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MICROSPONGES: A PROMISING APPROACH FOR DRUG DELIVERY

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ABSTRACT: Micro sponges are patented polymeric drug delivery systems consisting of porous microspheres. The physical appearance of microsponges is tiny spherical sponge-like with the surface with large spores. Micro sponges are typically used and nowadays used as the oral dosage form. The inert and indestructible tiny spherical particles do not pass through the skin. But, it collects in the tiny nooks and crannies of skin. Thus slowly release the drug for a prolonged period. It prevents the excess accumulation of drugs within the epidermis and dermis. They have a modified drug release pattern with lesser side effects. Micro sponges are biologically safe and provide a selective advantage of programmable drug release. Micro sponges Drug Delivery System provides entrapment of ingredients because of its porous nature and is believed to contribute lesser side effects, improve drug stability, increase elegance, and enhance formulation flexibility. One of the best features of microsponges is their self- sterilizing property. Several studies have confirmed that Micro sponges are non-mutagenic, non-allergic, non-irritant, and non-toxic. This review focused on preparation, characterization, release mechanism, and other Micro sponges Drug Delivery System parameters.

INTRODUCTION: Micro sponges are extremely cross-linked, non-collapsible, porous, polymeric microspheres having a particle size range from 5 to 300 μm that can entrap a wide range of active ingredients and release them over an extended time. Micro sponges have unique dissolution and compression properties due to their sponge-like texture. They are highly effective, stable, non-irritant, non-toxic, non-allergic, non-mutagenic, and also minimum side effects with improved patient compliance. Various polymers like Eudragit RS100, ethylcellulose, polystyrene; PHEMA, *etc*., have been utilized in forming microsponges. Further, these active microsponges can be incorporated into formulations, such as capsules, gel, and powders, and share a broad package of benefits.

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The microsponges have demonstrated their use in cosmetics and pharmaceuticals *viz*. antifungal vaginal gel, in augmented arthritis therapy, as silver sulfadiazine-loaded microsponge gel for burn wounds, in gastro retentive delivery, as matrix tablet and in colon-specific drug delivery system *etc* [1]. Like a true sponge, each microsphere consists of many interconnecting voids within a non-collapsible structure with a large porous surface. Won developed the microsponge technology in 1987, and the original patents were assigned to Advanced Polymer Systems, Inc. This

company developed a large number of variations of the technique and applied those to cosmetic and over-the-counter (OTC) and prescription pharmaceutical products. At present, this interesting technology has been licensed to Cardinal Health, Inc., for use in topical products. The size of the microsponges can be varied, usually from 5 - 300 μm in diameter, depending upon the degree of smoothness or after-feel required for the end formula. Although the microsponge size may vary, a typical 25 μm sphere can have up to 250000 pores and an internal pore structure equivalent to 10 ft in length, providing a total pore volume of about 1 ml/g; which results in a large reservoir within each microsponge, which can be loaded with up to its own weight of the active agent.

The microsponge particles themselves are too large to be absorbed into the skin, which adds safety to these micro sponge materials. Another safety concern is the potential bacterial contamination of the materials entrapped in the microsponge. As the size of the pore diameter is smaller, the bacteria ranging from 0.007 to 0.2 μm cannot penetrate into the tunnel structure of the microsponges [2].

Micro sponges are generally prepared by solvent removal from microemulsion templates. These sponge-like carriers are chiefly composed of polymers dispersed in an aqueous system with the aid of a stabilizing agent. Removal of the solvent from microemulsion droplets leads to the porosity of resultant carriers. Their inherent features of enhanced drug payload and stability, along with the potential for reduced irritation, mutagenicity, and allergenicity, contribute to their superiority over the contemporary colloidal carriers. Because of the structure and physiology of human skin, microsponges offer enhanced efficacy of dermatological agents and reduce local adverse effects.

The characteristic size of microsponges (5-300 μm) is the most crucial feature for topical application, because it hinders their passage through stratum corneum. Hence, these carriers are especially advantageous as delivery systems for dermal applications, as these allow the drug to be present on the skin surface/epidermis for a prolonged period. At the same time, the transdermal penetration of the active agent is minimized.

This attribute is of paramount importance in the context of topical delivery of drugs. Additionally, owing to their porous nature, microsponges permit controlled release of the entrapped drug, resulting in minimum deposition of the active moiety in the epidermis and dermis. However, the particulate nature of microsponges makes them less appropriate for direct topical application. Therefore, they are incorporated in topical bases, such as gel, emulgel, ointment, or cream for better efficacy [3].

Advantages of Micro Sponges as A Novel Drug Delivery System:

- Micro sponges are liable to withstand high temperatures up to approx. 130 °C.
- Micro sponges provide stability over a wide range of Ph of ≈ [1, 11].
- They have a loading efficiency of 50- 60%.
- They generally pass first-pass hepatic metabolism.
- Micro sponges resist moisture absorption.
- Skin absorbent property of the microsphere is good.
- Unwanted reactions are generally not shown by microsponges.
- Relative to other drug delivery systems, micro sponges provide a longer half-life.

Ideal Properties of Micro Sponges as A Novel Drug Delivery System:

- The spherical structure of microsponge should maintain its integrity and should not collapse.
- Slightly solubility of microsponges should be maintained; water immiscibility is preferred.
- It should not react with polymerization catalyst and must be stable.
- It should be inert to monomers, and during formulation viscosity of the mixture should not be increased,
- The particle size of microsponges is 10-25 μm in diameter.

Suitability of Drug to Dosage form:

- MDS is generally used in treating skin diseases like fungal infections, which include Athlete's Foot, Sporotrichosis, ringworm, Candidiasis (Yeast Infection), and viral infection like Varicella Zoster (chicken
- Pox), herpes simplex virus infection, Cytomegalovirus (Epstein bar virus).
- MDS is suitable for an anti-inflammatory drug as they release API for a prolonged period (sustained-release).
- The molecular weight of API should be very less, i.e., 600 g/mole, to penetrate easily.
- t1/2 of the drug should be less than 5hrs, suitable for sustained action of the drug.

Formulation Consideration: The vehicle will deplete the Microsponges if the solubility of the active component is not limited before the application to avoid problems not more than 10-12% w/w. Optimization of Polymer design and payload of the Microsponges for the active form is required for release rate for given period 4.

Methods of Preparation of Micro Sponges:

Liquid-Liquid Suspension Polymerization: By suspension polymerization technique, Micro sponges are formulated in a liquid-liquid system. Firstly the monomers are dissolved with the active ingredients and then dispersed in the aqueous solution considering that the API should be less soluble than the solvent. In order to formulation into suspension, the aqueous phase consists of additives such as surfactants and suspending agents. Once the suspension is formed with discrete droplets of the desired size, polymerization is carried out by activating the monomers by catalysis, increased temperature/irradiation. Continuing the polymerization process, a spherical structure is formed containing thousands of microsponges forming interconnecting reservoirs that look like a bunch of grapes. As the polymerization is completed, the solid particles are separated from the suspension. The particles are washed thoroughly and processed until they are ready for use.

Styrene and divinylbenzene or methyl methacrylate and ethylene glycol dimethacrylate can be used as the starting material for the production of micro sponges material [5, 6].

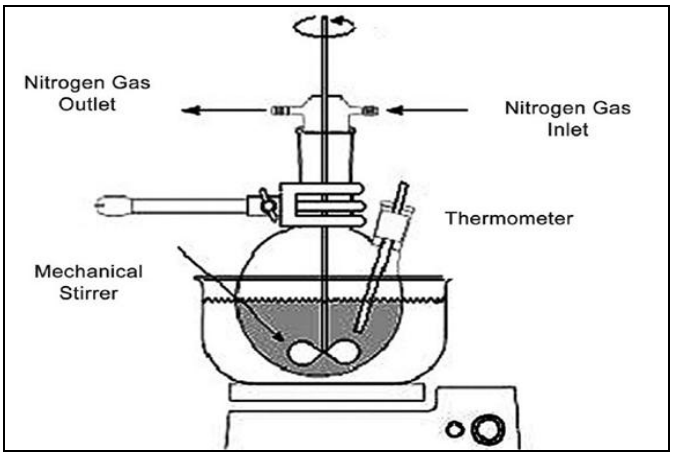

FIG. 1: REACTION VESSEL FOR MICROSPONGE PREPARATION BY LIQUID-LIQUID SUSPENSION POLYMERIZATION

Quasi-Emulsion Solvent Diffusion: For the preparation of the inner organic phase, Eudragit RS 100 is generally dissolved in ethyl alcohol. Then the drug is added to the solution and ultrasonified at 35 °C. The inner phase is then poured into polyvinyl alcohol after dissolving in water which is an outer phase **Fig. 2.** It is stirred for 60 min and the mixture is filtered to separate the micro sponges. Following the micro sponges are dried at 40 °C for 12 h in an air-heated oven.

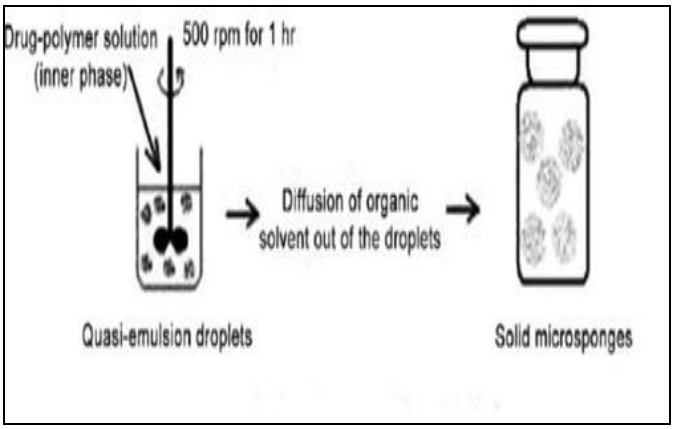

FIG. 2: QUASI EMULSION SOLVENT METHOD.

If the ingredients are labile to withstand polymerization conditions, they are post-entrapped after the formation of microsphere structure, or the ingredients are entrapped in the microsponges during synthesis. In general, the former processes are generally used as the cosmetics ingredients, and

other pharmaceutical products can't withstand high temperatures and generally decomposes at high temperatures **Fig. 3.** [2].

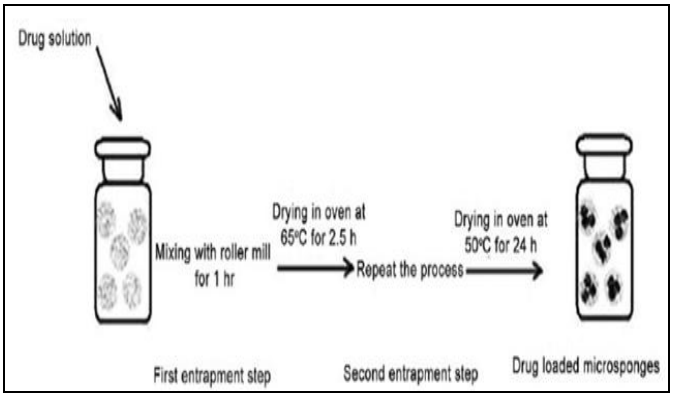

FIG. 3: DRUG ENTRAPMENT

Hypothetical Mechanism of Action: In an entrapped form, the ingredients are added to the vehicle. The active form is free to move in and out into the particle from the vehicle as the microsponges have open structure until and unless the equilibrium is reached, *i.e.,* the vehicle becomes saturated. As soon as the product is applied onto the skin, the active ingredients will deplete the vehicle and be absorbed into the skin, thus disturbing the equilibrium of the vehicle as it becomes unsaturated. This starts a flow of the active ingredients into the vehicle from the microsponges and next to the skin until full drying or fully absorbed of the vehicle.

The microsponge particles are retained on the surface of the stratum corneum and will gradually release the active ingredients to the skin, enhancing prolonged release. This hypothesis focused on the importance of formulating vehicles for the use of microsponge entrapments. If the solubility of the active form is much more into the vehicle during the formulation of the finished products, then the prolonged-release mechanism of the microsponges will be hampered. Thus in the formulation of microsponge entrapment, the vehicle should have the minimal solubilizing capacity for the active ingredients. This principle is different from the conventional method for preparing topical products, as the conventional method maximizing the solubility of the active form in the vehicle is much more needed. The microsponge polymer should be formulated with some entrapped as well as free active ingredients so that the vehicle is pre-saturated to avoid undesirable premature leaching of the active ingredients. The rate of release of the active ingredients will depend on the partition coefficient between the polymer of the active ingredient and the vehicle and on some of the parameters responsible for the characterization of the beads. Examples are surface area, which generally means pore diameter. The active ingredients' release depends on different parameters like pH, moisture, temperature, and fiction [7, 8].

Evaluation of Micro Sponges:

Particle size Analysis: Particle size and size distribution are generally evaluated using an optical microscope or electron microscope. The surface of the formulation and its stability greatly depends on the size of the particle. Particle size analyses of loaded and unloaded microsponges are generally carried out by using laser light diffractometry. The values of (d50) are the mean size range for all formulations. Cumulative percentages of the release of active ingredients from the vehicle of the different particles are plotted against time for the study of the effect of particle size on the drug release from microsponges.

Determination of Entrapment Efficiency:

The loading efficiency (%) of the microsponges is generally calculated using the following equation:

By calculating the initial weight of the raw material used and the final weight of the product formed, the production yield of the microsponges are calculated:

Surface Topography and Morphology of Micro Sponges: For these studies, various techniques are used, such as:

- Transmission emission microscopy (TEM)
- Scanning electron microscopy (SEM)
- Photon correlation spectroscopy (PCS)

The surface morphology of microsponges is studied by coating the microsponges with gold-palladium under an argon atmosphere at room temperature. For this method, SEM is used.

Characterization of Pore Size: The efficacy and concentration of the active ingredients in the microsponges are determined by pore diameter and pore volume. The transfer of the active ingredients

from micro sponges into the vehicle and drug release rate is affected by the pore diameter. Other parameters of

Micro Sponges Are Also Studied Such as:

- total pore surface area,
- intrusion-extrusion isotherms,
- pore size distribution,
- average pore size diameters,
- shape and morphology of the pores,
- bulk and apparent density

Determination of Pore Diameter: The conventional method of measuring pore sizes and the pore diameter is by B.E.T equation, nitrogen multipoint analysis. For the measurement of the pore volume the mercury intrusion method is used.

Determination of True Density: Ultra-pycnometer is used for the measurement of the true density of microparticles under helium gas and calculated from the mean of repetitive obtained values.

Drug-Polymer Compatibility Studies: To ensure that there is no reaction between drug and polymer the drug- excipients compatibility studies should be done during the formulation of the dosage form. The studies are carried out by the Differential Scanning Calorimetry (DSC) of the chemicals that are the API and excipients individually adding or deleting peaks.

Approx. 5 mg samples are accurately weighed into aluminum pans and sealed and heated at 15 °C /min at a temperature range of 25-430 °C an atmosphere of nitrogen. (FTIR) spectroscopy is also used to calculate the incompatibilities that occur between the chemical moieties.

Resiliency: Resiliency is a viscoelastic property of Microsponges modified to produce beads softer or firmer for the formulation of the final products.

The rate of release of drugs is slowed down by increasing the cross-linking. Thus resiliency study of microsponges is done and optimized as per the requirements.

***In-vitro* Release Studies:** Dissolution apparatus USP XXIII which is equipped with a basket-type 5 µm stainless steel mesh are used for the in-vitro release studies and is maintained at 37 °C, 150 rpm speed. Ensuring sink condition and considering the solubility of the active ingredients the dissolution medium selected. Samples are withdrawn and analyzed in a UV-Visible spectrophotometer at regular intervals.

Evaluation of Microsponges Gels

Organoleptic Properties: The organoleptic properties such as color, homogeneity, consistency, texture, and physical appearance of gel containing microsponges are examined.

pH Measurement: Digital pH meter is used to calculate the pH of the final gel formulation. 5 g of gel is dispersed in 45 ml distilled water at 27 °C and pH of the solution is measured.

Spreadability Studies: Wooden block and glass slide apparatus is used to determine spread ability, which consists of two slides out of which the lower slide is non-movable, and the upper slide is movable. Weights of about 20 gm are generally added to the pan and time is noted for the upper slide to separate completely from the non-movable slides. And then spreadability is calculated.

S = M.L/T= Where, S= Spread ability w = weight tide to upper slide L = length of glass slide T = time taken to separate the slide completely from each other

Viscosity: Brookfield viscometer is used to measure the viscosity of the gel formulation by using 1 × model and cone number 01, having an angular velocity of 5 rpm at 25 ºC. An average of five readings were used to calculate viscosity.

Skin Irritation Studies: The score for erythema was studied by giving the formulation from 1-10 and was seen with 1 represent least irritation and 10 represents highest serious irritation [9, 10].

Use of Microsponges:

- Microsponge is used as sunscreen for long-lasting effects [11].
- It is used as anti-acne agent using benzoyl peroxide. It helps to get relief from skin

irritation [12]. It is also used as anti dandruffs agent using zinc pyrithione [12].

- It is used as skin de-pigmenting agent (hydroquinone) [13]. Flucinolone acetonide, an anti-inflammatory gel, is prepared using eudragit micro sponge which helps to reduce skin inflammation and to get relief from skin irritation [14].
- Miocrosponge prepared based on liquid suspension used Fluconazole. This is active against fungi and used in topical formulation to get relief from itching [15].
- Aceclofenac is used in microsponges having anti-inflammatory and analgesic properties. This is prepared based on Quasi emulsion methods [16].
- Micros ponges which is prepared using Quasi-emulsion solvent diffusion technique used Itraconazole which also has anti fungal activity. It is useful in treating both systemic and superficial fungal infections [17].
- Micro sponge loaded with fluorouracil prepared based on emulsion solvent diffusion technique used in primary and secondary fungal infection [18].

  Hydroxyzine HCl can be used in microsponge prepared using solvent diffusion technique. Eudragit RS-100 polymer is used in this case.
- Acetone is used as dispersing solvent, and liquid paraffin is used as the continuous medium.

  To prevent flocculation of Eudragit RS-100 microsponges, Magnesium stearate was added to the dispersed phase [19].

TABLE 1: MARKETED PREPARATIONS [20]

Product name	Manufacturing Company	Features
Retinol cream	Biomedic	The retinol molecule, which is kept in the microsponge system gives protection to the potency of vitamin A. It helps maintain healthy skin, hair and mucous membranes
Retinol 15 night cream	Biomedic, sothys	This microsponge system contains pure retinol. The use of Retinol 15 will result in the visible diminishment of fine lines and wrinkles and improve in skin discolorations
Carac cream, 0.5%	Dermik Laboratories, Inc. Berwyn, PA19312 USA	Carac cream is prepared using 0.5% fluorouracil, with 0.35% is incorporated into a patented porous microsphere (Microsponge . It is also composed of methyl methacrylate / glycol dimethacrylate cross-polymer and dimethicone
Line eliminator dual retinol facial treatment	Avon	Lightweight cream with retinol (Vitamin A) in MDS, It helps to deliver immediate and time-released action against wrinkle.
Sports cream RS and XS	Embil Pharmaceutical	It has topical analgesic-anti-inflammatory and counterirritant actives in a Microsponge® Delivery System (MDS). It is used to manage the problem of musculoskeletal problem
Micro peel plus	Biomedic	The MicroPeel® Plus helps in stimulating to turn over the cell by applying, salicylic acid in the form of microcrystals using Microsponge® technology
Oil control lotion	Fountain Cosmetics	Feature-light lotion microsponges helps to absorb oil on the skin surface in day time and give a matte finish The natural-antibiotic Skin Response Complex helps to get relief from inflammation and promoting healing, Acne-Prone, oily skin conditions
Retin-A-Micro	Ortho-McNeil Pharmaceutical,Inc	0.1 And 0.04% tretinoin entrapped in MDS, has a topical activity to treat acne vulgaris. The formulation is prepared using patented methymethacrylate / glycol+8 dimethacrylate cross-polymer porous microspheres
Lactrex™ 12% moisturizing cream	SDR Pharmaceuticals, Inc., Andover, NJ, .S.A. 07821	It has a composition of 12% lactic acid as the neutral ammonium salt and ammonium lactate. Lactrex™ also contains water and glycerin, which is a natural humectant. It helps in softening and to moisturize dry, flaky, cracked skin
Ultra guard	Scott Paper	This Microsponge system contains dimethicone giving protection a baby's skin from diaper rash

Future Prospects: For the topical delivery of the drugs microsponges are generally used as one of the novel drug delivery systems. Biodegradable polymers are used in controlled drug delivery system and tissue engineering in the application of microsponges. Micro sponges have many advantages, such as the Liquids can be transformed into free-flowing powders. The use of preservatives can be eradicated as incompatible ingredients can be formulated with microsponges for prolonged stability. Transdermal delivery systems micro-sponges can find a wide range of use as an ideal drug delivery system as it requires high concentration of vehicles to dissolve the API for effectiveness of the therapy. It causes irritation and hypersensitivity reactions in some users. Topical drugs that are made of conventional formulations work on the outer layer of the skin. Thus, there is a need to increase the contact time of the active ingredients that are present on the skin or present in the skin epidermis. Recent studies say that there are some micro sponges based products that are approved and some others are under clinical development and assessment [2].

CONCLUSION: Micro sponge Delivery System (MDS) is successfully applied in the field of controlled drug delivery for its uniqueness. It offers entrapment of a wide variety of drugs and other ingredients, providing reduced side effects, improved stability and elegance, and formulation flexibility. This system does not allow the excessive accumulation of drugs within the epidermis and dermis.

The indestructible micro sponge particles potentially reduce skin irritation without reducing its efficacy. MDS is an effective carrier for localized drug delivery. Studies have shown that this system is non-toxic, non-irritating, non-mutagenic, and non-allergic. Currently, this delivery approach has been widely applicable not only in pharmaceuticals but also in the cosmetic industries.

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