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MICROSPONGES: AN EMERGING FORMULATION TOOL FOR TOPICAL DRUG DELIVERY

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ABSTRACT

Pharmaceutical companies have emphasized the controlled release of dosage forms such as solid formulation, semi-solid preparation, and topical preparation in the last ten years due to efficacy and patient acceptance. A transdermal drug delivery system is impossible for compounds whose final purpose is the skin. Common topical treatments have various drawbacks, such as a foul odour, greasiness, and skin irritation, as noted in case studies. In rare instances, many topical treatments do not reach the systemic circulation in sufficient concentrations. The latest formulation as a microsponge in fields of research overcomes this issue. Microsponges with a particle size of 10 to 25 microns in diameter have such a large amount of entrapment and release of multiple constituents in a single microsponges system. It is a new polymeric delivery system and sponge-like spherical particles with porous surfaces. External stimuli cause drug release in microsponge by (pH, temperature, and rubbing). Topical and oral delivery, are also possible with this method. In this review, the potential for oral, topical, antifungal, and other applications of the pharmaceutical ingredient to be entrapped in microsponges is discussed with it's limitations, benefits, and release mechanism. Also includes information on recent advancements and future prospects. A diverse variety of applications is preferred to develop medications with improved safety and efficacy. Cosmetics, over-the-counter skin care, sunscreens and prescription products are all utilized in microsponge drug delivery technology. Particle size, entrapment efficacy, true density, per cent drug content and dissolve tests, dissolution tests, compatibility studies and in-vitro study are carried out.

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Introduction

In recent years, the research landscape has shifted toward the innovative medication delivery technologies are being developed with high therapeutic activity and patient acceptance as goals. The field of medication delivery applications is becoming tremendously demanding and is quickly evolving [1]. The healthcare system would benefit greatly from a medication delivery mechanism that could accurately manage the release rate as well as deliver medicines to particular bodily parts [2]. Drug delivery systems are increasingly being used to improve the potency and cost-value of drug treatment. Peptides, proteins, and DNA-based therapies are inadequate when delivered by traditional means [3]. External medications work on the skin's outermost layers in their conventional forms. Usually, such treatments release their active components as soon as they are applied, resulting in a thin layer of highly concentrated active substances that are quickly absorbed. Furthermore, there are other issues with topical medicine application, such as greasiness, stickiness related to ointments, and much more, frequently resulting in a lack of patient adherence. Traditional dermatological medications frequently include many active ingredients that have a brief duration of effect. That may lead to a phase of overmedication for a shorter amount of time, followed by lengthy treatment with medicine [4]. Numerous drug classes evolve daily as drug delivery technology advances. A novel medication delivery system with predefined, determined rates at the distinct desired location of action should be designed to succeed against any disease. Drug Delivery Systems could modify the release rate or deliver medications to particular body regions, enhancing

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therapeutic effectiveness, the value of cost, and patient acceptance. A pharmaceutical company has a tremendous problem controlling the quantity at which APIs are released to such a particular region in the body. The invention of a microsponge medication delivery device mitigated the existing challenges. Microsponge technologies enable a uniform and long-lasting release, decreasing irritation while maintaining efficacy [5].

The MDS (Micro-sponges Delivery System) is a "very porous, inter-connect system of polymers comprised of microspheres with pores which may bind a wide region of active drug ingredient. Then after delivering them appropriately into the layers of skin over time in response to a stimulus." The diameter varies around 10-25 microns. Micro-sponge polymers are adaptable enough for it to incorporate a variety of active ingredients even while enabling increased product potency, safety, product stability, and enhanced exposure to a variety of skin treatments [6]. Many reliable and trustworthy methods for systemic medications have already been produced above the wide range of the TDS (transdermal delivery system) that employs the skin as the site of application. Many drugs' efficacy and safety have improved as a result of TDS. On the other hand, TDS is impractical for delivering materials whose destination is the skin itself. As a result, a technique that extends the duration of an active component is primarily available on the superficial layers of skin, while reducing transdermal permeation into the human body is required [7, 8]. They are polymeric, having a highly porous structure and particles with a spherical shape that look like sponges. They also minimize adverse effects, improve safety, and greatly enhance medication delivery. Micro-sponge technology is a unique drug delivery device due to its multiple approaches. Micro-sponge system is a microsphere made of tiny polymers that may well sustain or entrap a variety of substances before becoming integrated into manufactured products, for example, gel, cream, liquid, or powder [9]. Microsponges can efficiently deliver active pharmaceutical components to the targeted region at a low concentration, reducing significant systemic degradation [10]. Solid-phase porous microspheres are a patented microparticulate device known as the MDS (Micro-sponge delivery system) [11]. As a local carrier drug system, these micro-sponges can bind to a large variety of active chemicals, including emollients, fragrances, flavouring oils, sunlight protecting creams, and anti-infectives. Such porous microspheres contain active compounds used in skincare products, lotions, and powder formulations [12]. MDS can effectively boost the efficacy of topically active medicines while improving their safety, product stability, and cosmetic qualities [5].

The micro-sponges range from 5-300 m in diameter, including 250000 pores per sphere. Micro-sponges are intended to efficiently release a pharmaceutically active substance at a low dose, minimize side effects, improve stability, and alter the drug release profile. As a result, each micro-sponge contains a large reservoir that can hold up to its weight in the active agent [13, 14]. Microsponges are non-folding entities with porous surfaces that permit active compounds to be delivered slowly. Based on the size, the average porous length may be approximately 10 feet, and the pore volume may become equivalent to 1 millimetre/gram. When the MDS is introduced to the layers of skin, it emits its active component at a time and then responds to other stimuli like rubbing, temperature, and pH [12]. Won invented this micro-sponge technique in 1987 and gave Advanced Polymer Systems, Inc. the original patents [15]. Multiple elements of the technology were introduced by this business and employed in beauty products, OTC (over-the-counter), and prescribed medications. Cardinal Healthcare, Incorporated has been granted permission to apply this unique technology to the layers of skin. SEM displays the interior structure of its micro-sponge particles as a "bag of marbles." The intercellular gaps cause the porosity among the marbles. Intercellular gaps absorb sunscreens, fragrances, emollients, essential oils, anti-infective and anti-inflammatory agents, and other active substances [16]. The diameter of the micro-sponges can range from 5 - 300 µm, depending on the fluidity. Even though the dimension of the micro-sponge varies, a normal 25-meter sphere often has up to 250000 holes and 10-foot interior micropores, giving it an overall pore space of one ml/g. As a result, each micro-sponge has a large reservoir capable of weighting the active agents. Because micro-sponge materials are so significant to be retained by the epidermis, they must be applied topically, so they are considered harmless. Bacteria with pore diameters varied between 0.007 to 0.2 m are unable to pass through the microsponges structural frame due to the decreased pore diameter [6, 12, 17].

Micro-sponges can retain or pack large amounts of active substances in and out of the particle surface. They are distinguished from other dermatological delivery systems by their enormous capacity for trapping actives up to three times their weight. The primary attractiveness of this technology arises from the difficulties of releasing active chemicals over a long period using traditional topical formulations. Cosmetics and skincare products are designed to function exclusively based on the surface layer of the skin. The usual active substance in traditional therapies, on the other hand, is available in substantial quantities but will be quickly absorbed once administered topically. Typically, overmedication occurs, described as a time of lower than medicine through till the following administration. As active components permeate underneath the top layer of the skin quickly, redness, and other serious side effects, might arise. The micro-sponge innovation is built to enable a slower release rate of active compounds, perhaps lowering adverse effects while preserving therapeutic efficacy [12].

Benefits of Micro-Sponge Drug Delivery Systems

- Micro-sponges can absorb 6 times their weight in oil instead of the need for drying.
- They are a prolonged-release product that has a continual activity for 12 hours.
- The Purity (stable, effective & Safe) is improved.
- Improved patient compliance is achieved by reducing discomfort and increasing tolerance. It can also enhance therapeutic efficacy.
- They are more thermally, physically, and chemically stable [18].
- They are non-toxic, non-irritating, non-allergenic, and non-mutagenic substances.

- Micro sponge Delivery System permits immiscible products to be incorporated.
- They have a more excellent range of formulation choices.
- Unlike other methods like microencapsulation and liposomes, MDS offers a broad chemical stability range and a higher dosage and is simple to formulate [18].
- Liquids can be turned into powders, resulting in more efficient material processing.
- It can come up with more innovative product forms [19].
- MDS may help increase medication bioavailability.

Potential Features of Micro-Sponge Drug Delivery System

- Micro-sponge formulations are stable up to pH 1 to 11 [20].
- Micro-sponge preparations temperature is reliable until 130 °C; [21].
- Micro-sponge preparations may be used with a wide range of mediums and components [22].
- The standard particle dimensions of 0.25 m, which microorganisms are incapable of passing, thus make micro-sponge preparations self-disinfectant [23].
- Micro-sponge preparations are highly probable up to 50 to 60 % and are, until now, streaming as well as economical [24].

Characteristics of Actives Moieties Entrapped into Micro-Sponges

- Micro-sponge-entrapped active ingredients can be used in various products, including creams, gels, powders, lotions, and soft soaps [25].
- While manufacturing media, several aspects have been considered to attain the intended quality attributes.
- It is highly soluble in the polymer or can become completely soluble with the addition of a low proportion of a water-impermeable solution [26].
- They may also be monomer inert, so they do not affect the consistency of the solution throughout the preparation.
- They must be aqueous-insoluble or quietly miscible in water.
- The sphere-like structure of the micro-sponges should not be collapsed.
- They must be stable in the presence of the polymerization catalyst and the polymerization conditions.
- The solubility of the active ingredients, mostly in mediums, should be restricted.
- The contents and design of the polymer action micro-sponges must be modified for the appropriate release rate over time [27].

Advantages Over Other Formulations

Micro-sponges provide many benefits over other commercially available preparations.

Conventional formulation: The surface layer of the skin is the target of traditional topical medication compositions. These products release all active ingredients after application. They cover the surface with a concentrated coating of active ingredients, which are rapidly absorbed. It will cause an overabundance of components to build up there in the epidermis and dermis. The Micro-sponge system may considerably minimize all adverse effects of drug-like irritation without affecting efficiency, such as Micro-sponge Delivery System Benzoyl peroxidase preparations, which have high efficacy and minimum discomfort, by gently spreading the active ingredient to the skin [5].

Microencapsulation and liposomes: Other methods, such as microencapsulation and liposomes, have advantages that the MDS may have. In most cases, the rate of active medication release in microcapsules cannot be regulated. Once the wall of the microcapsule is burst, the active components inside will be released. Liposomes have small dimensions, seem challenging in preparation, have weak chemical stability, and are microbially unstable [5].

Ointments: Due to its cosmetically unappealing, viscous, and oily character, patient adherence to ointments is limited. Because these chemicals require large concentrations of active components for successful therapy, ointments are ineffective as drug delivery techniques, causing irritation and sensitization. Another disadvantage of external preparation (topical) is that they have an unpleasant odour, excessive evaporation of active ingredients, as well as the possibility of drug-vehicle incompatibility. On the other hand, the microsponges delivery system extends the duration an active component is present in the epidermis or on the skin surface.

Preparation of Microsponges

The Amounts of drugs in micro-sponges can be accomplished in one of two ways, based upon the physical and chemical characteristics of the medicament. The medication will form a porogen, which is a porous structure, whether it is inactive or non-polar. Porogen is a single-phase drug that neither prevents nor promotes polymerization and is devoid of free radicals [28].

Liquid-Liquid Suspension Polymerization

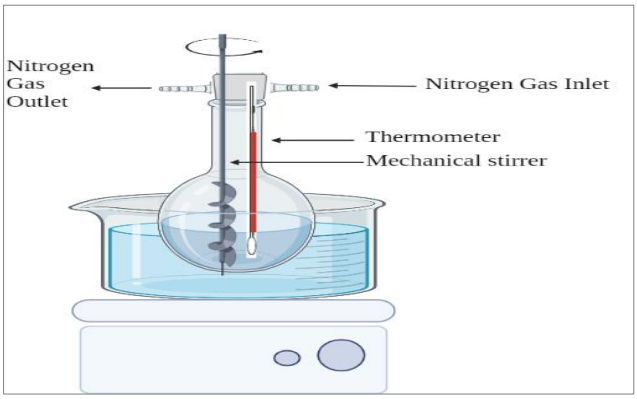

Figure 1. Method of Preparation of Microsponges by Liquid-Liquid Suspension Polymerization

The suspension polymerization process had to be used to make porous microspheres in polar solvents. Initially, the insoluble polymers were solubilized in a suitable monomer solution containing nonpolar active components [29]. They are then distributed in an aqueous phase containing a surfactant or suspending agents to aid in preparing suspension. Temperature, irradiation, or a catalyst activates the polymerization process. In a round bottom flask as shown in **(Figure 1)**, styrene or methyl methacrylate polymerization occur [30]. In the monomer, a liquid phase is introduced to a nonpolar drug solution, generally with a detergent as well as a dispersion to improve the suspension [31]. These polymers are initiated via catalytic reactions or by raising the temperature once a mixture containing distinct particles within the necessary size also was formed. Just as the medication is susceptible to polymerization processes, two different processes can be used. Under mild experimental conditions, a replacement porogen is used to polymerises the functional material, which is then replaced by the active substance. A reservoir-type device including a circular shape is generated due to the polymerization process. The liquid is eliminated following the polymerization process, concluding the nanostructure, i.e., micro-sponges [11, 32, 33].

Quasi-Emulsion Solvent Diffusion

The polymer quantities make micro-sponges using a quasi-emulsion solvent diffusion technique [10]. In spontaneous emulsification dispersion, each medications affinity against the soluble solution is more potent than that of the soluble mixture affection towards the poor solution [34]. The drug solubility is mostly in the ideal solution. The mixture was spread further into the poor solution, resulting in emulsified (quasi) particles, although pure solvents are soluble [35]. This clean solution disperses into the droplet size through the substandard liquid solvent around them, while a substandard solvent disperses through into particles, where the drug crystallizes [36]. In a two-step method, the polymer is injected into an external aqueous phase with the effective plasticizer and diffusible component (Porogen).

Micro-sponges were also made using a quasi-emulsion liquid permeation technique (2 step procedure), with an interior phase including a monomer and Eudragit RS 100, dispersed in ethyl alcohol. This medication can then be mixed into the polymer mixture and ultrasonically solubilized around 35°C. A plasticizer, including Triethyl citrate, is employed to increase the elasticity. The interior phase is transferred to an external phase made up of polyvinyl alcohol and filtered water after 2 hours of stirring. The solution is subsequently filtered to differentiate individual micro-sponge. In an oven that has been preheated with air set to 50°C, the component of the microsponge will be thoroughly cleaned and then left to dry for 12 hours [37]. **Figure 2** summarises the procedures needed to produce microsponges using the quasi-emulsion solvent diffusion method.

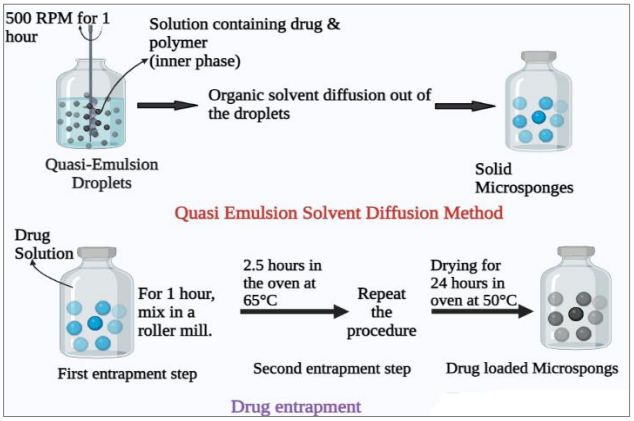

Figure 2. Method of Preparation of Microsponges by Quasi Emulsion Solvent Diffusion Method

Water in Oil in Water (W/O/W) Emulsion Solvent Diffusion

Biodegradable porous microspheres were formed using such an innovative approach. In this approach, emulsifying agents such

as span, polyethyleneimine, as well as stearyl amine were dispensed in an organic polymeric solution by an interior water phase. The w/o emulsion is distributed in an exterior aqueous solution containing PVA to develop a double emulsion. This technique will benefit from trapping medicines that are both aqueous soluble or water-insoluble. They could even entrap thermolabile substances such as proteins [38]. Xanthan gum has also been characterised as an emulsifier to stabilise an interior w/o emulsion by so many researchers [5].

Addition of Porogen

In this method, the interior water phases in oil in water (w/o/w) emulsion were altered with a porogen such as H2O2 or NaHCO3. The porogen is diffused in the polymeric solution to produce a homogenous dispersion system that has been redistributed in an aqueous phase containing PVA. The w/o/w emulsion was then given an initiator, and the organic solvents were allowed to evaporate, leaving the microparticles. Integrating hydrogen peroxide resulted in the production of pores with sizes ranging from 5 to 20 m that were dispersed equally and interrelated [39].

Oil in Oil Emulsion Solvent Diffusion

Unlike the w/o/w methodology, the oil in oil emulsion was made with a volatile organic liquid as such an internal phase, which also was permitted to evaporate gradually over time while maintaining stirring. The internal phase was dichloromethane, the polymer was polylactide glycolic acid, and the exterior phase was a mixture of fixed oil (corn or mineral) as well as dichloromethane containing sorbitan Trioleate, according to the researchers. To make the microsponges, the internal phase has been poured dropwise to the dispersion medium with continuous stirring [40]. Using acetone as the dispersing solvent and liquid paraffin as the continuous medium, this approach has been used to produce hydroxyzine HCl-loaded ERS-100 microsponges [41].

Lyophilization

The gelation process was employed to convert the microspheres into porous microspheres, and lyophilization is often used as a technique. The microspheres were incubated in a chitosan hydrochloride solution and subsequently lyophilized in this technique [42]. The production of pores in the microspheres was caused by solvent evaporation too quickly. This process is fast and effective, but it has the drawback of producing broken or shrunken micro particles due to the removal of the solvent so quickly.

Vibrating Orifice Aerosol Generator Method

The synthesis of lipid bilayered mesoporous silica particles were initially reported using a vibrating orifice aerosol generator (VOAG). Using a VOAG technique, porous particles were synthesised by evaporation-driven surfactant templating in microdroplets. The stock solution for core particle tetraethylorthosilicate was made by refluxing water, ethanol and dilute HCL. VOAG was used to dilute this stock solution with the surfactant-containing solvent and stir it to allow the generation of monodisperse droplets [43]. The microspheres were formed and enclosed in liposomes. These encapsulating particles deliver active ingredients to specific locations in the body.

Ultrasound-Assisted Production

To produce the nanosponges, this technique is altered to use β -cyclodextrin (beta-CD) as the monomer as well as diphenyl carbonate as the cross-linking agent. The mixture was then heated as well as sonicated to control the size of the microparticles. The reaction mixture was permitted to cool, and the resulting product was crushed into coarse particles that were later rinsed in distilled water and ethanol as illustrated in **Figure 3** [44]. Cross-linked Beta-CD microparticles with porous microparticles can be used as drug carriers. Moreover, this technique does have the problem of trapping cross-linking agent residue, which might be hazardous.

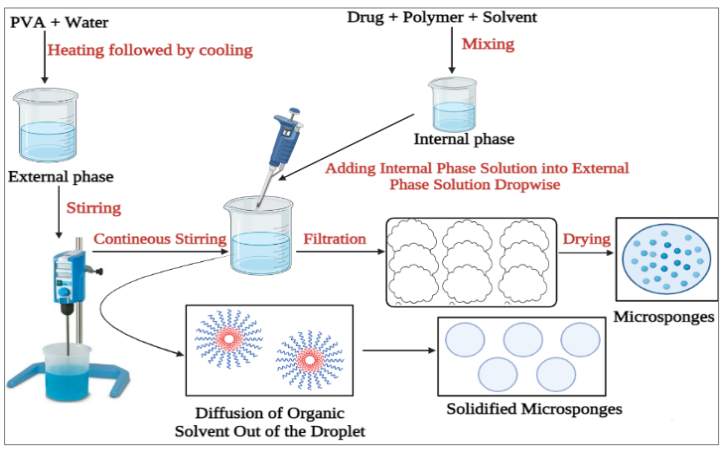

Figure 3. Ultrasound – assisted Microsponge method

Electrodynamic Atomization Method

Pancholi *et al*., in 2009, used this technique to form porous chitosan microspheres. The chitosan solution was sonicated to produce bubbles [39]. The resulting bubble suspension was collected into a syringe, transfused via a steel capillary with a syringe pump, and electro hydrodynamically atomization. The capillary diameter was chosen to ensure that all bubbles in the suspension were retained as it went through it. The chitosan content exclusively determines the voltage utilized in the tests in the solution. Except when the most significant concentration was utilized, which was challenging to electrospray, the flow rate and applied voltage combination resulted in the stable cone-jet mode in each case. A 4% w/v NaOH aqueous solution was used to cross-link the chitosan microspheres [45].

Although several techniques for fabricating microsponges were published, each has its own set of benefits and drawbacks. These concerns are listed in **(Table 1)**.

Micro-sponges can be tested for safety using the following methods

- Eye irritation experiments in rabbits can be used to determine the safety of micro-sponges.
- Rabbits were used in tests on skin irritation.
- Bacterial mutagenicity
- Rat research on oral toxicity.
- In guinea pigs, allergenicity [46].

Table 1. Advantages and Disadvantages in preparation of microsponges

Method	Advantages	Disadvantages
Liquid-Liquid Suspension Polymerization	They may be easily converted from either a one-step or two-step drug entrapment method	Undissolved monomers, as well as solvents residues, may be retained. The structure is not even uniform. The reactions with monomers take an extended period. For heat-sensitive pharmaceutical materials with limited drug loading, a two-step technique is required.
Quasi-emulsion solvent diffusion	There is no trapping of monomers. Solvent traces are limited. Drug loading is high. There is no contact between the medication and the environment. Controlling the stirring may readily alter the size of microsponges.	It could not be used to load water-soluble medicines. The monomer reaction takes a long period. A volatile water-dissolvable solvent must also be capable of dissolving the drug.
w/o/w emulsion solvent diffusion	It is an excellent way to load water-soluble medicines. It is also possible to use it to entrap proteins and peptides.	Water-insoluble surfactants are used, which can retain residues in the microsponges.
Addition of porogen	Pores are well dispersed and interlinked in this porous structure.	It is possible that the structure will be disturbed.
o/o emulsion solvent diffusion	Surfactant traces were not detected in microsponges.	To remove the residues of organic solvents, vigorous rinsing is necessary.
Lyophilization	Simple, rapid, and reproducible result	Microparticles may break either shrink as a result.
VOAG method	Microsponges are produced, which may be utilized for targeted drug delivery.	Requires the presence of gastric reflux.
Ultrasound-assisted production	There are no residues of solvent. Results that are easily predictable	The structure is irregular. Cross-linking agents that are possibly hazardous are required.
Electrohydrodynamic atomization method	Results that are easily produced	The pharmaceutical composition may bond to the monomer. Controlling particle and pore size needs skills.

Polymers and Formulation Aid in Micro-Sponges

Polymers such as Eudragit RS-100, Eudragit RSPO, Eudragit, poly lactide-co-glycolic acid, polylactic acid, polyvinyl benzene, as well as polyhydroxy butyrate have all been studied as polymers for making oral micro-sponges. Eudragit RS-100 was about the majority of extensively utilized monomers because of its versatility, which allowed researchers to use it in a variety of applications. Eudragit RSPO also controlled drug release and increased the solubility of the drug by generating a solid dispersion-like structure, which was primarily used to develop colon-targeted micro-sponges because of their high pH values (around 7); they permitted the release can be protected at lower pH. The delivery of proteins and peptides was investigated using polylactide-co-glycolic acid and polylactic acid. In accordance with the polymer's hydrophobic nature, which also inhibited the molecules from being wet by a liquid vehicle, micro-sponges manufactured with these polymers also had the potential to float. As a result, these microparticles can be used to make floating micro-sponges. The use of a wide range of polymers to create micro-sponges shows that micro-sponge preparation may be changed to meet the needs. In a combination of polymers as well as active compounds, some researchers utilized triethyl citrate as a plasticizer to help stabilize the

microsponges robust properties [47]. It has been observed as though using the quasi-emulsion solvent diffusion technique to make micro-sponges, an emulsifier is necessary to keep the liquid medium viscosity constant [10]. Researchers analyzed cellulose ethers as well as Polyvinyl Alcohol for this purpose and concluded that PVA is a better emulsifier.

Drug Release Mechanism

The action freely travels to move around both insides as well as outsides of the droplets or then through the medium till the equilibration is attained. At the same time, the diluents get saturated since the structure of micro-sponge particles is free. (A continuous membrane does not enclose particles.). The action will flow through most of the micro-sponge molecules inside the medium, then into the layer of skin till the vehicle becomes dried and disperses the action. Once a final formulation is applied to a layer of the epidermis, the action in the liquid medium would be diffused via the layers of skin, diminishing the liquid medium, which becomes unbalanced, altering the equilibrium. The activity will be gradually released to the skin by the micro-sponge particles that remain on the stratum corneum surface, providing a long-term release. The relevance of developing vehicles for usage with micro-sponge entrapments is highlighted by this proposed mechanism of action [48]. MDS-based topical drug formulation can take various forms, including gel, cream, and lotion. After the preparation has been externally applied to such a targeted region of the surface or layers of skin, the therapeutic additives disperse out from the microspheres into the medium and then onto the layers of skin. Micro-sponges may be intended to start releasing a specified concentration of active compounds throughout time in the relationship between one or more different stimuli, including pressure, changes in temperature, or solubility, as shown below in **Figure 4** [49].

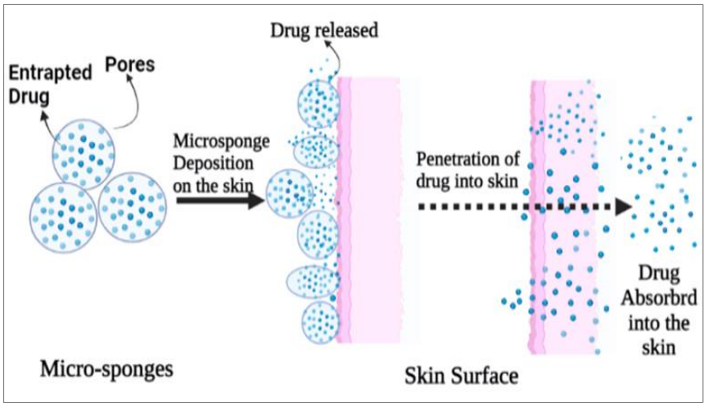

Figure 4. Mechanism of Drug Release

Temperature Change

Several enclosed active compounds are slightly viscous about to flow through micro-sponges over to layer of skin immediately at room temp 20°-25° c. The flow rate increases as the skin temperature rise, and as a result, the release rate rises as well.

Pressure

Rubbing or applying pressure to micro-sponges might cause the active substance to be released onto the skin.

Solubility

Micro-sponges prepared by water-soluble compounds disinfectants as well as deodorants may liberate their constituent whenever they come in contact with water. Diffusion might even play a significant role in the release of medication. Therefore, each component's partition coefficient among the micro-sponges also with the exterior environment must be considered [32, 50].

Drug Release from the Micro-sponge Delivery System is Affected by the Following Factors

- Physicochemical properties of any Micro-sponge system, including pore diameter and pore volume. And, robustness, as well as the properties of the vehicle.
- By rubbing and sometimes exerting pressure, active chemicals from micro-sponges can be released onto the layer of skin.

- *Temperature Change*
  Many encapsulated actives in the micro-sponge have been so viscous to flow freely through micro-sponges onto layers of skin at room temp. An increase in the flow rate and, as a result, a release can occur when body temperature increases [29].

- *Solubility*
  Micro-sponges with water-soluble compounds, including deodorants and disinfectants, may release their substance whenever they contact water. Diffusion, which considers the ingredient partition coefficients between the micro-sponges

and the rest of the system, could also be utilized to trigger the release.

Limitations of Microsponges Drug Delivery

Organic solvents are commonly used as porogens, hazardous to the environment and can be very combustible, providing a safety risk. Traces of residual monomers have been found in some situations, which could be poisonous and dangerous to individual health.

Evaluations Tests of Micro-sponges

Particle Size and Size Determination

Adjusting particle size while polymerization may result in free-flowing powders having good properties [51]. The particle size of loaded as well as unloaded micro-sponges could be determined by Laser Light Diffractometry or some other suitable methodology [52]. These D50 values might be demonstrated as the average size ranges for all formulas [53]. The cumulative % change of drug release through micro-sponges of particle size ranging would be plotted versus time to study the influence of the size of particles on the release of the drug. Particles larger than 30 m could have a rough feel; thus, in the finished topical application, particles around in the range of 10 and 25 m should be employed [54]. One of the most traditional techniques for visualizing microscopic particles is light Microscopy and SEM (scanning electron microscopy). Microparticle shape and exterior structure can be determined using both methods. Light Microscopy allows users to change the coating conditions for double-walled microparticles. Before and after coating, the shape of the microparticles can be observed, as well as the changes may be evaluated through microscopic examination. In comparison to the Light Microscope, the Scanning Electron Microscopy seems to have a higher resolution [55]. After the molecules have also been cross-sectioned, Scanning Electron Microscopy may be used to analyze the surface areas of microparticles as well as double-walled structures. The structural characterization of multiple walled microparticles is done using confocal fluorescence microscopy. Laser light scattering as well as a multi-size coulter counter, in addition to instrumental techniques, is used to analyze the sizes, shapes, as well as morphological characterization of microparticles (micro-sponges) [56].

Morphology and Surface Topography

Manufactured micro-sponges could be sprayed or coated with gold-palladium in an argon environment at room temperature for morphology and surface topography. SEM could then be used to investigate the surface morphology of the micro-sponges. An SEM may also be used to analyze the ultrastructure of a fragmented micro-sponge particle [57, 58].

Determination of True Density

Average various readings by using an Ultra-Pycnometer as well as helium gas were used to calculate the true density of microparticles [59].

$$\text{Production Yeild} = \frac{\text{Practical Mass of Microsponges}}{\text{Theorotical Mass (Polymer + Drug)}} \times 100 \quad (1)$$

Compatibility Studies

The drug compliance with reactions to pharmaceutical excipients could be examined by TLC (thin-layer chromatography) as well as FT-IR. The effects of polymers on the crystallinity of a medication may be examined by XRD as well as DSC [60]. Approximately 5 mg samples could be weighed and measured into an alumina crucible, covered, and then heated at 15° C/min in a nitrogen environment across a range of temperatures between 25° C – 43° C for DSC [61].

Dissolution Tests

A modified USP XXIII dissolution apparatus with a 5m stainless steel mesh basket can be used to study the solubility as well as dissolution rate or dissolution profile of micro-sponges. The rotating speed was 150 revolutions per minute. The dissolution media was selected when examining the dissolution of active ingredients to ensure sink conditions. Samples from the dissolution media could be analyzed using an appropriate analytical technique at various time periods [59].

Determination of pH

pH can be determined by using a pH meter, the pH should be in the range of 1-11 [18].

Determination of Loading Efficiency and Production Yield

The total % Yield is also calculated by using these formulae [62].

$$\% \text{ Yeild} = \frac{\text{Initial Weight of the Product}}{\text{Total Weight of the Product}} \times 100 \quad (2)$$

$$\text{Loading Efficiency} = \frac{\text{Drug Content in Microsponges}}{\text{Theorotical Drug Content}} \times 100 \quad (3)$$

Characterization of Pore Structure

The duration and intensity of an active ingredient's activity are determined by the volume and diameter of the pores. Pore diameter influences the migration of active compounds from microsponges into the medium in which the product is disseminated. Mercury incursion porosity can be used to investigate the effect of pore diameter and volume on the rate and extent of drug release from microsponges. Porosity parameters of microsponges such as pore size distribution, bulk and apparent density, percent porosity filled, total pore surface area, interstitial void volume per cent porosity, shape and morphology of the pores, intrusion-extrusion isotherms, and average pore diameters can all be determined using mercury intrusion porosity.

Pore Diameter

The Washburn Equation can be used to calculate the diameter of a pore,

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

Where,
γ = Surface Tension of mercury (485 dyne cm -1)
P = Presuure(psi)
D = Pore diameter (μm)
θ = Contact angle (130°)
Total Pore Area

Equation was used to calculate the result,

$$\mathrm{Atot} = \frac{1}{\gamma \mathrm{Cos}\theta} \int_{0}^{\mathrm{Vtot}} \mathrm{P.dV} \quad (5)$$

P = Pressure (psi)
V tot = Total Specific Intrusion volume (ml g -1)
V = Intrusion Volume (ml g -1)

Average Pore Diameter (Dm)

It can be calculated by using Equation,

$$D\mathrm{m} = \frac{4V\mathrm{tot}}{Atot} \quad (6)$$

A tot = Total Pore Area
V tot = Total Specific Intrusion volume (ml g -1)

Bulk Density

From this below equation bulk density can be calculated,

$$Pse = \frac{\mathrm{Ws}}{\mathrm{Vp} - \mathrm{VHg}} \quad (7)$$

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

Absolute Density

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

Vse= Volume of the Penetrometer minus the Volume of the mercury (ml)

Percent Porosity

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

Pse = Bulk Density
Psa = Absolute Density

Kinetics of Release Scanning Electron Microscopy (SEM)
The morphological, surface characteristics, as well as particle size diameter, can all be investigated with the SEM.

Fourier Transform Infrared Spectroscopy (FTIR)
The FTIR spectra of the medicine, a physical mixture of the drug and Eudragit RS-100, and formulations in a potassium bromide disc were recorded using any FTIR model. Use an FTIR spectrometer to verify compatibility [63].

Differential Scanning Calorimetric (DSC) Analysis
DSC thermally analysed a physical mixture of the medication and Eudragit RS-100; suitably weighted samples were placed into aluminium pans and sealed. All samples were heated at a rate of 20° C/min throughout a temperature range of 40° C to 43° C [9].

Application of Micro-Sponges
Microsponges have a wide range of uses. It is usually used topically, although it has been recently taken orally. It can be utilised as an excipient, according to several patents, because of its loading capacity and long-term releasing ability [64].

In oral Drug Delivery
Microsponges are used to enhance the solubility rates of weakly hydrophilic drugs in oral administration by trapping them in the pores of the micro-sponge system. Controlled oral administration of Ketoprofen and Flurbiprofen was developed using the ERS 100 polymer by quasi-emulsion solvent diffusion technique [65-68].

Topical
It has been discovered that topical delivery of benzoyl peroxide with a controlled release reduces side effects while increasing percutaneous absorption. Before being evaluated for its ability to treat irritated or sensitive skin and to combat bacteria, microsponges were developed and distributed on a gel basis. A topical delivery approach with less irritancy was successfully developed [65, 69, 70].

Micro-Sponge for Bone and Tissue Engineering Bone- Substitute
Collagen microsponges were delivered as well as displayed angiogenesis action locally in such a dose-dependent manner once the collagen was integrated into the mice sub-cutis. These findings highlight type I collagen's therapeutic potential and primary function as a BFGF (Basic Fibroblast Growth Factor) reservoir [71].

Cardiovascular Engineering Using Microsponge Technology
In cardiovascular surgery, collagen microsponge has the potential to use as a bioengineered material to enhance in situ cellularization and autologous tissue regeneration. As a biodegradable substrate, poly (lactic-co-glycolic acid) was mixed with collagen microsponge to deliver a vascular patch material [48].

Reconstruction of the Vascular Wall Using Microsponge Technology
A biodegradable polymeric scaffold of polyglycolic acid knitted mesh was coupled with a collagen-Microsponge. Moreover, it strengthened the exterior contains polylactic acid weaved to create the tissue-engineered patch. Tissue-engineered patches were grafted without pre-cellularization. No thrombosis formed in some of the animals. The grafts exhibited excellent in situ cellularization using hematoxylin/eosin. Two months after implantation, a polymerase chain reaction analysis of the cell population revealed many endothelial and smooth muscle cells [48, 72].

Anti-Ulcer
In peptic ulcers, microsponges can be used to targeting to enteric cells with anti-ulcer medicines. High medicine loading capacity made them easy to include in a traditional capsular system to treat stomach ulcers. Such delivery methods have potential advantages in terms of better therapeutic response and consistent rate of release.

Antifungal Drugs
Many antifungal drugs are available in gels or creams, which promote faster absorption. Microsponges preloaded gels shown controlled and sustained release, as well as a high drug yield and loading capacity. Topical fluconazole treatment for severe life-threatening skin fungal infections is an effective medication.

Anticancer Drugs

Chemotherapy, radiation, and surgery are common cancer treatments today, but they have significant mental and physiological side effects that mostly harm the patient's healthy cells. They can treat colorectal cancer, pancreatic cancer, stomach cancer, breast cancer, and. Anticancer medication delivery is a rapidly evolving subject, with several delivery techniques developed for specific cancer types.

Anti-Arthritis Medications

Microsponges of antipyretic drug diclofenac sodium were developed for the treatment of rheumatoid arthritis.

Antiepileptic Drugs

Carbamazepine (CBZ) is an anti-epileptic drug used to treat trigeminal neuralgia, epilepsy, and bipolar disorder. With different compositions of EC as well as PVA, CBZ microsponges were produced utilizing a quasi-emulsion solvent diffusion approach (PVA). FTIR, DSC, and XRD were used to analyze microsponges [73].

Microsponge-Based Self-Assembled DNA Hollow Spheres

A team of researchers has developed a simple technique for manufacturing DNA, HSs, enabling them to be used in drug administration and bio-imaging. Such procedure was carried out in a water-based system without the use of organic solvents, enabling for the creation of biologically and environmentally friendly products [13]. A list of microsponge uses can be found in the **(Table 2)** below:

Table 2. Application of microsponges with advantages

Sr. No.	Applications	Advantages
1	Sun-Screen	Long-lasting therapeutic efficacy of the product, including better to prevent sunburn and sun-related injury protection even at high concentrations, as well as decreasing skin irritation and sensitivity.
2	Anti-acne for ex-Benzoyl Peroxide	Reduced skin irritation and sensitivity while maintaining effectiveness.
3	Anti-inflammatory for ex-Hydrocortisone	Long-term action includes a decrease in skin allergic reactions and dermatoses
4	Anti-dandruff for ex- selenium Sulphide	Reduced pungent odor and irritation, as well as increased safety and efficacy.
5	Skin pigmenting agents for ex- hydroquinone	The stability of formulation against oxidation has been enhanced, resulting in increased effectiveness and aesthetic appeal.

Table 3. List of Marketed Products based on Microsponges

Brand Name	Manufacturer	Name Pharmaceutical Uses
Ultra-Guard	Scott Paper Company	Defends Baby Skin
Retinol Cream	Biomedic	Helps to maintain healthy skin
Salicylic Peel 20	Biophora	Very good exfoliator Sunscreen
Oil-free matte block SPF 20	Dermalogica SDR	Sun Cream
Retinol 15 Night cream	Sothys	Anti-wrinkle
EpiQuin Micro	SkinMedicaInc	Hyperpigmentation

List of microsponges-based products that have been commercialized can be shown in **(Table 3)**: [70, 74].

Recent Advances in Microsponge Drug Delivery System

Modifying the processes for making nanosponges, nanoferrosponges, and porous microbeads resulted in a few breakthroughs. Apart from polymeric micro or nanosponges, beta-CD nanosponges have been produced that can be employed for both hydrophobic and hydrophilic medicines. In most of these innovative methods, itraconazole, doxorubicin hydrochloride, serum albumin, dexamethasone, and flurbiprofen were tested as model pharmaceuticals. These nanosponges being created by re-acting the beta-CD molecule with diphenyl carbonate and cross-linking it. Nanosponges have also been reported by certain researchers to be a good transporter for the transfer of gases. Scientists also discovered that including a cytotoxic in a nanosponge carrier system can boost the efficacy of a drug, implying that these carriers could be utilised to target malignant cells [75]. Porous microbeads could pave the way for new siRNA delivery routes. Researchers noticed enhanced RNA stability and a relatively effective siRNA encapsulation technique. The monomer had a continuous oil phase, a cross-linking agent, and water as an internal phase emulsion [76, 77].

Conclusion

Microsponge drug delivery system has many benefits against traditional topical drug delivery systems, including ease of

manufacture, basic components, as well as the ability to entrap a wide range of medicines and basically designed to deliver medications such as rubefacients, anti-fungal, antipruritis, anti-inflammatory, anti-dandruffs, anti-acne etc. Microsponges have been recognized as a possible new target for controlled drug release so enhancing patient adherence by delivering to several portions of the GIT, along with the right colon and stomach. Bioerodible polymers are often used for oral medicine administration. Based on research work on microsponges, it seems that they can successfully manage dosing frequency. Throughout this context, we focused solely on the various techniques for preparing microsponges. Microsponge properties and characteristics have also been properly shown. Microsponge delivery innovation seems to be more probably towards becoming important in the future for a variety of therapeutic purposes. Microsponges have a great potentiality and this is an area of great interest that has to be researched shortly with considerable study work in order to properly develop this technology, as this system has a lot of potential for developing numerous unique pharmaceutical purposes.

Future Prospects

MDS has unique qualities such as better extended-release, enhanced medication release profile, minimize irritation and improves physical, chemical, and thermal stability. Such particles may be used as cell culture media, which means they may could be used for stem cell cultivation as well as cellular renovation in the human body. In addition, these carrier systems have been discovered that are used in beauty products due to their elegance. These advancements allowed scientists to use them in a variety of ways. These formulative innovations also open up the latest avenues for medication delivery [77, 78].

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