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Review Article

Toward Application of Microsponges for Topical Drug Delivery: A Review

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ABSTRACT

The sunscreen industry is a growing industry because of the increasing need for skin protection and increased awareness of the harmful effects of sunlight by the consumer. Day by day more effective sunscreen actives, novel cosmetics are added to the formulator's repertoire. Microsponges hold a bright future due to their wide pharmaceutical application and unique property like high loading efficiency, small size, better target delivery and controlled release. Sunscreen should be long-lasting to reduce frequency of application and also should have less side effects; microsponges drug delivery helps reach reaching the goal of controlled and site-specific drug delivery. Microsponges enhance the safety and efficacy of Active Pharmaceutical Ingredients (APIs) in sunscreens, cosmetics, and various over-the-counter skin preparations by minimizing side effects. This article includes the methods, evaluation, application, advantages, limitations and recent advancements in microsponges with respect to sunscreens. This study conducted a comprehensive review of all available information on Microsponges; it presents promising new therapeutic drug delivery with respect to sunscreens. Sunscreen agents are mostly unstable, hence microsponges help to extend product stability. According to review, patent activity signifies continued interest, suggesting significant potential for enhancing patient care.

Keywords: Cosmetics, Delivery, Drug Safety, Microsponges, Sunscreen, UVA and UVB Protection.

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INTRODUCTION

To protect from harmful effects of sunlight, one should avoid overexposure to sunlight, one should use sunscreens frequently and wear protective clothes (Ma and Yoo, 2021). UV radiation from the sunlight (UVA and UVB) has a huge influence on the skin, causing photo aging, sunburns, cancerous lesions and immunosuppression (D'Orazio *et al.*, 2013). The incidence of non-melanoma skin cancer is increasing worldwide, despite increasing use of sunscreens (Stoddard *et al.*, 2018). Hence, there is need for advances in the sunscreen formulation, there is a need to formulate the sunscreen more photo stable and long-lasting. Sunscreens contain active agents, commonly referred to as filters. These filters can be inorganic, such as Titanium Dioxide and Zinc Oxide, or organic, such as Oxybenzone, Avobenzone, Octinoxate, and Octisalate (Schneider and Lim, 2019; Smijs and Pavel, 2011).

Organic filters generally demonstrate higher efficacy in sun protection, inorganic filters are typically considered less toxic and have a lower incidence of side effects compared to their organic counterparts (Serpone *et al.*, 2007). Topical delivery of drugs shows many problems like unpleasant odor, uncontrolled release of the API, the use of vehicles that makes the formulation sticky, greasy causing lack of consumer compliance (Adepu and Ramakrishna, 2021). To overcome the above problem, new carrier technology is commonly used nowadays. Microparticles and nanoparticles show sustained and controlled release. These include Microspheres, liposomes, microsponges, nanoparticles (Lengyel *et al.*, 2019). Microspheres do not show controlled release because once the outer layer is ruptured the drug inside is released out (Kircik, 2011). Liposomes show some demerits like low drug entrapment, less chemical stability, less microbial stability (Liu *et al.*, 2022). The microsponges-based polymeric microspheres overcome the above limitations. Microsponge share a Novel drug delivery system which are porous microspheres, capable of entrapping a variety of actives such as anti-inflammatory agents, anti-acne agents, cosmetics etc. Size of microsponges varies from 5 to 300 µm with the pore volume up to 1 mL/g (Latha *et al.*, 2013). They reduce toxicity of sunscreen agent and improve efficacy along with prolonged action (Kumari *et al.*, 2016). Microsponge matrix consists of a myriad of interconnecting nanopores having a large internal surface area in a non-collapsible structure (Mahant *et al.*, 2020). Microsponges entrap the actives inside and they do not penetrate the skin initially, hence shows

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reduced toxicity (Arya and Pathak, 2014). Microsponges act as reservoirs, enabling the controlled and sustained release of the encapsulated active ingredient, allowing for gradual permeation through the skin or mucous membranes (Schaefer *et al.*, 1994). Microsponges, spherical particles composed of clusters of smaller spheres, are widely used in cosmetic skin preparations due to their unique structure. This structure allows them to absorb and hold a significant amount of material, up to four or five times their weight in skin secretions (Embil and Nacht, 1996). Microsponges, being porous in nature, can absorb skin secretions such as oil and sweat. This property helps reduce the oiliness and greasy feel of the skin, making them particularly beneficial in sunscreens and other skin care preparations (Tiwari *et al.*, 2022). Microsponges are typically incorporated into cream, gel, or lotion formulations. Recent studies are going on to study the oral drug delivery of microsponges (Khule *et al.*, 2019). This article provides information regarding the structure, application, methods, characterization and future of microsponges in cosmetics (Figure 1).

Advantages of Microsponge

- Demonstrates patient adherence.
- Convert liquids into powders to advance material handling.
- This will improve treatment efficiency and bioavailability.
- Makes the product more elegant.
- Because *bacteria* are too big to fit into the microsponge, shelf-life and item soundness may be postponed without the need for additives.
- Enhanced product aesthetics.
- Advanced oil control as it can absorb oil up to 6 times its weight without drying.
- Improves efficacy in treatment.
- Fluids can be converted into free streaming powder, which provides benefits for fabric care.
- Because of the increased tolerance and decreased pain, consumer acceptance is high.
- Prevent the active substance from building up in the dermis and epidermis.
- Microsponge conveyance frameworks are non-allergic and non-toxic, and their definition is straightforward.
- Give a larger dose of the medication and engage in continuous activity for up to 12 hr (Aloorkar *et al.*, 2012; Mahant *et al.*, 2020; Gidde *et al.*, 2021; Kaur *et al.*, 2024; Murkute *et al.*, 2023; Jadhav *et al.*, 2013).

Limitations

The medication techniques generally use organic solvents as porogens.

- An environmental hazard.
- Highly combustible.
- Posing a safety hazard.

In some cases, the traces of residual monomers have been observed, which may be poisonous and dangerous to health.

Characteristics of microsponges

Microsponges when applied on skin, it releases the API onto the surface of the skin. The release can be enhanced by rubbing or temperature or pH change of the skin (Borawake *et al.*, 2021; Nidhi *et al.*, 2021; Bhatia and Saini, 2018).

- Microsponges show compatibility with most of the ingredients and solvents.
- Shows stability between pH range 1 to 11 and temperature upto 130°C.
- Microsponge have high Entrapment Efficacy upto 50 to 60%.
- They show free flowing property.

Since microsponges are too large in size they do not get absorbed into the skin. This can be used for API which should act on the skin surface. Hence the API will not get absorbed into the skin and there will be no toxicity, hence shows increased safety.

Microsponge preparation can be cost-effective, particularly for mass-market cosmetic applications where the cost of raw materials is a significant factor. Microsponges can be used for extended release formulations for having the action up to 12 hr. Hence it can be useful in sunscreen preparations to reduce frequency of application.

Microsponge pore size is about 0.25 µm, which cannot be penetrated by *bacteria*, and hence the microsponge acts as self-sterilizing formulations.

Characteristics of the active candidates

- Actives should be solid or liquid.
- It should be stable in contact with polymerization catalysts.
- Should be fully miscible in monomers or miscibility can be achieved by adding a co-solvent.
- It should be sparingly soluble or insoluble in water.

- The active ingredients must be chemically stable in the presence of the monomers and should not significantly affect the viscosity of the final formulation.
- It should retain the spherical structure of the microsponges.

The actives commonly incorporated in microsponges are Diclofenac Sodium, Paracetamol, Fluconazole, Benzoyl Peroxide, Hydroxyzine HCl, Mupirocin, Ketoprofen, Mefenamic acid, Dicyclomine, Ibuprofen, these are all anti-inflammatory, anti-acne, anti-spasmodic, anti-fungal, NSAID agents. Polymers commonly used in the preparation of microsponges are Eudragit RS 100, Eudragit S 100, Ethyl Cellulose, PHEMA and Polystyrene (Srivastava and Pathak, 2012).

METHODOLOGY

Methods of preparation of microsponges

The two most common methods used for preparation of microsponges are:

- Free radical suspension polymerization.
- Quasi-emulsion solvent diffusion.

Recently few new techniques have been developed for preparation of microsponges, which have different characterization parameters than the above two methods (Chadawar and Shaji, 2007). Among the two common methods, Free Radical Polymerization method is complex due to various limitations like irradiation, high temperature, the catalysis to activate the monomer in indispensable reaction condition and poor reproducibility. Whereas the Quasi-emulsion solvent diffusion method is easy to be performed in laboratory as well as in factory (Deasy, 1984).

Free radical suspension polymerization (Bottom-up approach)

Microsponges are prepared in a liquid-liquid emulsion system. Where polymerization process takes place in two phases. First is the 'monomer' or dispersed phase' and second is the immiscible liquid phase 'polymerization medium' which when mixed gives polymerization reaction. A monomer diluent or 'porogen,' miscible with the monomer but immiscible with the polymerization medium, can be added to the reaction. This results in the formation of polymeric beads with an open, porous structure resembling sponges, hence the name 'microsponges. Initially suspension is obtained with droplets of desired size than polymerization reaction takes place by activating the monomer by catalysis or elevated temperature resulting in a series of polymer ladder overlapping to form a solid microsphere. Further with the progress of polymerization process they occurs formation of a spherical structure with thousands of microspheres entrapped into it, forming a interconnecting reservoir in which the porogen is entrapped. After completion of polymerization the solid particles are separated by filtration or centrifugation followed by washing and recovery of microsponges. For preparation of microsponges the requirements are monomers like styrene, PHEMA, toluene as porogen and cross-linking agent like Divinyl benzene Figure 2.

Quasi-emulsion solvent diffusion method (Top Down approach)

This method involves two phases. The first phase is the internal phase containing the drug-polymer solution made in a volatile solvent like dichloromethane, ethanol or acetone. The second phase is the external phase containing aqueous Polyvinyl Alcohol (PVA) solution. The internal phase containing drug and polymer solution is added to the external phase in slow rate with continuous continuation and vigorous stirring. A plasticizer like Triethylcitrate (TEC) is added to increase plasticity to the particles. The solution is stirred for 1 to 2 hr which leads to formation of discrete emulsion globules called quasi-emulsion globules. Once the globules are formed, the solvent is extracted, resulting in the formation of insoluble, rigid microspheres. These microspheres, known as microsponges, are then collected through filtration. The microsponges were subsequently dried in a hot air oven. Microsponge formation occurs through a process of solvent diffusion. Fine droplets of a polymeric solution containing the drug solidify in the aqueous phase as the organic solvent diffuses out and water diffuses into the droplets. This leads to a decrease in the solubility of both the drug and the polymer, resulting in their co-precipitation, continued diffusion of the organic phase further solidifies the droplet, resulting in the formation of matrix-type porous microsponges (Figure 3) (Kawashima *et al.*, 1992; Çomoğlu *et al.*, 2003; Jyothi *et al.*, 2019).

Advanced techniques for microsponge synthesis

The drug entrapment method involves loading of the drug after the formation microsponges. First empty microsponges are formed than roller milled for 1 hr with ethanol solution of drug. The mixture was then placed in an oven at 65°C for 2 hr to remove residual solvent (Jayasawal *et al.*, 2022; Lohot *et al*, 2020; Yousif *et al*, 2023). Then the procedure is repeated for second entrapment step (Table 1) (Alburyhi *et al*, 2025; Rajab and Jawad, 2016; Shukla *et al.*, 2016; Mohite, 2016; Mohiuddin, 2019; Wani *et al.*, 2022).

Mechanism of drug release on topical application of microsponge sunscreen or any other cosmetic agent

The Microsponge has an open porous structure which facilitates free in and out movement of particles into the vehicle until equilibrium is obtained and the vehicle becomes saturated. The vehicle can be a cream base, gel or lotion (Sander *et al.*, 2020). When applied to the skin, these finished products allow for the absorption of the sun protection agent or cosmetic actives into

the skin (Pramila and Ramraj, 2019). As the drug is absorbed, the concentration of actives in the vehicle reduces leading to unsaturation which disrupts the equilibrium which was maintained by the free movement of the drug particles from the microsponges. Further again, movement of active particles from the microsponges into the vehicle takes place (Sharma *et al.*, 2020). This process continues until the whole vehicle is absorbed onto the skin (Figure 2). The slow release on actives occurs from the microsponges therefore retaining the active on the skin for a prolonged duration. The selection of vehicle plays a very important role in the drug release mechanism (Figure 3) (Das *et al.*, 2022). Achieving gradual release becomes challenging when the active ingredient exhibits high solubility within the delivery vehicle. Therefore, a vehicle with low solubility power with the active should be selected. Another way to prevent undesired leaching of active from the microsponges is by addition of free and some entrapped active in the product so that the vehicle is pre-saturated (Figure 4) (Wani *et al.*, 2022; Mansi *et al.*, 2019).

Release kinetics and release mechanism

Microsponge release mechanisms primarily encompass two categories: sustained release and on-demand release. To achieve controlled release of functional substances over time, microsponge delivery systems can be designed to respond to external stimuli through the implementation of specific programmed parameters (Christensen *et al.*, 1977).

Sustained or time-release

The Physicochemical parameters considered for development of sustained release microsponges are viscosity, volatility, and solubility of entrapped active substances. Whereas parameters related to polymeric microsponges are pore diameter, volume and resiliency (Latha *et al.*, 2013).

Release on command

Drug release from microsponges can be modulated by external stimuli to achieve controlled release over time. The various triggers are: pressure release, where the microsponge is pressed releasing out the active particles on the skin, pH-based release of the particle is obtained by modifying the coating of the microsponge (Sato *et al.*, 1988). Temperature is also an important trigger. An increase in skin temperature leads to an increase in both blood flow and drug release rate (Jain and Jain, 2016). Water solubility of the active is also a trigger for release of the drug from the microsponge.

Release kinetics

Various kinetic models are used to explain the true release mechanism of drug from a dosage form (Ozturk *et al.*, 1988). *In vitro* drug release studies on microsponges have consistently shown an inverse relationship between the polymer amount within the microsponge and the rate of drug release (Mauger *et al.*, 1986; Polli *et al.*, 1997). Description of various release kinetic models used to determine release kinetics of microsponges are as follows:

Zero order kinetics

A graph of cumulative drug release plotted against time can demonstrate slow drug release from a dosage form. Zero-order release kinetics are typically observed in dosage forms that maintain their structural integrity, such as transdermal systems, polymeric microspheres, matrix tablets, and osmotic systems (Banker *et al.*, 2002).

Equation t=Q0+K0t

First order kinetics

A graph of the logarithm of the cumulative amount of drug retained plotted against time can be used to analyze first-order processes, such as drug absorption, elimination, and the dissolution profiles of dosage forms like transdermal patches and matrix systems (Korsmeyer *et al.*, 1983).

Equation: InQt=InQ0+KIt

Korsmeyer and Peppas model

A graph is plotted of log cumulative drug release and log time. Explains the drug release from polymeric system (Peppas, 1985; Higuchi, 1963).

Equation: Qt/Q∞=KKP*tn

Higuchi model

A graph of cumulative drug release against the square root of time is commonly used to analyze drug release data. This method, often referred to as Higuchi kinetics, is particularly useful for describing drug release from matrix systems, such as transdermal patches and polymeric matrices, where diffusion through a polymeric barrier is the primary release mechanism (Hixson and Crowell, 1931).

Equation: $Qt=KH*\sqrt{t}$

Hixon Crowell model

A Hixson-Crowell plot, where the cube root of the amount of drug remaining is plotted against time, demonstrates a relationship between the surface area and volume of a dissolving particle. This model is particularly useful for describing drug release from dosage forms where dissolution occurs predominantly through parallel planes, such as in certain types of tablets or pellets (Baker and Lonsdale, 1974).

Equation: Q01/3-Q1/3=Kst

Baker and Lonsdale model

A graph between [d(Mt/M∞)]/dt and root of timeinverse. This model gives the release of drug from spherical matrices (Martin,1960).

Equation: (3/2) [1-(-1(Q1/Q∞))2/3]-(Q1/Q∞)=KBLt

Therefore, from studying the above various models and comparing the studies, the release kinetics of microsponges can be analyse using the following mathematical model:

Q=kltnor logQ=logkl=n logt

By plotting the logarithm of the cumulative amount of drug released (log Q) against the logarithm of time (log t), the slope and intercept of the resulting line can be determined. These values can then be used to calculate kinetic parameters, providing insights into the drug release mechanism. Further the data can also be subjected for comparison study using Higuchi equation.

Characterization parameters of Microsponges used as sunscreens

Particle size and distribution

Particle size and size distribution are determined using optical or electron microscopy. Particle size analysis of loaded and unloaded particles can be performed using laser light diffractometry. Particle size is an important parameter, as it affects the texture and stability of the formulation. For all formulations, the d50 is represented by a mean size range (Kumar, 2018). The effect of particle size on drug release is shown by plotting cumulative release against time (D'Emanuele and Dinarvand, 1995).

Characterization of Morphology and Surface Topography

To determine morphology and surface topography different methods are used, like Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), Photon Correlation Spectroscopy (PCS). SEM is commonly used to examine the surface morphology of microsponges coated with gold-palladium under argon at room temperature (Kaur, 2024).

Determination of pH

The pH of a topical treatment or microsponge containing gel can be measured using an advanced pH metre.

Production yield and Loading efficiency

To determine production yield, the final weight of the microsponges is compared to the initial weight of the raw materials.

$$\% \text{ Production Yield } = \frac{\text{Practical Drug loading}}{\text{Theoretical Drug loading}} \times 100$$

The loading efficiency is obtained by drug extraction and calculated by using the following equation (Kılıçarslan and Baykara, 2003).

$$\% \text{ Loading efficiency } = \frac{\text{Practical Drug loading}}{\text{Theoretical Drug loading}} \times 100$$

True density, rheological properties and compressibility

The true density was determined using Ultra-pycnometer which is performed under helium gas environment. The compressibility

Figure 1: Benefit of Microsponge Delivery System.

was determined by simple tapping method. Microsponges generally show good compression characteristics (Washburn, 1921). The rheological property includes the viscosity which was determined using Brookfield Viscometer. Viscosity is determined by the final product that is either gel, cream or lotion.

Microsponge Pore Structure and Volume

Mercury intrusion porosimetry and gas sorption were used to determine pore structure. Pore volume controls the intensity and duration of API effectiveness. Mercury intrusion porosimetry can determine various microsponges porosity parameters, including pore size distribution, intrusion-extrusion isotherms, total pore surface area, average pore diameter, pore shape and morphology, and bulk and apparent density (Orr, 1969; 2004). Pore diameter is calculated using the Washburn equation:

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

The % porosity of a sample was found from equation.

$$\text{Porosity (\%)} = (1\text{-Pse/Psa}) \times 100$$

Polymer/Monomer composition

Microsponges drug release is optimized by controlling particle size, drug loading, and polymer composition. Here various polymer and monomer combinations are screened for their suitability with the drugs by studying their drug release profile. The polymer composition plays a critical role in controlling the release rate of the entrapped drug, as it directly influences the equilibrium distribution (partition coefficient) of the drug between the vehicle and the microsponges. Polymers with diverse electrical charges and hydrophilicity/lipophilicity are synthesized to offer versatile drug release profiles (Ford and Timmins, 1989).

Compatibility Studies

The drug-excipient compatibility studies are necessary to prevent unwanted chemical reactions that could compromise the efficacy or safety of the final drug product. Compatibility is studied by using different methods like X-ray Diffractometry (XRD), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FT-IR), and Thin layer Chromatography (TLC). X-ray Diffraction (XRD) and Differential Scanning Calorimetry (DSC) are commonly employed techniques to investigate the influence of polymerization on the crystalline structure of a drug (Jones and Pearce, 1995; Barkai *et al.*, 1991).

Resiliency

Resiliency means the viscoelastic property of the microsponges which makes it softer or firmer. The resiliency of the microsponge is to be studied to prepare the microsponges per the need of the final formulation. But there are no optimized methods developed to determine the resiliency of microsponges. Hence resiliency is studied by considering releases function of crosslinking with time (Bandara *et al.*, 2023).

Drug release profile determination

The dissolution profile of microsponges can be determined using USP XXIII or dissolution apparatus II The dissolution apparatus USP II is usually used for oral use formulation where parameters are set as temperature 37 ± 0.5°C, rotation of 100 rpm and using physiological pH mediums for a stated period. In the case of topical microsponges, the dissolution profile is typically assessed using the USP XXII apparatus. This apparatus is fitted with a modified basket incorporating a 5 µm stainless steel mesh. The rotation speed is maintained at 150 rpm, and the dissolution medium is chosen according to the solubility of the active pharmaceutical ingredient (Andini, 2023).

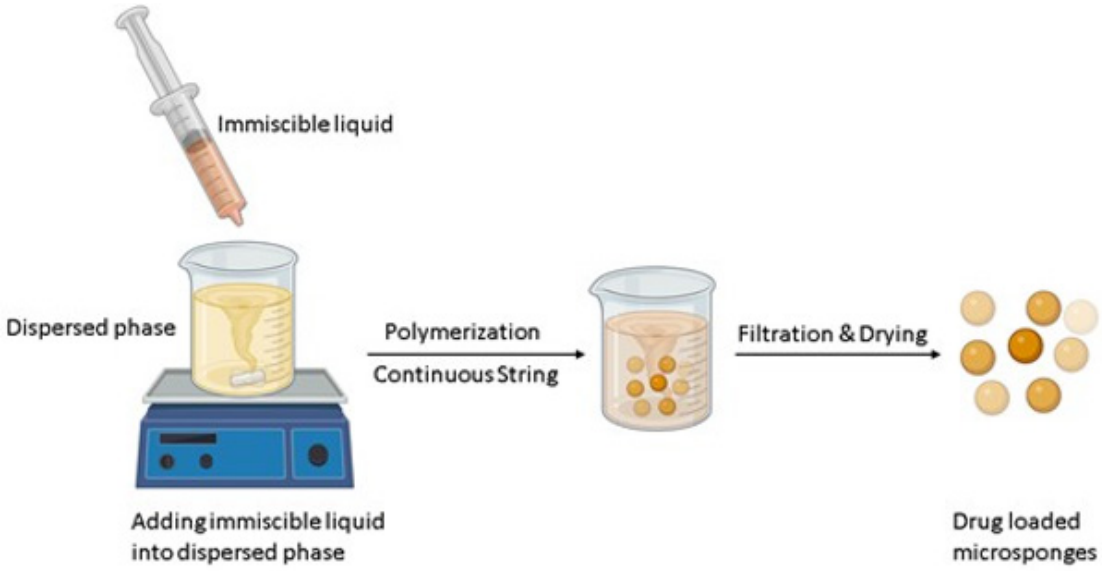

Figure 2: Free radical suspension polymerization.

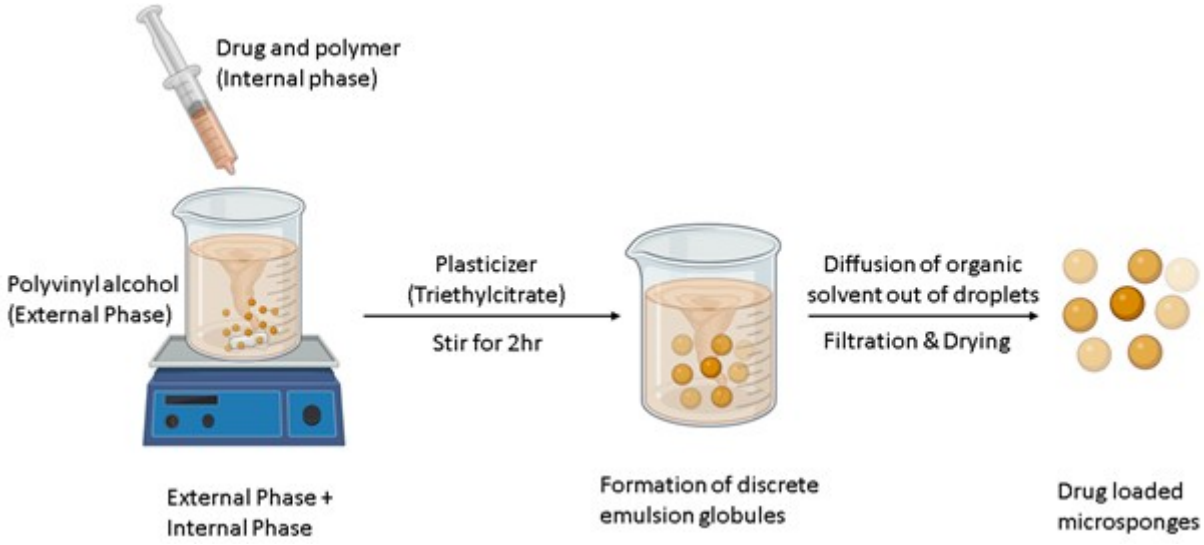

Figure 3: Quasi-emulsion solvent diffusion method.

Sun Protection Factor testing (SPF)

Microsponges after incorporating into a vehicle and forming the final product, which can be a gel, cream or lotion, is to be tested for its efficacy as a sun protective agent/Sunscreen.

Nowadays even various other cosmetics have sun protective properties. Hence these formulations should be tested for the SPF. This is done by determining the Minimal Erythemal Dose (MED). MED is determined by using two groups of *Wister rats*. The dorsal region is shaved. First group is kept under Mercury Vapor lamp that emits UV radiation without applying the formulation. While the second group is applied with formulation and kept under the Lamp. The minimum time required for erythema to occur, i.e., MED is to be noted for both groups. And SPF is determined by using the given formula (Choudhary and Akhtar, 2022).

$$SPF = \frac{\text{MED (PROTECTED SKIN)}}{\text{MED (UNPROTECTED SKIN)}}$$

Safety considerations of Microsponges

A comprehensive safety evaluation of microsponges involves assessing skin and eye irritation, oral toxicity, and allergenicity using appropriate animal models (rabbits, rats, and guinea pigs, respectively) (Li *et al.*, 2013).

APPLICATION

Application of microsponges with respect to their advantages

The microsponge delivery system offers significant benefits for drug products, including enhanced stability, improved safety profiles, increased effectiveness, and better overall quality. Microsponges are most used as topical preparations, but recently there are also used in oral administration. Microsponges give controlled and sustained release of the actives. It helps to deliver a minimum dose of the drug onto the surface. Microsponges are widely used in pharmaceutical industries as well as cosmetic industry. There are various patents regarding the microsponge preparations. Some over the counter products made of microsponges are moisturizers, sunscreens, anti-acne creams, and Rejuvenating products.

Application of microsponges for Topical Drug Delivery

Microsponges show targeted delivery of drug at low dose, with modified drug release pattern, enhanced stability and reduced side effects. Increased skin residence time is seen in the *ex vivo* drug disposition study. Due to enhanced residence time microsponges also show better Bioavailability. Microsponges show reduced side effects because less amount of drug enters into the systemic circulation (Deshmukh and Poddar, 2012). Microsponges are used in Anti-acne agents like Benzoyl Peroxide, to manage acne lesions and reduce oiliness of skin. Skin depigmentation agents like hydroquinone are also formed of microsponges, which showed better stabilization against oxidation and an improved efficacy (Thavva *et al.*, 2019). Anti-fungal agents like fluconazole were also evaluated for its activity. The studies showed a 13.5 mm zone of inhibition, indicating enhanced antifungal activity of the microsponge formulation over conventional formulations (Osmani *et al.*, 2015). Further studies were conducted on Oxybenzone, sun protective agent, where the marketed Oxybenzone sunscreen caused skin irritation, but microsponge incorporated Oxybenzone not only reduced the skin irritation but also enhanced the SPF of the sunscreen. Anti-arthritis agents like Diclofenac sodium in microsponge formulation show better drug release than the conventional formulations and also shows a Viscous module with pseudo plastic flow (Kumar and Akhtar, 2022). Microsponges are useful for anti-dandruff agents like zincpyrithione, because it reduces the unpleasant odor of

the drug. It also reduces skin irritation. Commonly used for Anti-pruritic agent and anti-inflammatory agents, because of its long-lasting activity.

Application of microsponges for oral drug delivery

It is a novel drug delivery system for microsponges. Drugs with poor water solubility can been trapped in the pores of microsponges which enhancing drug solubilization. Since microsponges show targeted drug delivery, it is useful in colonic-specific drug targeting Owing to their small size (≤200), microsponges are easily phagocytosed by colonic macrophages, resulting in a localized drug action at the target site (Draize, 1944). Examples of microsponge drug delivery with their different formulation (Table 2) (Mandava and Thavva, 2012; Patravale and Mandawgade, 2008; Leyden *et al.*, 2002; Wester *et al.*, 1991; Disouza *et al.*, 2001; Gajendra *et al.*, 2024; Iwai *et al.*, 2004; Chen *et al.*, 2005; He *et al.*, 2020; Yadav *et al.*, 2017; Maheshwari *et al.*, 2017; Rajab and Jawad, 2016; Patel, 2017; Gangadharappa *et al.*, 2013). Patents related to microsponge technology (Table 3) (David, 2011).

Recent advances in Microsponges

Several advancements in microsponge technology have been achieved through modifications of existing methods, leading to the development of nanosponges, nanoferrosponges, and porous microbeads. By reacting β-cyclodextrin with diphenyl carbonate, β- cyclodextrin-based Nano sponges are obtained. This β-cyclodextrin-based nanosponges are 3 to 5 times more effective to deliver drug to target site compared to Direct Injection (Torne *et al.*, 2013). Nanosponges loaded with cytotoxic agents offer a targeted approach to cancer therapy due to increased drug potency. Nanoferrosponges, a novel carrier system incorporating self-pore-forming mechanisms, enhances the penetration of the active agent to its target site. The advantage of Ferro sponges is that it shows higher swelling ratio with excellent elasticity and hydrophilicity (Hu *et al.*, 2007).

Recently open cell microsponge Polyimide (PI) film is produced, which shows heat insulation, thermal stability and chemical resistance (Kwon *et al.*, 2015). A recent development in microbead technology is the production of porous microbeads via a high internal phase emulsion method. This method involves a continuous oil phase containing monomer, a crosslinking agent, and an aqueous internal phase. The use of microbeads as a delivery system for siRNA presents a novel therapeutic route due to their demonstrated ability to improve RNA stability and facilitate relatively effective siRNA encapsulation (Roh *et al.*, 2014).

Table 1: Novel methods of preparation of microsponge.

Methods	Merits	Demerits
w/o/w emulsion solvent diffusion	Suitable for delivering proteins, peptides, and water-soluble medications	The use of water-insoluble surfactants in this method may result in residual surfactants within the final microsponge product.
o/o emulsion solvent diffusion	Free of surfactant residues	Thorough washing is necessary to remove any traces of organic solvents. Can be time consuming.
Porogen incorporation	Produces microsponges characterized by a highly porous structure and acceptable content uniformity.	Sometimes cause disruption of the microsponge.
Vibrating Orifice Aerosol Generator [VOAG] method	Suitable for targeted drug delivery, with specific applications in colon-specific drug release.	Should be performed under reflux conditions.
Ultrasound- assisted Production	Faster and reproducible results shall be obtained. No traces of solvent observed.	Irregular structure is obtained. Requires crosslinking agents that may be toxic and the drug may bind to the monomers.
Lyophilization	Quick results are produced and easy to manufacture.	The process may lead to cracking or shrinking of the Microsponges.
Electron-hydrodynamic atomization method	Quick results obtained	Controlling the particle size and pore size is difficult and needs expertise.

Table 2: Different formulations of microsponge drug delivery with examples.

Microsponge delivery system	Drug	Purpose
Gels	Oxybenzone	Sun protective agent
	Lornoxicam	Analgesic
	Oxticonazole nitrate	Anti-fungal agent
	Dapsone	Anti-acne agent
	Benzoylperoxide	Anti-acne agent
	Fluconazole	Anti-fungal agent
	Mupirocin	*Anti-bacterial* activity
	Diclofenacsodium	Anti-inflammatory agent
	Acyclovir	Anti-viral agent
	Hydroxyzine HCl	Dermatitis treatment
	Terbinafine HCl	Anti-fungal agent
Lotions	Benzoyl peroxide	Anti-acne agent
Creams	Hydroquinone and retinol	Melanoma
Tablets	Nicorandil	Anti-angina agent
	Piroxicam	Analgesic
	Nifedipine	Hypertension treatment
	Resveratrol	Antioxidants
	Indomethacin	Anti-inflammatory agent
	Chlorpheniramine maleate	Hay fever
	Ketoprofen	Musculoskeletal pain
	Fenofibrate	Gout treatment
	Flurbiprofen	Metabolic ratio
	Dicyclomine	Anti-cholinergic agent
	Meloxicam	Anti-arthritis agent
Implants	Poly(DL-lactic-co-glycolic acid)	Skin tissue engineering
Injection	Basic fibro blast growth factor	Growth factor
Grafts	Poly(Lactic-Co Glycolic Acid)	Cardiovascular surgery
Others	Mefenamic acid	Rheumatoid arthritis
	Ibuprofen	NSAID

Future of Microsponges

Microsponges holds a bright future due to its wide pharmaceutical application and unique property like high loading efficiency, small size, better target delivery, controlled release. Improved stability (physical, chemical, and thermal) and reduced side effects. Microsponges possess a greater capacity for drug loading than liposomes and provide enhanced control over drug release compared to microcapsules. Microsponges offer advantages such as ease of preparation and better compressibility than powder mixtures (Çomoglu *et al.*, 2002). The future challenges are the development of drug delivery system for oral peptide delivery. Microsponges require further development for administration via alternative routes, including parenteral and pulmonary. Beyond drug delivery, these particles show promise as cell culture media, potentially including applications in stem cell culture and cellular regeneration. The cosmetic industry widely uses microsponges because of their elegant properties. These novel formulations also open new avenues for drug delivery.

Table 3: Various patents filed related to microsponges.

Patent number	Inventors	Topic	Publication date
US4690825	Won, Richard	For incorporation of drug compound in to the microsponges.	1987
US4863856	Dean *et al.*	Weighed collagen microsponges for immobilizing microorganisms.	1989
US5292512	Schaefer *et al.*	Cosmetic composition for topical preparations	1989
US5135740	Katz *et al.*	Immiscible phases	1992
US5679374	Fanchon; Chantal et al.	Management of acne with two-steps	1994
US5316774	Eury, Robert P *et al.*	Formulation of polymeric particle matrix for the controlled release of Bioactive compound.	1994
US5725869	Lo; Ray J.R.	Microsphere prepared by solvent evaporation.	1996
US6395300	Straub *et al.*	Entrapping of poorly water-soluble drug in the microsponges.	1999
US6211250	Tomlinson *et al.*	Topical application microsponges.	2001
US20030232091	Shefer *et al.*	Microsponges	2002
US20040247632	Cataneo, Maurizio	Microsponges	2004
US20050271702	Wright, Steven *et al.*	Microsponges	2005
KR20160131487A	Korean	Microsponges having controlled solubility	2015

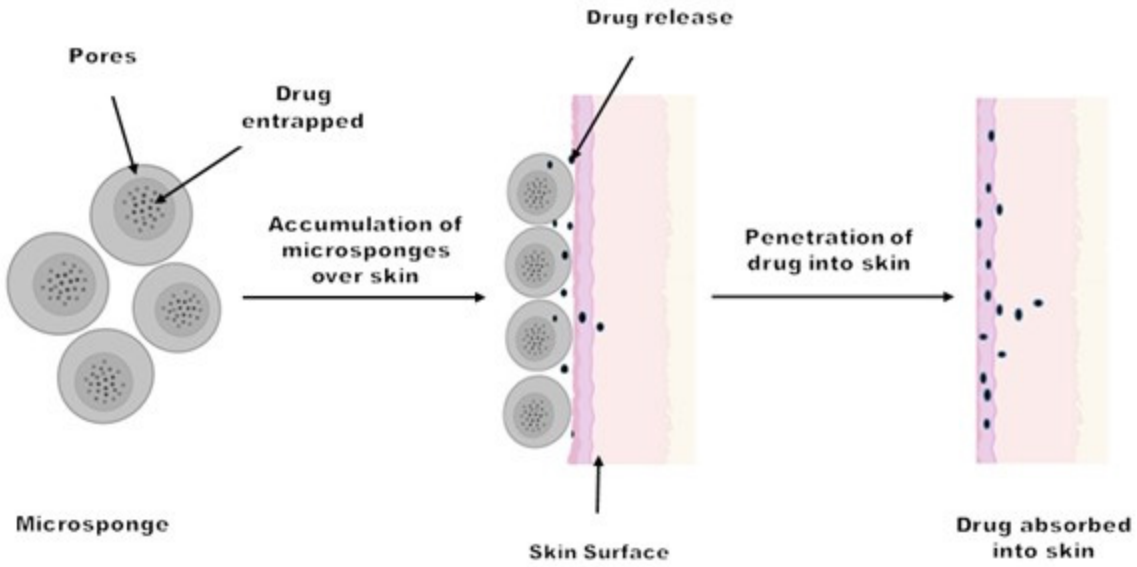

Figure 4: Schematic representation of drug release from the loaded microsponges.

CONCLUSION

The microsponges offer a versatility in application and advantages. The microsponges are widely used in cosmetic industry because of its aesthetic appearance and elegance. They are also employed in pharmaceutical industry as they show controlled release, enhanced loading efficiency, smaller size, improved stability and increased drug release profile. The main property that is seen in microsponges is reduced side effects, non-irritant, non-toxic, non-mutagenic giving an enhanced safety. Compared to the conventional delivery system, the microsponges delivery system gives better treatment for topical diseases. It also has potential for use in oral delivery system and ocular delivery system. Microsponges also has a better ingredient compatibility and are easy to prepare. Consequently, the microsponge drug delivery system represents a promising area of development within both the cosmetic and pharmaceutical industries and merits further investigation.

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ABBREVIATIONS

SPF: Sun Protection Factor; **UVA:** Ultraviolet A; **UVB:** Ultraviolet B; **API:** Active Pharmaceutical Ingredients; **NSAID:** Nonsteroidal Anti-Inflammatory Drug; **SEM:** Scanning electron microscopy; **TEM:** Transmission electron microscopy; **PCS:** Photon correlation spectroscopy; **RNA:** Ribonucleic Acid; **MED:** Minimal Erythemal Dose; **PVA:** Polyvinyl alcohol; **TEC:** Triethyl citrate; **PHEMA:** Poly (2-hydroxyethyl methacrylate); **UV:** Ultraviolet; **USP:** United States Pharmacopeia; **HCL:** Hydrochloric acid; **XRD:** X-Ray diffractometry; **DSC:** Differential Scanning Calorimetry; FT-IR**:** Fourier Transform infrared Spectroscopy; **TLC:** Thin layer Chromatography; **VOAG:** Vibrating orifice Aerosol Generator; **PI:** polyimide; **siRNA:** small interfering ribonucleic acid; **PLGA:** Poly(DL-lactic-co-glycolic acid).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed significantly to the preparation of this manuscript. Rajashree Shashidhar Masareddy and Archana Sidagouda Patil conceptualized the review theme and designed the manuscript framework. Literature search and data mining were performed by Ankita Kashinath Patil and Ravikiran Ramachandra Kanabargi. The initial draft was written by Ravikiran Ramachandra Kanabargi, while Pooja Prakash Rayanade provided critical revisions and intellectual content. authors have read and agreed to the published version of the manuscript.

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