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AN OVERVIEW ON MICROSPONGES FABRICATION, ADVANTAGES & APPLICATIONS

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ABSTRACT

Microsponges based drug delivery and its manufacturing technology was introduced in pharmaceutical industry in the year 1987.The primary aim was to provide controlled and localized release of active drug ingredient by this technique. Their application to the skin proven to have decrease systemic exposure and reduce local dermal reaction to active drug moiety. Microsponges are polymeric delivery system composed of porous microspheres, typically 10-25 microns in diameter. They are tiny sponge-like spherical particles with a large porous surface. Their porous nature and reduced size decreases the side effects and modify drug release favorably. This delivery system provides extended release with reduced irritation, better tolerance, improved thermal, physical and chemical stability. The main goal of any drug delivery system is to achieve desired concentration of the drug in tissues, that is therapeutically effective and non-toxic over the entire duration of action. Several manufacturing techniques of microsponges based on diffusion, polymerization, sonication and vibration are considered effective and economical. Microsponges are mostly used for topical use and now its applicability for oral administration is also justified. Thus, microsponges based drug delivery system has got a lot of potential and is one of the most evolving fields which needs exploration to understand its future in pharmaceuticals and biological sciences. This review deals with different fabrication techniques of microsponges along with their advantages and applications in present era and the future it beholds.

Keywords: Microsponges, Delivery system, polymer, porous, topical

INTRODUCTION

Innovations in microsponges based drug delivery systems have received a lot of attention recently. In order to alter and regulate the release behavior of the several medications and to modify therapeutic index, duration of action of certain API's a carrier polymeric system was introduced. The use of substances like-hydroxy acids and vitamins in topical solutions that has advantages in preventing ageing or in protection of photo-damaged skin, has gathered public interest in skin care and skin treatment products. Despite having certain aids, these compounds caused frequent skin irritation in form of redness, burning or stinging. To overcome this issue, formulators worked on two techniques: Firstly, they decreased the concentration of active ingredient and secondly in order to make the product more skin-friendly they changed the vehicle **[1]**. But both these strategies lessen the end product's promising effects. Advancements in drug delivery systems and devices were thus required to cope with the growing market for novel medications that are both effective and safe. The healthcare system has been significantly dominated by novel medication delivery methods that regulate release rates of APIs for localized therapeutic effect. Transdermal and topical delivery systems (TDS), that uses skin as a channel for systemic drug administration offers various methods to deliver drug at a predictable rate **[2]**. Many medicationsthat are delivered through skin contact using novel delivery system techniques showed an improvement in effectiveness and safety. TDS, however, is not a viable delivery method for compounds limited to get deliver in skin. Recently a controlled drug release system targeting epidermis where the medication will remain mostly localized and won't reach the systemic circulation in considerable amounts have been created. The use of topical medications also has a number of issues, for e.g., ointments that are unappealing, has greasiness, stickiness, and other issues leading to poor patient compliance. Delivery systems, that need large concentrations of active substances for treatment often leads to irritability and allergic responses. Other downsides of topical preparations include uncontrolled evaporation of the active component, offensive odor, and possible drug-vehicle incompatibility. The outer skin layers are the target area for conventional topical medications. Usually, when applied, these products release their active components, creating a thin coating of highly concentrated active substance that is quickly absorbed. In order to optimize the release of active ingredients on the surface or inside the skin a novel delivery system was required. These limitations of TDS lead to

the discovery of microsponges. Microsponges are minute spheres that may absorb skin secretions, lessening the skin's oiliness and gloss. The capacity of spherical particles to store four times their weight in skin secretions is greater than that of clusters of even smaller spheres **[3]**.

Properties of Microsponges

Microsponges particles are micro sized tiny, comparatively safe, unbreakable spheres that do not penetrate the skin, instead, they gather in the tiny gaps of the skin and gradually release the medicine held there when requires. The microsponges system can prevent accumulation of substances in dermis and epidermis. Without compromising the effectiveness of the medications, the micro sponge technology has the potential to greatly minimize the discomfort caused. Microsponges based delivery method, has led to the development of a brand-new generation of very effective, unique drug delivery products that are also very well-tolerated. These products often come in the standard forms that consumers are familiar with, such as creams, gels, or lotions that has optimum concentration of active chemicals.

Microsponges are proprietary polymeric delivery systems made of porous microspheres that can hold a variety of active substances, including emollients, perfumes, essential oils, sunscreens, anti-fungal, and anti-inflammatory medications **[3]**. Each microsphere has a wide porous surface that contains a huge number of interconnected spaces, much like a real sponge. The initial patents for the micro sponge technology were given to Advanced Polymer Systems, Inc. by Won in 1987 **[4]**. The technology was created by this corporation and was used in a wide range of cosmetic, over-the-counter (OTC), and prescription drug items. For topical products, Cardinal Health, Inc. currently has the license for this technology. Depending on the level of smoothness and after-feel required from the final formulation, the size of the microsponges might vary, typically from 5 to 300 micro m in diameter. The size of microsponges can range from a characteristic 25-micrometer sphere having up to 250000 holes and an internal pore structure that can be10 feet long, giving it a total pore volume of around 1 ml/g **[8]**. Each micro sponge develops a sizable reservoir that can be filled with an active chemical eqv. to its own weight. These micro sponge materials provide an added level of safety since the micro sponge particles are too big to be absorbed into the skin. The possible bacterial contamination of the substances trapped in the micro spongecan call for safety concern. However, bacteria with pore diameters between 0.007 and 0.2 m cannot enter the microsponges tiny sized tunnel structure.

Advantages of microsponges based drug polymeric system [3]

- Microsponges increases the absorption rate of active ingredients up to 6 times.
- Microsponges shows stability over a wide range of pH (1 to 11).
- They are stable even at very high temperature of 130^0 Celsius.
- They significantly increase patient compliance, adds elegance and improves bioavailability of the formulation.
- They are economical and can be used for large number of drugs applied topically.
- Extended release, better therapeutic efficacy and predictable release rates can be achieved using microsponges technology.
- They are proven to better tolerated as they are non-mutagenic, non-allergic and nontoxic in nature.
- Microsponges has high entrapment efficiency of 50-60% in comparison to liposomes where it is only 20-30%.

Ideal properties of APIs for Entrapment into Microsponges

- **Solubility:** The active moiety should either be completely miscible in the monomer selected or its miscibility can be improved by the addition of a tiny amount of a water-impermeable solvent. Water immiscible or slightly soluble drugs can also be formulated in the form microsponges.
- **Inertness:** The active drug moiety should not alter the physical characteristics of the final formulation.
- **Stability:** During the polymerization process the active drug moiety must remain inert to monomers. It should remain stable so that the spherical structure of microsponges remains intact **[4]**.

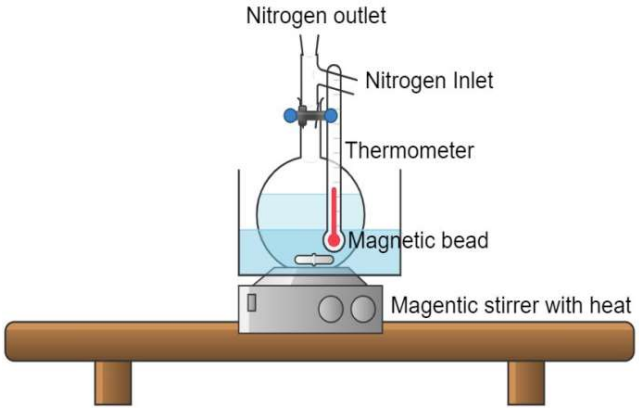
MATERIALS AND METHODS: TECHNIQUES TO LOAD DRUGS IN MICROSPONGES

To effectively load a drug in microsponges based polymeric system, a polymerization and a diffusion-based technique is generally used. There are two ways to prepare microsponges: liquid-liquid suspension polymerization is a one-step procedure whereas quasi-emulsion solvent diffusion is a two step technique. Various other procedures were also established and were used depending on the benefits and the drawbacks accompanied.

1.Liquid-liquid suspension polymerization

To achieve polymerization and to prepare a porous spherical structure this technique is used. The first step is to select a monomer or

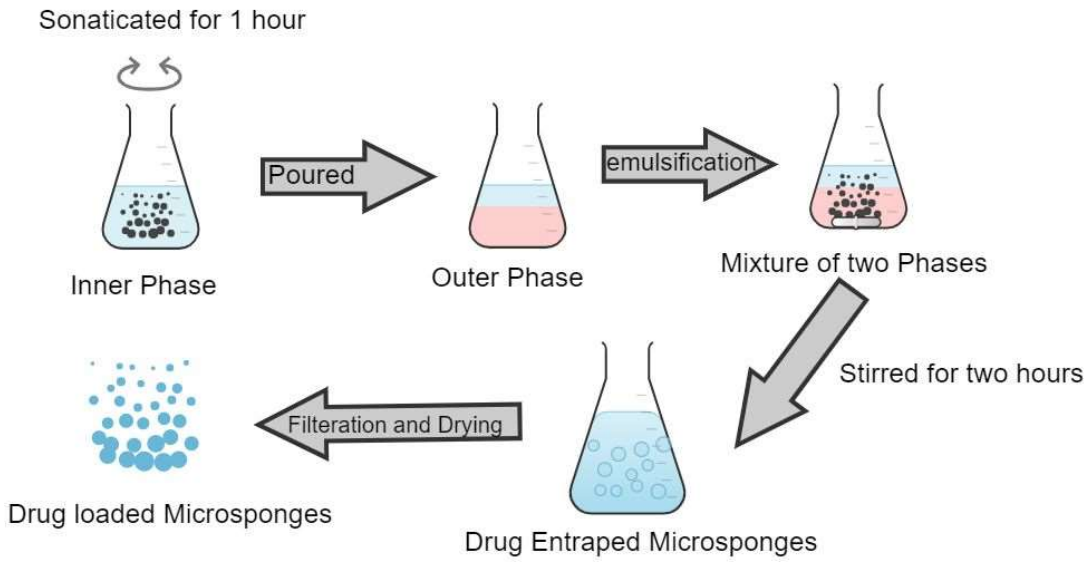
a combination of monomers for e.g., beta-cyclodextrin monomer and diphenyl carbonate etc. to form chain of monomers by crosslinking. Active drug moiety is also added to this monomeric solution. Consider this as phase I. This Phase I is then suspended by continuous stirring to aqueous phase that consists of additive and surfactants. The aqueous phase is considered as phase II. After the suspension of Phase II in Phase I discrete globules of desired size will be obtained. The polymerization process can be altered by variation in temperature, catalyst and irradiation. A reservoir-type system with a spherical structure continues to be formed through the polymerization process. These microspheres congregate to form microsphere bunches. Microspheres are bound together to create tiny sponges and can be separated from suspension. The reaction was conducted in a flask with three necks that had a round bottom. The flask is additionally equipped with a stirrer, a water condenser, and a thermometer **[5]**.



Liquid liquid polymerization technique

2. **Solvent diffusion using a quasi-emulsification technique**

Quasi means partial or almost. This is a two step procedure that works on selection of two phases: Inner and outer phase. The inner organic phase is to be prepared by using a suitable polymer like Eudragit RS or ethyl cellulose and dissolving this in ethyl alcohol. The active drug is added to inner phase and subjected to ultrasonication at a temperature of 35^0C. The outer phase can be prepared by using Polyvinyl alcohol and water. The inner phase was then poured to the outer phase at room temperature. The mixture was continually stirred for the following two hours after emulsification. To separate the microsponges, the mixture was filtered after that and was heat air dried at 40 degrees Celsius for 12 hours **[6]**.



Quasi Emulsification technique

3. **Solvent diffusion via multiple emulsion method**

This technique works on the principle of double emulsification. An internal aqueous phase with an emulsifying agent is to be mixed with an organic polymeric solution. A double emulsion is thus created by dispersing this water-in-oil emulsion once again in an external aqueous phase that consists of polyvinyl alcohol. Microsponges of both water immiscible and immiscible APIs, thermolabile substances can be formulated by using this multiple emulsion technique **[7]**.

4. **Inclusion of a porogen**

Porogens like hydrogen peroxide or sodium bicarbonate are used in the interior phase. Polymeric solution containing porogens to be redispersed in an aqueous phase containing PVA. After uniform mixing of the phases, hydrogen peroxide is added as initiator to build interconnecting pores with sizes ranging from 5 to 20 µm are created. After evaporation of organic solvent, microsponges can be collected. [9]

5. **Method using a vibrating orifice aerosol generator**

The technique vibrating orifice aerosol generator (VOAG) creates monodisperse particles of uniform size in the range of 20-50 µm. This device works on controlling two parameters (i) liquid flow rate, (ii) oscillation frequency. It was primarily used to prepare lipid bilayered porous particles of silica. Tetraethyl orthosilicate, ethanol, water, and diluted hydrochloric acid is to be refluxed to make stock solution, which is used to prepare the core particle. The stock solution was further diluted using solution of surfactant. A syringe pump is used to feed liquid solution through a small orifice. A piezoelectric ceramic cause continuous

oscillation creating vibration and producing uniform size droplets. The volatile component from these droplets gets evaporated leaving uniform sized solid microspheres **[10]**.

6. Electro-hydrodynamic Atomization Method

This method is utilized to produce a porous microsphere of chitosan. Chitosan solution is firstly sonicated to generate bubbles, and the resultant bubble suspension are to be extruded through a steel capillary utilizing a syringe pump before being subjected to electrohydrodynamic atomization. The diameter of the capillary was carefully chosen in order to keep all the bubbles within the suspension while it flowed through. The voltage used in the experiments is dependent upon the concentration of chitosan in the solution. The chitosan microspheres were cross-linked by 4% w/v sodium hydroxide aqueous solution.

CHARACTERIZATION OF MICROSPONGES:

Prepared Microsponges are to be characterized for following parameters

A. Physical Characterization

- Particle size determination by using techniques like microscopic diffractometry, DLS etc.
- Scanning electron microscope study for understand morphology of microsponges.
- Determination of loading potency and production yield by weight calculation method.
- True density by using Ultra pycnometer.
- Rheological properties, compressibility.
- Pore Structure by mercury intrusion porosimetery.
- Resiliency i.e., viscoelastic properties.

B. Chemical Characterization:

- Drug content and loading efficiency.
- Drug release by USP Type II apparatus.
- Compatibility study by DSC, FTIR and Xray diffraction etc.

Applications of Microsponges-based Delivery Systems:

Recent advancement in microsponges based drug delivery system made it accessible for applications to various delivery routes. Advancements in the technology had provided controlled drug release in response to stimuli such as Temperature, pressure, pH and solubility.

Applications of microsponges are not limited to TDS but it has also shown its promising results when delivered orally **[13]**.

- **Topical drug delivery using micro sponge technology**

Several active components were experimented to deliver via microspongic formulations. An emulsion solvent diffusion approach was be used to create an organic internal phase comprising benzoyl peroxide, ethyl cellulose, and dichloromethane for microspongic administration of benzoyl peroxide via suspension polymerization of styrene and divinyl benzene in a stirred aqueous phase containing polyvinyl alcohol **[14-16]**. The produced microsponges were mixed with a gel basis, and the microspongic gels were tested for their ability to inhibit bacterial growth and cause skin irritancy. A slower rate of drug release occurred in the system that was trapped than in the system that had free BPO. It was effective in developing the topical delivery technique with less irritancy **[16]**.

A novel formulation of hydroquinone (HQ) (4%), combined with retinol (0.15%), was created and fabricated in microsponge reservoirs to gradually release HQ, also to extend therapy response and reduced skin irritation. A 12-week, open-label research was conducted to assess the product's effectiveness and safety. HQ 4% with retinol 0.15% was both safe and efficient in open-label research **[17]**. It was also shown that the release might potentially be prolonged by using a microsponges method for topical administration of fluconazole gel **[18]**. Retinoic acid MDS was created and evaluated for drug release and anti-acne effectiveness. Greater lesions reductions, which were statistically significant, were attained with retinoin trapped in the micro sponge **[19]**. The therapy of the musculoskeletal system involves applying topical analgesic, anti-inflammatory, and counterirritant medications in a microsponge® **[20]**.

- **Oral drug delivery using microsponge technology**

By trapping ineffectively water-soluble pharmaceuticals in the pores of the microsponge system, it has been demonstrated that the microsponge system speeds up the rate of solubilization of such medications in oral applications. As a result of the medicine being effectively reduced to microscopic particles by these tiny holes, the surface area has been increased, which significantly accelerates the rate of solubilization. By adjusting the intraparticle density of ibuprofen microsponges, controlled oral administration of the medication is made possible with the acrylic polymer eudragit RS **[21]**. The dry impact blending method is used to create a chlorpheniramine maleate sustained release formulation for oral medication administration that uses powder-coated microsponges **[22]**.

Controlled oral administration of ketoprofen was created using the quasi-emulsion solvent diffusion approach using Eudragit

RS 100, and then the direct compression method was used to create microsponges. The physical combination of the medication and polymer, which produced mechanically robust tablets, showed enhanced compressibility, according to the results. This was attributed to the plastic deformation of the sponge-like microsponge structure. A commercial Microsponge® 5640 technology was used to administer flurbiprofen to the colon specifically and under regulated conditions. According to in vitro studies, the addition of the enzyme caused compression-coated colon-specific tablet formulations to begin releasing the drug at the eighth hour, which corresponds to the time the proximal colon arrived, in a modified release pattern. In contrast, the drug release from colon-specific formulations made by pore-plugging microsponges increased at the eighth hour, which was the time the enzyme addition was made **[23]**.

- **Microsponge-based Delivery Systems for Bone and Tissue Engineering**

Two aqueous dispersions of a-tricalcium phosphate grains and calcium-deficient hydroxyapatite powders were combined with pre-polymerized polymethylmethacrylate and liquid methyl methacrylate monomer powders to create bone-substitute compounds. The resulting composites had a porous appearance and served as microsponges **[24]**.

Basic fibroblast growth factor (BFGF), which was included in a collagen sponge sheet, was continuously released in the mouse sub-cutis in response to the sponge matrix's biodegradation and displayed local angiogenic activity in a dose-dependent manner. A considerable increase in blood flow was elicited in the ischemic hind limb of a mouse by intramuscular injection of collagen microsponges containing BFGF, which was not possible with bolus BFGF administration. The relevance and therapeutic value of type I collagen as a BFGF reservoir are suggested by these findings **[25]**. In order to allow for the regeneration of the autologous vessel tissue, a biodegradable graft material comprising the collagen microsponges was designed for cardiovascular tissue transplantation **[26]**. Human skin fibroblasts were cultured in three dimensions using a thin biodegradable hybrid mesh made of synthetic poly (DL-lactic-co-glycolic acid) (PLGA) and naturally produced collagen. In order to create the hybrid mesh, PLGA-knitted mesh holes were filled with collagen microsponges that resembled webs **[27]**. The in-situ regeneration at the venous and arterial walls of a tissue-engineered patch consisting of our biodegradable polymer and collagen-microsponges was excellent, indicating that this patch might be exploited

as a novel surgical material for the repair of the cardiovascular system **[28]**.

LIST OF ABBREVIATIONS:

1. m- meter
2. API- Active Pharmaceutical Ingredient
3. MDS- microsponges delivery system
4. ml/g- milliliter/gram
5. TEC- Triethyl citrate
6. PVA- Poly Vinyl Alcohol
7. HQ- Hydro quinone
8. BFGF- Basic fibroblast growth factor
9. BPO- Benzyl Peroxid

Patents and marketed formulation of microsponges [29, 30]:

Brand Name	Drug	Uses (in)	Manufacturer/ Patented
Neobenz®micro	Benzyperoxide, methylmethacrylate	Keratolytic	Intendis Inc. Morristown NJO7962 USA
Salicylic peel 30	Salicylic acid 30%	Removal of dead skin	John and ginger dermatologica skin care products
Carac cream 0.5%	5-FU	Actinic keratosis	Dermis lab. Inc. US
Retinol	Retinol	Healthy skin	Biomedic
Retin A micro	Retinol	Acne vulgaris	Ortho-mcneil pharmaceuticals Inc.
Retinol 15 nightcream	Retinol	Antiwrinkle	Sothys, Paris France
Epiquin micro	Retinol and hydroquinone	Hyperpigmentation	Skin medica Inc. US
Sunscream RS and XS	Antiinflammatory	Musculoskeletal conditions	Embil Pharmaceuticals
Latrex™12%	Lactic acid	Moisturization	SDR Pharmaceuticals, Inc., Andover, NJ U.S.A 07821
Ultraguard	Dimethicone	Diaper rash cream	Scott. Paper company
Melanin microsponge®	Melanin		Advanced polymer system Inc., US
Line eliminator dual cream	Retinol	Wrinkle fighting action	AVON

CONCLUSION AND FUTURE PROSPECTS:

Microsponges are one of the revolutionary drug delivery methods that were first created with the aim of topical medication administration. However, they can also be utilized for regulated oral medication administration and tissue engineering employing biodegradable polymers. It offers a broad variety of formulating benefits. Topical formulations have the drawbacks of uncontrolled evaporation of the active component, offensive odor, and possible drug-vehicle incompatibility. The outer skin layers are the target area for conventional topical medication compositions. Usually, when applied, these products release their active components, resulting in a thin film of the active substance that is quickly absorbed. In order to optimize the duration an active substance is available, either on the skin's surface or inside the epidermis, a microsponge based mechanism is thus required. While many more are still being developed and are undergoing clinical evaluation, certain microsponges-based products have already received approval. Presently, sunscreens, over-the-counter skin

care, and prescription medicines all make use of this technology. This kind of drug delivery technique might improve our knowledge of how various diseases are treated. Oral delivery of microsponges still need pilot plant scale up to thoroughly understand its potential.

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