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A NEW ERA IN TOPICAL FORMULATIONS – MICROSPONGE DRUG DELIVERY SYSTEM

Avhad Pawan S.* and Patil Prashant B.

Department of Pharmaceutics, S.N.D. College of Pharmacy, Yeola, Dist – Nashik -423401. Maharashtra, India.

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Correspondence to Author:
Avhad Pawan S.

Asst. Professor,
Department of Pharmaceutics, S.N.D. College of Pharmacy, Yeola, Dist – Nashik - 423401. Maharashtra, India.

E mail: pawanavhad@gmail.com

ABSTRACT: Microsponge is recent novel technique for control release as well as target specific drug delivery system. Therefore many researchers are attracted towards the microsponge drug delivery system. Microsponge technology has been introduced in topical drug products to increase the controlled release of active drug into the skin in order to reduce entry of drug in blood and maintain drug on skin surface. Microsponge technology offers entrapment of ingredients, improved stability, reduced side effects, increased elegance, and enhanced formulation flexibility. Various studies have shown result that microsponge systems are non-irritating, non-allergenic, nonmutagenic, and non-toxic. This technology is used currently in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products. This technology has the best feature that it is self-sterilizing. In this article we focused on method of preparation, characterization (Particle size and its distribution, surface morphology, porosity, density are covered), advantages, disadvantages and application of microsponge.

INTRODUCTION: [1-5] Transdermal drug delivery system supplies the drug to systemic circulation with the help of number of penetration enhancers. The target of TDDS is to provide maximum amount of drug in blood circulation by crossing skin layers. Sometimes there is needed to keep drug in skin layers for local effect without entering in systemic circulation is a challenging task. To achieve this goal carrier and microparticle technology is required, by using these technology one can maintain drug in skin only. Generally ointments, creams, and pastes are the formulations applied to the skin for its local action.

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These formulations give many disadvantages such as greasiness, stickiness, and requires high amount of drug in formulation, also evaporation of many drugs takes place. These formulations also give particular odors and sometimes allergy with skin. So to avoid such a drawbacks we have to make such formulation which can give more drug release on skin surface without entering in blood stream by using new technology.

The microsponge technology was developed by Won in 1987 and the original patents were assigned to ad-vanced polymer system. Microsponges are spherical shape particles having pores and myriad of interconnected voids of particle size range of 5-300µm. They are tiny sponge like particles; (As shown in **Fig.1**) these microsponges have capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, and anti-infective and are used as a topical carrier

system. Further these porous microspheres with active ingredients can be incorporated into formulations such as creams, lotions and powders.[4] Various techniques have been developed for systemic delivery of drugs below the heading of Transdermal delivery system (TDS) using the skin as portal of entry. It has improved the efficacy and safety of many drugs that may be better administered through skin. But TDS is not practically useful for those drugs whose target is only a skin and blood.

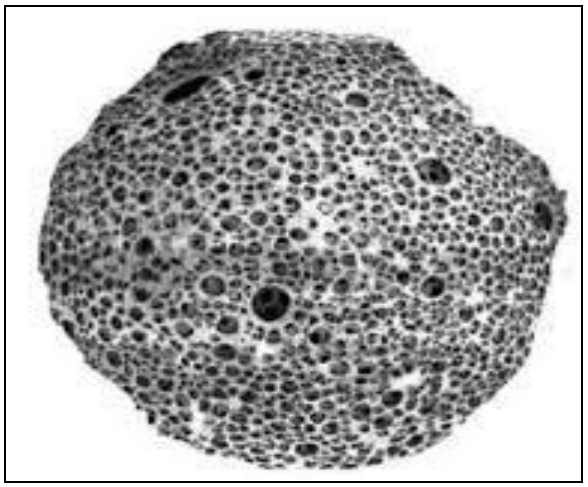

FIG.1: MICROSPONGE IMAGE

Characteristic of Microsponge drug delivery systems:

1. Microsponges are stable over the long Ph range from 1 to 11.
2. Microsponges are stable up 130 ^{0} c temperature.
3. Microsponges are compatible with many of ingredients and excipients.
4. Average pore of microsponge is 0.25 μ, so there no need of sterilization.
5. About 50 to 60 % drug may be entrapped in microsponges.
6. Microsponges show free flowing properties.
7. These are inert molecules without any allergy, irritation and toxicity.

Advantages of microsponge drug delivery systems:

1) These are act as controlled drug delivery system.

2) Drug directly applied on target organs.

3) It increases stability of drug.

4) Drug loading capacity is higher compare with other topical formulations.

5) These are capable of absorbing skin secretions and reduce oiliness.

Requirement of material to be formulated in to a Microsponge:

1) Material must be either fully miscible in monomer or capable of being made miscible by addition of small amount of co solvent.

2) Material should be water immiscible or only slightly soluble.

3) Material should be inert to monomers.

4) Material should be stable in contact with polymerization catalyst and conditions of polymerization.

Method of Preparation of Microsponges:

1. **Liquid- Liquid Suspension Polymerization:**
   In this method two phases are mixed one phase contains active ingredient and monomer are mixed together to form a solution (which is non polar). This phase is suspended in second phase containing additives like surfactant or dispersing agents. Once the suspension is obtained with desired particle size polymerization is done by activating monomer either by increased temperature, irradiation or catalysis. (As shown in **Fig.2**)

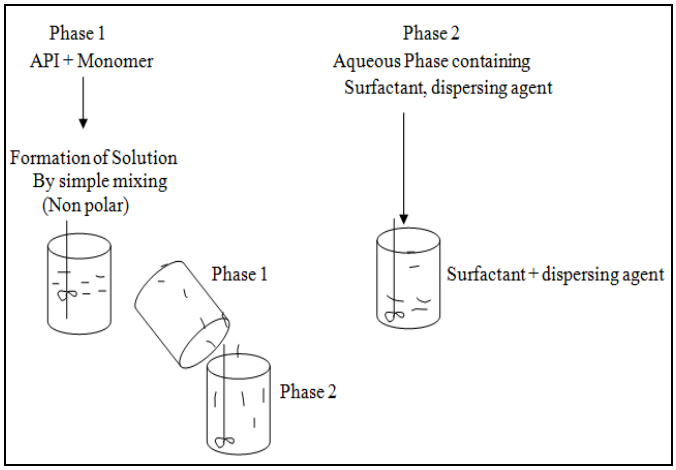

FIG.2: FORMATION OF SUSPENSION FOR PREPARATION OF LIQ-LIQ SUSPENSION POLYMERIZATION.

2. **Quasi Emulsion Solvent diffusion method:**
   In this method there is a formation of two different phases one is internal and second is external phase like an emulsion. Internal phase consist of solution of drug and polymer made with volatile solvents like ethanol, acetone, dichloromethane. This phase is added in second phase i.e. external phase which consist of aqueous polyvinyl alcohol with vigorous stirring. Also triethylcitrate is added in concentration of 20 % to facilitate plasticity. (As shown in **Fig.3**)

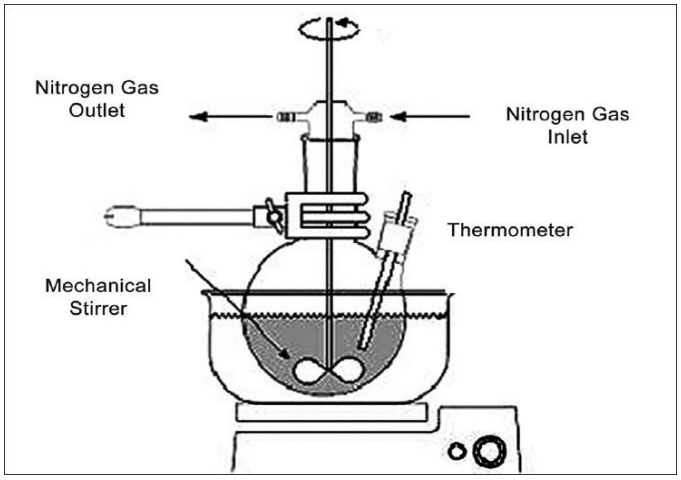

FIG.3: FORMATION OF SUSPENSION FOR PREPARATION OF QUASI EMULSION SOLVENT DIFFUSION METHOD

Hypothetical Mechanism of Action:

The active ingredient is added to the vehicle in an entrapped form. As the microsponge particles do not have a continuous membrane surrounding them have an open structure, the active is free to move in and out from the particles and into the vehicle until equilibrium is reached, when the vehicle becomes saturated. Once the finished product is applied to the skin, the active that is already in the vehicle will be absorbed into the skin, depleting the vehicle, which will become unsaturated, therefore, disturbing the equilibrium. This will start a flow of the active from the microsponge particle into the vehicle, and from vehicle to the skin, until the vehicle is either dried or absorbed. After drying or absorbed vehicle microsponge particles are retained on the surface of the stratum corneum will continue to gradually release the active to the skin, providing prolonged release over time. This proposed mechanism of action highlights the importance of formulating vehicles for use with microsponge entrapments.

If the active is very soluble in the particular vehicle during compounding of the finished products, the products will not provide the desired benefits of gradual release. Instead they will behave as if the active was added to the vehicle in a free form. Therefore, while formulating microsponge entrapments, it is important to design a vehicle that has minimum solubilizing power for the actives. This principle is vice varsa to the conventional formulation principles usually applied to topical products. For these conventional systems it is generally recommended to maximize the solubility of the active in the vehicle.

Evaluation of Microsponge: [12-18]

(i) Particle size Analysis:

Particle size analysis of loaded and unloaded microsponges can be performed by laser light diffractometry or any other suitable method. The values can be expressed for all formulations, size range. Cumulative percentage drug release from microsponges of different particle size will be plotted against time to study effect of particle size on drug release. Particles larger than XY µm can impart gritty feeling and hence particles of sizes between PQ and 25µm are preferred to use in final topical formulation.

(ii) Morphology and surface topography of microsponges: Prepared microsponges can be coated with gold–palladium under an argon atmosphere at room temperature and then the surface morphology of the microsponges can be studied by scanning electron microscopy (SEM). SEM of a fractured microsponge particle can also be taken to illustrate its ultra-structure.

(iii) Determination of loading efficiency and production yield: The loading efficiency (%) of the microsponges can be calculated according to the following equation:
Loading efficiency = Actual Drug Content in Microsponges X 100 …….. (1)
Theoretical Drug Content: The production yield of the micro particles can be determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponge obtained.
Production Yield= Practical mass of Microsponges X 100…… (2)
Theoretical mass (Polymer+drug).

(iv) Characterization of pore structure: Pore volume and diameter are vital in controlling the intensity and duration of effectiveness of the active ingredient. Pore diameter also affects the migration of active ingredients from microsponges into the vehicle in which the material is dispersed. Mercury intrusion porosimetry can be employed to study effect of pore diameter and volume with rate of drug release from microsponges. Porosity parameters of microsponges such as intrusion– extrusion isotherms pore size distribution, total pore surface area, average pore diameters, interstitial void volume, percent porosity, percent porosity filled, shape and morphology of the pores, bulk and apparent density can be determined by using mercury intrusion porosimetry.

(v) Dissolution tests: Dissolution release rate of microsponges can be studied by use of dissolution apparatus USP XXIII with a modified basket consisted of 5µm stainless steel mesh. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. The samples is removed and analysed at various intervals from the dissolution medium by suitable analytical methods.

(vi) Determination of true density: The true density of micro particles is measured using an ultra-pycnometer under helium gas and is calculated from a mean of repeated determinations.

(vii) Viscoelastic properties: Resiliency (visco elastic properties) of microsponges can be modified to produce beadlets that is softer or firmer according to the needs of the final formulation. Increased cross-linking tends to slow down the rate of release.

Applications of Microsponges: [19-22]

Microsponge delivery systems are used to improve the safety, effectiveness and quality of topical prescription, over-the-counter and personal care products. Microsponges can be used in variety of applications. It is used mainly for topical and now a days for oral administration. It can be used as an excipient due to its high loading capacity and sustained release ability. It offers the manufacturer a range of alternatives to develop drug and cosmetic products. Microsponges are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and they also enhance stability, reduce side effects and modify drug release. Over-the-counter products that incorporate microsponge drug delivery system include numerous moisturizers, specialized rejuvenated products, and sunscreens.

1. Microsponge used for topical delivery- The Microsponge systems are based on microscopic, polymer-based microspheres that can bind, suspend or entrap a wide variety of substances and then it get incorporated into a formulations, such as a cream, gel, liquid or powder. A single Microsponge is as tiny as a particle of talcum powder, measuring micron in diameter. Like a true sponge, each microsphere consists of a myriad of interconnecting voids within a non-collapsible structure that can

accept a wide variety of substances. The outer surface is typically porous, allowing the controlled flow of substances into and out of the sphere. Several primary characteristics, or parameters, of the Microsponge system can be defined during the production phase to obtain spheres that are tailored to specific product applications and vehicle compatibility. Microsponge systems are made of biologically inert polymers. Extensive safety studies have demonstrated that the polymers are non-irritating, non- mutagenic, non-allergenic, non-toxic and non-biodegradable. As a result, the human body cannot convert them into other substances or break them down.

2. Microsponge used as oral delivery- In oral applications, the microsponge shown increase the rate of solubilisation of poorly water soluble drugs by entrapping such drugs in the microsponge system's pores. As these pores are very small, the drug is in effect reduced to microscopic particles and the significant increase in the surface area thus greatly increases the rate of solubilisation. Colon-specific, controlled delivery of Flurbiprofen was conducted by using a commercial Microsponge 5640 system. In vitro studies exhibited that compression-coated colon-specific tablet formulations started to release the drug at the eighth hour, corresponding to the proximal colon arrival time, due to addition of the enzyme, following a modified release pattern, while the drug release from the colon-specific formulations prepared by pore plugging the microsponges showed an increase at the eighth hour, which was the point of time when the enzyme addition was made.

3. Microsponge used for Bone and Tissue Engineering- Bone like Compounds were obtained by mixing pre polymerized powders of polymethyl methacrylate and liquid methyl methacrylate monomer with two aqueous dispersions of tricalcium phosphate grains and calcium deficient hydroxyapatite powders. The final composites appeared to be porous and acted as microsponges. Basic fibroblast growth factor (bFGF) incorporated in a collagen sponge sheet was sustained released in the mouse sub-cutis according to the biodegradation of the sponge matrix, and exhibited local angiogenic activity in a dose-dependent manner. The injection of collagen microsponges incorporating bFGF induced a significant increase in the blood flow, in the murine ischemic hind limb, which could never have been attained by the bolus injection of bFGF. These results suggest the significance and therapeutic utility of the type I collagen as a reservoir of bFGF.

4. Recent advances in microsponge drug delivery system- Various advances were made by modifying the methods to form Nan sponges, nanoferrosponges and porous micro beads. β - CD nanosponges were also developed that can be used for hydrophobic as well as hydrophilic drugs, in contrast to polymeric micro or nanosponges. These advanced systems were studied for oral administration of dexamethasone, Flurbiprofen, doxorubicin hydrochloride, itraconazole and serum albumin as model drug. These nanosponges were developed by cross- linking the β CD molecule by reacting the β-CD with biphenyl carbonate. Some researchers also observed the nanosponges as good carrier for the delivery of gases. Researchers also observed that incorporating a cytotoxic in a nanosponge carrier system can increase the potency of the drug suggesting that these carriers can be potentially used for targeting the cancerous cells.

CONCLUSION: There is a very high demand in international market for new and very efficient Pharmaceutical and Cosmetic products. The market requires potential and versatility for Microsponge technology. During formulation consideration formulator can realize the full capabilities of these unique materials which provides improved stability, enhanced safety, reduction in side effects from API, enhanced multifunctionality and improved ingredient compatibility. Microsponge delivery system is a challenging for a new generation of Pharmaceutical and Cosmetic industry.

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