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Microsponges as a Novel and New Approach Delivery System

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Abstract

Topically applied Drug Delivery is ineffective for delivering materials whose final destination is the dermis directly. Because of enhanced percutaneous absorption of medicines into the skin, topical agents commonly cause redness, itchiness, and burning sensations. Some traditional dosages, such as gels and ointments, are cosmetically unappealing, greasy and sticky, and so on. This frequently results in patient noncompliance. Microsponge technology has distinct advantages over conventional drug administration in terms of reducing these negative effects. Another method is the microsponge-based drug delivery system, which allows for controlled medicine release and greater drug deposition on the skin while minimizing transdermal penetration. A topical agent the active ingredient-loaded microsponge is made up of microporous beads with a quintessential diameter of 10-25 m. Cosmetic, over-the-counter skincare products, sun protection, and prescriptions pharmaceuticals all use MDS technology.

Keywords: *Drug delivery, Microsponges, Drug administration, MDS technology*

1. Introduction

In 1987, Won pioneered microsponge technology, and the first patents were awarded to an improved polymer system (Won, 2012). The Delivery Technology for Microsponge MDS is a one-of-a-kind drug delivery system. Microsponge DS technology has been utilized in topical medicinal solutions to limit the release of active pharmaceuticals into the skin, lowering systemic exposure and minimizing specific cutaneous reactions to active drugs. A Microsponge delivery system is a patented, porous, highly, cross-linked polymeric microspheres polymeric system composed of porous microspheres that can entrap a widerange of actives and then release them onto the skin over time and in response to a trigger (Newton, 1991).Several systemic drug delivery systems that employ the skin as a portal of entry have been invented under the label of Transdermal Delivery Systems (TDS) (Kydonieus and Berner, 1987). Controlled drug release in the epidermis, ensuring that the medication remains primarily localised and does not enter the bloodstream in considerable quantities. There

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are no effective vehicles for the regulated and targeted delivery of medications into the stratum corneum, underlying layers of skin, or beyond the epidermis (Chowdary and Rao, 2004).

Traditional topical medicine compositions are intended to work on the skin's surface layers. When such products are administered, their active ingredients are typically released, resulting in a concentrated covering of active material which is rapidly absorbed (Cooke, 1903). The use of topical drugs has various drawbacks, including ointments that are frequently visually unappealing, stickiness, greasiness and so on, which frequently lead to a lack of patient compliance. As a result, delivery strategies that maximize the amount of time an active chemical is available on the skin's surface or within the epidermis while minimizing percutaneous transfer into the body are required (Madgassi and Touitou, 1999; Benita, 1996; Osborne and Amann, 1990).

Microsponges are a microsphere capacity to absorb skin secretions and so reduce skin excess oil and shine. Skin secretions can include four times the mass of spherical particles of even smaller spheres. Such products, which have a relatively high proportion of active ingredients, are frequently supplied to the consumer in traditional forms such as creams, gels, or lotions. Their use for oral medication administration has recently been studied. This page gives succinct information on the many aspects of microsponges' construction, development, applications, and future. It is meant to serve as an introduction to the massive amount of research that has been done and the multiple opportunities that exist in the field of microsponges (Kaity *et al.*, 2010). Another use of MDS technology in the medical field is the usage of "Collagen Microsponge," which is mostly employed in tissue engineering and Bio-Engineering (Dean *et al*., 1991).

2. Microsponge Characteristics

Once placed on the skin, the microsponge gradually releases its active ingredient over time in response to stimulation such as rubbing, pH change and heat among others, with excellent efficacy and minimal irritation.

The characteristics of microsponges are as follows: (Parthiban *et al*., 2011; D'souza *et al*., 2004; Aritomi *et al.*, 1996).

1. pH variety of one to eleven microsponge compounds are stable
2. Microsponge compositions are sustainable at temperatures up to 1300 ^{o}C.
3. Most vehicles and substances are suitable for microsponge compositions.
4. Because their usual pore size is about 0.25 micrometer. Microsponge compositions are self-sterilizing, preventing microorganisms from reaching its pore.
5. Entrapment efficiency of microsponge compositions ranges from 50% to 60%.
6. Compositions of Microsponge are freely flowable and economical.
7. Because the microsponge debris is too huge to be absorbed onto the skin, they offer a few protection to those microsponge substances by fending off the poor consequences of microsponge adjutants.
8. Microsponges compositions may be competitively priced even withinside the beauty mass market, wherein the value of substances is essential.
9. Microsponges may also take in up to 6 instances their weight in oil without drying.
10. It gives sustained interest for as much as 12 h, that is, launch profile.
11. These have much more compositional flexibility.

2.1. Active Properties for Trapping in the Microsponge (Kawashima et al., 1992; Ruckenstein and Hong, 1992; Vyas et al., 2010; Zaki et al., 2011; Jelvehgari et al., 2006; Shah, 1989).

1. If it isn't completely miscible it is made miscible by adding a small amount of watermiscible solvent or it must be completely miscible with monomer.
2. It must be a nontoxic monomer that has no effect on the consistency of the formulation.
3. It should be slightly soluble or insoluble in water.
4. The microsponge formulation should not lose its shape.

5. It must have stability in interaction with the polymerization process and polymerization catalyst.
6. For release rate the polymer design and payload of active microsponge need to be optimized.

2.2. Advantages (Shah et al., 2010)

1. Insoluble materials can be used in MSD formulation.
2. Innovative formulation.
3. Extended-releases formulae with less irritation and harmless.
4. Continuous activity for up to 12 hours
5. Better formulation aesthetics, giving the product a more elegant appearance
6. Increases thermal, physical, and chemical stability.
7. Enhances material processing, for example, liquids can be turned into powders.
8. Improve overall condition control.
9. Maximum Bioavailability of drug.
10. Increases therapeutic effects.
11. Appearance of the formulation is elegant.

2.3. Drugs Explored in MDS (Tansel et al., 2003; Wester et al., 1991)

Ketoprofen

Benzyl peroxide

Retinol

Fluconazole

Ibuprofen

Tretinoin

Trolamine

2.4. Formulation Helper

Polymers can be used to create a microsponge cage. Ethyl Cellulose, Eudragit RS100, Polystyrene, and PHEMA are among them (Chadawar and Shaji, 2007). In conjunction with actives, certain microsponges contain plasticizers, which aid in structural stability.

2.5. Release Mechanisms (Christensen and Natch, 1983; Sato et al., 1988)

The active component is encapsulated and introduced to the vehicle. Due to the open structure of the microsponge particles, the active component is able to move until equilibrium is reached. When the final product is applied topically to the skin, the drug already present in the carrier is absorbed, depleting the carrier, causing it to become unsaturated, and disturbing the equilibrium. The drug will flow from the microsponge particle into the vehicle and subsequently to the skin until the vehicle is absorbed or dried. Once applied to the skin's surface, the formulation will gradually release the medication, resulting in prolonged release over time. External stimuli such as heat, solubility, and pressure or diffusion can also be employed to modulate release (Embil and Natch, 1996; Khopade *et al*., 1996).

2.5.1. Temperature Change (Guyot and Fawaz, 1998).

At normal temperature, some entrapment agents could be too viscous to release naturally from the microsponges over the surface of the skin. An increase in temperature of the skin might cause an increase in flow rate and therefore discharge. Viscous sunscreens, for example, were discovered to have an increased temperature causes increased release from microsponge formulation; hence, when exposed to heat from the sun sunscreen would be released from microsponge.

2.5.2. Pressure

Rubbing / pressure given to the microsponge system can release the entrapped material, allowing active ingredients from the microsponges to be released onto the skin. The amount emitted is determined by the sponge's varied features. The type of polymer and other processing variables can be adjusted to provide the best microsponge for a certain activity. When compared to other microcapsules, mineral oil containing microsponge softened substantially more. Microsponge systems also have a substantially longer time of emolliency.

2.5.3. pH-Triggered Systems

The pH-based release of the activity can be initiated by changing the coating on the microsponge. This has numerous applications in drug delivery.

2.5.4. Solubility

In the presence of water, microsponges containing water misible compounds such as antiperspirants and anti-septics will release the API. Diffusion can also be used to activate the release, taking into account the partition coefficient of both the microsponges and an outside system. The Microsponges which are sustained-release are also a possibility. Among the various considerations to be addressed during the production of such compositions are Encapsulated actives' physical and chemical characteristics Microsponge system physical features such as pore diameter, pore volume, resilience, and so on. The microsponge is gradually dispersed in the vehicle. Pore properties, monomer composition, particle size and resilience, are all programmable features, and microsponges can be release a certain quantity of components in reaction to some external triggers, such as solubility of components, pressure and temperature.

3. Materials and Methods

3.1. Strategy for Preparation of Microsponge Drug Delivery System

A drug neither slows nor activates the process of polymerization, and it also shows resistant to free radicals. It is a one-step procedure entrapped in (liquid-liquid suspension polymerization). Microsponges can be formulated either ways:

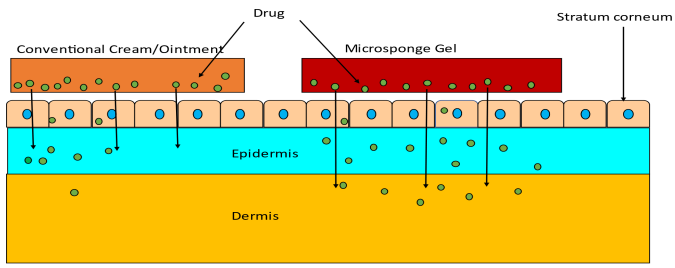

Figure 1: Systematic Representation of Conventional Topical Preparation and Microsponge Formulation. The Formulation Improves Permeation Through Skin

3.1.1. Liquid-Liquid Suspension Polymerization (Panwar et al., 2011; Vikrant et al., 2011; Horak et al., 1981)

An emulsified liquid-liquid is a Free radical suspension polymerization system was used to easily create microsponges (Michel, 2007; Patrick and Deasy, 1984). Polymerization combinations of particles are typically two-phase systems. "Polymerization medium" is referred to as a soluble monomer in the insoluble aqueous phase. The monomers are termed the "monomer phase" or "dispersed phase".

The suspension polymerization process in liquid-liquid systems is used to create porous microspheres. In this process, insoluble monomers are first dissolved with active constituents in an appropriate solvent monomer before being dispersed in aqueous phases containing additives such as surfactants and suspending agents to enable suspension formation. The polymerization is then initiated by raising the temperature, irradiating it, or adding a catalyst. The polymerization process continues to build a reservoir-type system with a spherical structure. The extract was filtered after the polymerization process, leaving the spherical structured porous microspheres, also known as microspongesPorous structures can be created, and under SEM, they resemble sponges, hence the term 'MICROSPONGES' (Friedrich, 1962). Microsponge requires the following monomers: Styrene, PHEMA, Divinyl Benzene as a crosslinking agent, and Toluene as a porogen (Brunton *et al.*, 2006).

The following stages describe the numerous steps involved in the preparation of microsponges:

Step 1: Choose a monomer and combine it with others.

Step 2: As polymerization begins, chain monomers form.

Step 3: Ladder formation as a result of chain monomer cross-linking.

Step 4: Folding the monomer ladder to create spherical particles.

Step 5: Aggregation of microspheres results in the formation of microsphere bunches.

Step 6: Bunches are bound together to form microsponges.

3.1.2. Quasi-Emulsion Solvent Diffusion Method (Kawashima et al., 1992; Jones and Pearce, 1995; D'souza and Harinath, 2008; Kaiti et al., 2010; Comoglu et al., 2003; Jain et al., 2011)

A quasi-emulsion solvent diffusion approach (two-step procedure) was also used to create porous microspheres (microsponges) from an internal phase containing polymer such as Eudragit RS 100 dissolved in ethyl alcohol. The medication is then slowly added to the polymer solution and dissolved under ultrasonication at 35 ^{o}C, with the addition of a plasticizer such as triethyl citrate (TEC) to aid in the plasticity. The inner phase is then placed into the exterior phase, which contains polyvinyl alcohol and distilled water, and stirred continuously for 2 hours. The mixture was then filtered to separate the microsponges. The product (microsponges) was washed and dried for 12 h in an air-heated oven set to 40 °C.

3.2. Characterization of Microsponges

3.2.1. Particle Size and Size Distribution

An optical microscope or an electron microscope is used to examine particle size and size distribution. This is an incredibly important stage since the particle size has a significant impact on the appearance and stability of the formulation. Controlling particle size during polymerization allows for the creation of free-flowing powders with fine aesthetic properties. Particle size analysis of loaded and unloaded Microsponges can be accomplished using laser light diffractometry or any other relevant method. For all formulations, the values (d50) can be represented as the mean size range. The cumulative percentage of drug release from Microsponges of various particle sizes will be plotted against time to investigate the effect of particle size on drug release (Martin and Swarbrick, 1991). Particles greater than 30 m can create a gritty feeling, thus particles between 10 and 25 m are suggested for use in final topical formulations (Emanuele and Dinarvand, 1995).

3.2.2. Scanning Electron Microscope (SEM) Study

Various techniques, such as Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), Photon Correlation Spectroscopy (PCS), and others, have been employed to study morphology and surface topography. For morphology and surface topography, produced microsponges can be coated with gold-palladium under an argon environment at room temperature, and then the surface morphology of the microsponges can be analyzed using Scanning Electron Microscopy (SEM). SEM images of a fragmented Microsponge particle can also be used to demonstrate its ultrastructure (Orr, 1969).

The microsponges' loading efficiency (percentage) can be determined using the formula given:

Loading Efficiency = (Actual Drug Content in Microsponge X 100) / Theoretical Drug Content

The manufacturing yield of microparticles may be calculated precisely by calculating the initial weight of the raw materials and the final weight of the microsponge formed (Kumari *et al.*, 2011).

Production Yield = (Practical Mass of Microsponges X 100) / Theoretical Mass (Polymer + Drug)

3.2.3. Determination of True Density

Microsponges' True Density can be determined by a mean of several readings using helium gas and an ultrapycnometer (Barkai *et al.*, 1990).

3.2.4. Characterization of Pore Structure

Pore volume and diameter are critical in influencing the intensity and duration of the active ingredient's activity. The migration of active substances from microsponges into the vehicle in which the material is disseminated is also affected by pore diameter. The use of mercury intrusion porosimetry can be used to investigate the effect of pore width and volume on the rate of drug release from microsponges. Mercury intrusion porosimetry can be used to evaluate microsponge porosity parameters such as intrusion-extrusion isotherms, pore size distribution, total pore surface area, average pore diameters, pore shape, morphology, bulk, and an apparent density (Anonymous, 2010; Washburn, 1921).

3.2.5. Compatibility Studies

The drug-excipient compatibility tests are performed to verify that there is no unintentional response between the two when they are synthesized into a dosage form. These tests are generally carried out by recording the Differential Scanning Calorimetry (DSC) of the compounds, namely API and excipients, separately and combined, and checking for any additions or deletions of peaks or troughs. For DSC, roughly 5 mg samples can be carefully weighed into aluminum pans, sealed, and run at a heating rate of 15 ^{o}C / min in a nitrogen atmosphere throughout a temperature range of 25–430 ^{o}C. (46-48) (Jones and Pearce,1995; Bodmeier and Chen, 1989; Kawashima *et al.*, 1991). In addition, incompatibilities between chemical moieties can be revealed using infrared (IR) spectroscopy. Thin-Layer Chromatography (TLC) and FT-IR can also be used to investigate drug compatibility with reaction adjuncts (Anderson *et al.*, 1994). The effect of polymerization on drug crystallinity can be examined using powder using Differential Scanning Colorimetry (DSC) X-ray diffraction (XRD) (Ford and Timminis, 1989).

3.2.6. Polymer / Monomer Composition

The polymer composition of the MDS can change the partition coefficient of the entrapped drug between the vehicle and the microsponge system, which has a direct impact on the entrapped drug's release rate. Plotting cumulative percent drug release against time can be used to study drug release from microsponge systems with varied polymer compositions. The type of monomer used is determined by the vehicle in which it will be disseminated as well as the properties of the active ingredient to be entrapped. The drug release profile of various monomer combinations will be studied to determine their compatibility with the medicines. The release rate and total amount of medication released from the methyl methacrylate / ethylene glycol dimethacrylate system are slower than those from the styrene / divinylbenzene system. To give flexibility in the release of active substances, polymers with various electrical charges or degrees of hydrophobicity or lipophilicity may be created (Wakiyama *et al.*, 1981).

3.2. 7. Resiliency

The resiliency (visco-elastic characteristics) of microsponges can be altered to produce beadlets that are softer or stiffer depending on the final formulation's requirements. Increased cross-linking has the effect of slowing down the rate of release. As a result, the robustness of microsponges will be researched and optimized based on the requirements, taking into account release as a function of cross-linking with time (D'souza, 2008).

3.2.8. Drug Release

Microsponges' dissolving profiles can be examined using the dissolution equipment USP XXIII and a modified basket made of 5 m stainless steel mesh. The speed of rotation is 150 rpm. To achieve sink conditions, the dissolution medium is chosen with active solubility in mind. At various times, samples from the dissolution medium can be examined using a suitable analytical method (Jayaweera, 1980).

3.2.9. Dissolution Tests

At 37 ° C and 150 rpm, the dissolving profile of microsponges can be examined using the dissolution apparatus USP XXIII and a modified basket constructed of 5m stainless steel mesh. The dissolution media is chosen with medicine solubility in mind to establish sink conditions. Samples from the dissolution medium can be evaluated using a suitable analytical method at various periods (D'souza, 2001; Franz, 1975).

3.2.10. Drug Release and Drug Deposition Investigations from Semi-Solid Dosage Forms

Static diffusion cells of the Franz type are used to release medicines from semisolid dosage forms. The skin's epidermal side was exposed to the elements. While keeping the dermal side of the skin facing the receptor solution. The receptor compartment, which held 20 mL of pH 5.8 phosphate buffer, was set to 320.5 °C and spun at rpm. the skin was soaked with a diffusion medium for 1 h before applying the sample. 200 mg of sample was applied to the donor compartment. To assess the amount of medication deposited in the skin, the diffusion cell was deconstructed after 4, 8, 16, and 24 h. The skin was gently peeled, and any drugs discovered on its surface were rinsed away with distilled water (Hiremath, 2011; Amrutiya *et al*., 2009).

3.3. Safety Consideration (Draize et al., 1994)

3.3.1. Skin Irritation Studies in Rabbits

3.3.1.1. Skin Irritation Test on Rabbits

The erythema scores for undamaged and exfoliated skin were totaled for all rabbits at 24 and 72 h. The total number of measured reactions was divided by 24 to calculate the primary irritation index (Sergio and Martin, 1992). (two score intervals multiplied by two test parameters multiplied by six rabbits).

3.3.1.2. Anti-Inflammatory Activity by Ear Edema Measurement

The experiments described in this paper were carried out with approval from our College's Animal Ethics Committee and by CPCSA guidelines. Male Swiss mice (25–35 g) were housed at 222 °C on a 12-h light / 12-h dark cycle with food and water, and the anti-inflammatory activity was done during the light part of the cycle. Before being evaluated, the animals were given at least two hours to adjust to the laboratory environment, and they were only used once. Edema was created in the right ear by topically administering 0.1 mg / ear of croton oil diluted in 20 L of acetone. FA gels contained free entrapped medicine, and the marketed gel was used topically in conjunction with croton oil. Before and after-hours ear thickness was measured using a vernier caliper (Jain and Singh, 2010).

3.3.1.3. Primary Eye Irritation Study (Unwashed Eyes)

One of six rabbits' eyes gets injected with test material (unwashed eyes), after instillation at 1, 24, 48, and 72 h the cornea, iris, and conjunctiva tissue of treated eyes are examined. To examine the reversibility of the reported effects, the observation period may be extended for up to 21 days.

3.3.1.4. Other Evaluation Tests

Include rat oral toxicity assays, bacterial mutagenicity, guinea pig allergenicity, and compatibility testing employing Thin-Layer Chromatography (TLC). After installation at 1, 24, 48, and 72 h the cornea, iris, and conjunctiva tissue of treated eyes are examined.

Table 1: List of Applications of Microsponge Drug Delivery System

S. No.	Active Agents	Applications
1.	Anti-acne (Benzoyl peroxide)	With less skin irritation and sensitization, effectiveness was maintained (Vyas and Khar, 2002).
2.	Antiinflammatory (hydrocortisone)	Long-lasting activity with reduction of skin allergic response and dermatomes (Clarkson *et al.*, 2004).
3.	Antidandruff (zinc pyrithione, selenium sulfide)	Reduced unpleasant odor with lowered irritation with extended safety and Efficacy (Attaran, 2004).
4.	Antifungal	Sustained release of actives.
5.	Antipruritics	Antipruritics Extended and improved activity.
6.	Skin depigmenting agents. (Hydroquinone)	Hydroquinone Improved stabilization against oxidation with improved efficacy and aesthetic Appeal. Hydroquinone prevents the overproduction of melanin while lightening the brown spots
7.	Rubefacients	Less greasiness and odor with sustained action 8. Sunscreens (Palumbo *et al.*, 1991).
8.	Sunscreens	Efficacy of the product is sustained, sunburns and sun-related protection are improved even at higher concentrations, and less sensitization and irritancy (Nishimura *et al.*, 1995)

Table 2: List of Marketed Products Using Microsponge Drug Delivery System

Product	Manufacturer	Advantages
Oil Control Lotion	Fountain	A light lotion containing technically advanced microsponges that absorb oil on the skin's surface during the day, leaving it matte. This lightweight lotion with oil-absorbing Microsponge technology and moisturizing botanicals removes shine for hours. To encourage healing, the naturally antibacterial Skin Response Complexes alleviate inflammation and stiffness. Acne-prone skin and oily skin problems (Delattre and Delneuville, 1995).
Oil-free matte	Dermalogica	With this invisible sunscreen, you can protect your skin from harmful UV rays while also controlling oil production. Microsponge technology absorbs oil and prevents shine without leaving a powdery residue, resulting in an all-day matte look. Microsponges made of cornstarch and Vinyl Dimethicone/Methicone Silsesquioxane Crosspolymer absorb excess surface oils on the skin (Patel *et al.*, 2010).
Retinol cream	Biomedic	Retinol is a vitamin A derivative used topically to maintain healthy skin, hair, and mucous membranes. The retinol molecule is encapsulated in the MDS to protect the effectiveness of vitamin A. This allows you to get the most out of your retinol while minimizing the risk of discomfort (Talisuna *et al.*, 2004).
Salicylic Peel	Biophora	Biophora Salicylic Peel 20 and 30. Salicylic acid (20% and 30%), microsponge technology exfoliates well and is used to stimulate the skin for more resistant skin types or speedier results. It will significantly improve pigmentation, fine wrinkles, and acne issues. Salicylic acid penetrates the pores readily, cleaning them while lowering inflammation. This treatment successfully combats acne, resulting in incredibly smooth and clear skin (Chen *et al.*, 2001).

4. Conclusion

With a high demand for creative and highly efficient Pharmaceutical and Cosmetic products, the market for Microsponge technology and the variety it provides has significant potential. As formulators examine new innovative ways to administer actives, they will be able to fully utilize the capabilities of these unique materials, which will provide greater safety, improved stability, fewer side effects from actives, enhanced multifunctionality, and improved ingredient compatibility. Microsponge delivery technology, when combined with fresh development approaches and creative formulation processes, can be a winning strategy for a new generation in the Pharmaceutical and Cosmetic sector. Microsponges have a particular advantage over existing traditional topical dosage forms for the treatment of tropical diseases; it is a one-of-a-kind technology for the controlled release of topical drugs that can also be used for oral and biopharmaceutical medication delivery. This product is superior to others since it is non-mutagenic, non-toxic, and non-irritant. So, the microsponge medication delivery system has a lot of potentials and is a fairly new topic that has to be studied in the future with further research.

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Appendix

Abbreviaitons
MSD (Microsponge Delivery System)
TDS (Transdermal Delivery System)
PCS Photon Correlation Spectroscopy)
SEM (Scanning Electron Microscopy)
TEM (Transdermal Delivery System)

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