than 30 μm may feel rough on the skin, so particle sizes between 10 and 25 μm are preferred for topical applications [54, 55].
- Microscopic techniques: Light microscopy and scanning electron microscopy (SEM) are commonly used to visualize the shape and surface structure of microparticles. Light microscopy allows for the observation of changes in the shape and coating of double-walled microparticles before and after coating. SEM provides higher resolution and can be used to analyze the surface areas and structures of cross-sectioned microparticles. Confocal fluorescence microscopy is used for the structural characterization of multi-walled microparticles. Additional instrumental methods, such as laser light scattering and a multi-size Coulter counter, are employed for the analysis of particle sizes, shapes, and morphology [56].

Morphology and surface topography

To examine the morphology and surface topography of manufactured microsponges, they can be sprayed or coated with a gold-palladium layer in an argon environment at room temperature. Scanning electron microscopy (SEM) is then employed to study the surface structure of the microsponges. SEM can also be used to analyze the ultrastructure of fragmented microsponges [57, 58].

Determination of true density

The true density of microparticles is calculated by averaging various readings obtained using an ultra-pycnometer along with helium gas [59].

$$\text{Production yield} = \frac{\text{Practical mass of microsponges}}{\text{Theoretical mass (polymer + drug)}} \times 100 \quad (1)$$

Compatibility testing

To evaluate the compatibility of the drug with excipients, techniques such as thin-layer chromatography (TLC) and Fourier transform infrared spectroscopy (FT-IR) are used. The impact of polymers on the drug's crystallinity can be analyzed through X-ray diffraction (XRD) and differential scanning calorimetry (DSC). For DSC, a sample of about 5 mg is placed in an alumina crucible and heated in a nitrogen atmosphere at a rate of 15 °C per minute, within a temperature range of 25 to 43 °C [60, 61].

Dissolution assessment

The dissolution rate and solubility of the microsponges can be examined using a modified USP XXIII dissolution apparatus with a 5 mm stainless steel mesh basket. The basket rotates at 150 RPM. The appropriate dissolution medium is chosen to maintain sink conditions. Samples from the dissolution media are periodically analyzed using a suitable analytical method [59].

pH determination

The pH level is measured with a pH meter and should fall between 1 and 11 [18].

Loading efficiency and production yield calculation

The total percentage yield can be calculated using predefined formulas [62].

$$\% \text{ Yield} = \frac{\text{The initial weight of the product}}{\text{Total weight of the product}} \times 100 \quad (2)$$

$$\text{Loading efficiency} = \frac{\text{Drug content in microsponges}}{\text{Theoretical drug content}} \times 100 \quad (3)$$

Characterization of pore structure

The volume and diameter of the pores in microsponges play a significant role in determining the duration and intensity of an active ingredient's release. Pore size directly influences how the active compounds migrate from the microsponges into the surrounding medium. Mercury intrusion porosity is a technique used to examine how pore diameter and volume affect drug release. Key porosity parameters such as pore size distribution, bulk density, apparent density, percent porosity, pore surface area, void volume, morphology, and average pore diameter can be measured using this method.

Pore diameter calculation

The Washburn equation helps calculate the pore diameter, as shown below:

$$D = \frac{-4\gamma cos\theta}{P} \tag{4}$$

Where:

- γ = Surface tension of mercury (485 dyne/cm)
- P = Pressure (psi)
- D = Pore diameter (µm)
- θ = Contact angle (130°)

Total pore area

The total pore area can be determined by the following equation:

$$\text{Atot} = \frac{1}{\gamma \text{Cos}\theta} \int_{0}^{\text{Vtot}} \text{P. dV} \tag{5}$$

Where:

- P = Pressure (psi)
- Vtot = Total specific intrusion volume (ml/g)
- V = Intrusion volume (ml/g)

Average pore diameter (Dm)

To calculate the average pore diameter, use the equation:

$$D\text{m} = \frac{4V\text{tot}}{Atot} \tag{6}$$

Where:

- Atot = Total pore area
- Vtot = Total specific intrusion volume (ml/g)

Bulk density calculation

Bulk density can be calculated using the following formula:

$$Pse = \frac{\text{Ws}}{\text{Vp} - \text{VHg}} \tag{7}$$

Where:

- Vp = Volume of empty penetrometer (ml)
- VHg = Volume of mercury (ml)
- Ws = Weight of the microsphere sample (g)

Absolute density calculation

To calculate absolute density:

$$Pse = \frac{\text{Ws}}{\text{Vse} - \text{vtot}} \quad (8)$$

Where:

- Vse = Volume of the penetrometer minus the volume of mercury (ml)
- Vtot = Total specific intrusion volume (ml/g)

Percent porosity

Porosity (%) can be determined using the equation:

$$\text{Porosity (\%)} = [1 - \frac{\text{Pse}}{\text{Psa}}] \times 100 \quad (9)$$

Where:

- Pse = Bulk density
- Psa = Absolute density

Kinetics of release using SEM

Scanning electron microscopy (SEM) allows for the investigation of the morphological characteristics, surface features, and particle size distribution of the microsponges.

Kinetics of release using scanning electron microscopy (SEM)

SEM is utilized to study the morphology, surface characteristics, and particle size of microsponges. This analysis provides insights into how the structure of the microsponges impacts the release kinetics of the active ingredients they carry.

Fourier transform infrared spectroscopy (FTIR)

FTIR spectroscopy is used to verify the compatibility of the drug and the excipient (e.g., Eudragit RS-100) by recording the FTIR spectra of the drug, its physical mixture with the excipient, and the formulation. This helps ensure that no significant chemical interactions occur that might affect the drug's stability or effectiveness [63].

Differential scanning calorimetric (DSC) analysis

DSC is used to thermally analyze the physical mixture of the drug and Eudragit RS-100. Samples are heated at a constant rate (e.g., 20 °C/min) over a temperature range (e.g., 40 to 43 °C) to monitor thermal transitions and determine the compatibility and stability of the drug within the formulation [9].

Applications of microsponges

In oral drug delivery

Microsponges are effective in enhancing the solubility and bioavailability of poorly water-soluble drugs. For example, ketoprofen and flurbiprofen have been developed for controlled oral release using microsponges, particularly utilizing the ERS 100 polymer via the quasi-emulsion solvent diffusion technique [64-68].

Topical applications

Microsponges are used in topical drug delivery systems, such as benzoyl peroxide, where they help reduce side effects and enhance percutaneous absorption. This approach allows for controlled release with minimal irritancy, making it ideal for sensitive skin treatments [65, 69, 70].

Microsponges in bone and tissue engineering

Collagen microsponges have been used in tissue engineering, particularly for bone substitutes. When integrated into subcutaneous tissue, collagen microsponges show angiogenesis and therapeutic potential as a reservoir for basic fibroblast growth factor (BFGF), which promotes tissue regeneration [71].

Cardiovascular engineering

In cardiovascular surgery, collagen microsponges are used as bioengineered materials for in situ cellularization and tissue regeneration. Poly(lactic-co-glycolic acid) mixed with collagen microsponges creates a vascular patch material, offering a solution for tissue engineering in vascular repair [48].

Reconstruction of the vascular wall using microsponge technology

Microsponges are also used in reconstructing vascular walls, where biodegradable polymeric scaffolds, such as polyglycolic acid and polylactic acid, are coupled with collagen microsponges to create tissue-engineered patches. These patches, grafted without pre-cellularization, show excellent cellularization and prevent thrombosis, making them effective for vascular repair [48, 72].

Anti-ulcer applications

Microsponges can be used for targeting anti-ulcer drugs to enteric cells, improving drug loading capacity and enabling sustained release. This approach offers a more consistent therapeutic response and enhanced drug delivery for treating stomach ulcers.

Antifungal drugs

Microsponges have been employed to deliver antifungal drugs like fluconazole, improving the absorption and controlled release in topical formulations. These microsponges allow for sustained release, making them particularly effective for severe, life-threatening fungal infections.

Anticancer drugs

In cancer therapy, microsponges are used to deliver anticancer drugs with reduced side effects. These formulations improve the targeted delivery of chemotherapy agents to cancer cells, minimizing the impact on healthy tissue. This approach is rapidly evolving to provide better delivery options for various types of cancer, such as colorectal, pancreatic, stomach, and breast cancers.

Anti-arthritis medications

Microsponges containing diclofenac sodium, an antipyretic drug, were created to treat rheumatoid arthritis, providing controlled and sustained release for better therapeutic outcomes.

Antiepileptic drugs

Carbamazepine (CBZ), an anti-epileptic medication for conditions such as trigeminal neuralgia, epilepsy, and bipolar disorder, was formulated into microsponges using a quasi-emulsion solvent diffusion method with various compositions of Eudragit (EC) and polyvinyl alcohol (PVA). These microsponges were analyzed using FTIR, DSC, and XRD techniques to ensure their effectiveness and stability [73].

Microsponge-based self-assembled DNA hollow spheres

Researchers have developed a straightforward method for creating self-assembled DNA hollow spheres (HSs) that can be used in drug delivery and bio-imaging applications. This technique uses a water-based system, avoiding organic solvents, making it both biologically safe and environmentally friendly [13]. A summary of the uses of microsponges is provided in **Table 2**.

Table 2. Microsponges applications and their benefits

Sr. No.	Applications	Advantages
1	Sun-screen	Provides long-lasting therapeutic effects, preventing sunburn and sun-related damage, even at higher concentrations, while reducing skin irritation and sensitivity.
2	Anti-acne (e.g., benzoyl peroxide)	Minimizes skin irritation and sensitivity without compromising effectiveness.
3	Anti-inflammatory (e.g., hydrocortisone)	Offers prolonged action, reducing skin allergic reactions and dermatoses.
4	Anti-dandruff (e.g., selenium sulfide)	Decreases unpleasant odor and irritation, enhancing safety and efficacy.
5	Skin pigmentation agents (e.g., hydroquinone)	Improves the formulation's stability against oxidation, leading to better effectiveness and a more appealing result.

Table 3. Marketed microsponges-based products

Brand name	Manufacturer	Pharmaceutical use
Ultra-guard	Scott paper company	Protects baby skin
Retinol cream	Biomedic	Maintains healthy skin
Salicylic peel 20	Biophora	Effective exfoliator, sunscreen
Oil-free matte block SPF 20	Dermalogica SDR	Sun cream
Retinol 15-night cream	Sothys	Anti-wrinkle
EpiQuin micro	SkinMedicaInc	Treats hyperpigmentation

A list of commercialized products based on microsponges is shown in **Table 3** [70, 74].

Recent advancements in microsponge drug delivery systems

Recent innovations in the manufacturing of nanosponges, nanoferrosponges, and porous microbeads have resulted in significant progress in drug delivery technologies. In addition to the traditional polymeric micro or nanosponges, beta-CD nanosponges have been developed for the delivery of both hydrophobic and hydrophilic drugs. A variety of drugs, including itraconazole, doxorubicin hydrochloride, serum albumin, dexamethasone, and flurbiprofen, have been used as models to test these new systems. The production of these nanosponges involves reacting the beta-CD molecule with diphenyl carbonate, followed by cross-linking. Nanosponges have also been identified as effective carriers for gas delivery. Furthermore, researchers have found that incorporating cytotoxic agents into these carriers can enhance drug efficacy, potentially allowing for targeted drug delivery to malignant cells [75]. Additionally, porous microbeads have shown potential for siRNA delivery, demonstrating improved RNA stability and efficient encapsulation techniques. These formulations utilize a continuous oil phase, cross-linking agents, and water as an internal phase emulsion [76, 77].

Conclusion

Microsponge drug delivery systems offer numerous advantages over conventional topical drug delivery systems, including simplicity in manufacturing, use of basic components, and the ability to encapsulate a wide range of drugs. These systems have proven especially effective for delivering various medications such as rubefacients, anti-fungal, anti-inflammatory, anti-pruritic, anti-dandruff, and anti-acne treatments. Microsponges are increasingly recognized for their potential in controlled drug release, which can improve patient compliance by delivering drugs across different parts of the gastrointestinal tract, including the colon and stomach. Bioerodible polymers are often used in oral drug delivery systems. Research has shown that microsponges can manage dosing schedules effectively, allowing for more efficient drug administration. The techniques used for preparing microsponges, along with their properties and characteristics, have been thoroughly examined. Microsponge technology shows great promise for the future and may become a crucial tool for a wide array of therapeutic applications. This area continues to grow in importance and warrants further investigation to unlock its full potential in pharmaceutical development.

Future directions

Microsponge delivery systems (MDS) are recognized for their unique qualities, including extended-release capabilities, improved drug release profiles, reduced irritation, and enhanced physical, chemical, and thermal stability. These particles have also been found useful in cell culture media, suggesting their potential for stem cell cultivation and tissue regeneration within the human body. Additionally, due to their aesthetic appeal, microsponges have been incorporated into beauty products. These advancements open up new possibilities for the use of microsponges, extending their application across a variety of fields. These developments pave the way for innovative drug delivery systems and new therapeutic avenues [77, 78].

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