WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 3, Issue 9, 318-334. Review Article ISSN 2277– 7105

# MICROSPONGES: A NOVEL APPROACH FOR DRUG DELIVERY SYSTEM

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Article Received on
08 September 2014,

Revised on 02 Oct 2014,
Accepted on 26 Oct 2014

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## ABSTRACT

Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge- particles with a large porous surface which are spherical in shape having reduce side effects, enhance stability, modify drug release. In topical drug delivery system for retention of dosage form on skin, microsponges can be effectively incorporated. Allowing a sustained flow of substances out of the sphere, the outer surface is typically porous, This system can suspend or entrap a wide variety of substances, and incorporated into a formulated product such as a liquid, gel, cream, or powder. These formulations are stable over range of pH 1 to 11 and temperature up to 1300C; compatible with most vehicles and ingredients. Microsponges are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to, reduce side effects, modify drug release andenhance stability.

**KEYWORDS**: Controlled release, Topical drug delivery, Microsponges.

## INTRODUCTION

A Microsponge Delivery System (MDS) is a polymeric system consisting of porous microspheres that can entrap wide range of drugs and then release them over a time and in response to targeting site. Microporous beads are unique technology for the controlled release of topical agents which consists of 10-25 microns in diameter, loaded with active agent. [1] When applied to the skin the MDS releases its active ingredient on a time mode, and also in response to other stimuli (rubbing, temperature, pH, etc). MDS technology is being used in cosmetics, sunscreens, prescription products and over-the-counter (OTC) skin care. The system comprised of a polymeric bead having network of pores with an active ingredient held within was developed to provide controlled release of the active ingredients fotr the targetting

of skin itself. [4] For the improvement of performance of topically applied drugs, the system was employed. The incorporation of the active substance at its maximum thermodynamic activity in an optimized vehicle and the reduction of the resistance to the diffusion of the stratum corneum. and liposomes. Microcapsules cannot usually control the release rate of actives. Once the wall is ruptured the actives contained within microcapsules will be released.[2] Liposomes suffer from difficult formulation, lower payload, microbial instability and limited chemical stability. While microsponge system in contrast to the above systems are stable over range of pH 1 to 11, temperature up to 130˚C; compatible with most vehicles and ingredients; higher payload (50 to 60%), still free flowing, self-sterilizing as average pore size is 0.25µm where bacteria cannot penetrate; and can be cost effective. Most liquid or soluble ingredients can be entrapped in the particles. Active agents that can be entrapped in microsponges must full fill following requirements; It should be either fully miscible in monomer or capable of being made miscible by addition of small amount of a water immiscible solvent.

1. It should be water immiscible or at most only slightly soluble.
2. It should be inert to monomers.
3. It should be stable in contact with polymerization catalyst and conditions of polymerization Release can be controlled through diffusion or other triggers such as moisture, pH, friction, or temperature. This release technology is available for absorbent materials or to enhance product aesthetics. Microsponge delivery system can be incorporated into conventional dosage forms such as creams, lotions, gels, ointments, and powder and share a broad package of benefits. Systems can and improve its formulation flexibility. [3]

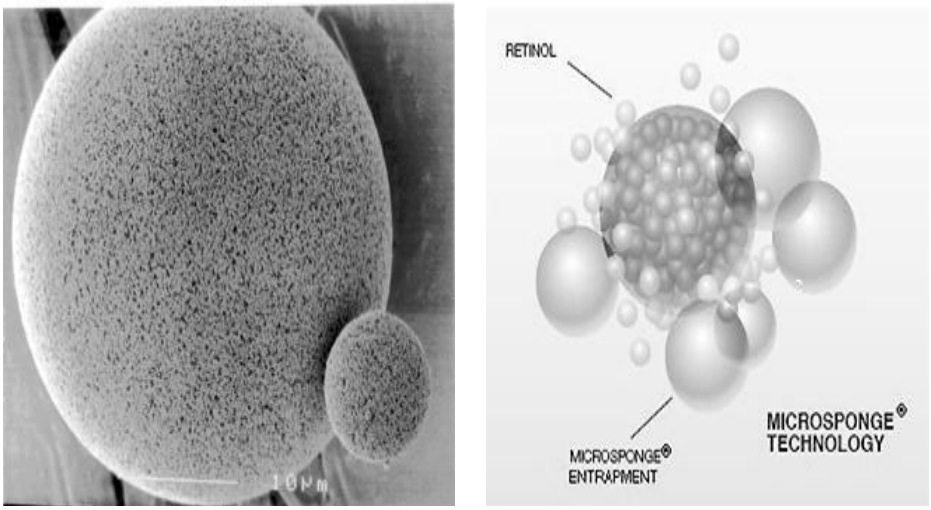



**Figure 1: View of Microsponge**

## CHARACTERISTICS OF MICROSPONGES [4]

1. Microsponge formulations are stable over range of pH 1 to 11;
2. Microsponge formulations are stable at the tem-perature up to 130oC;
3. Microsponge formulations are compatible with most vehicles and ingredients;
4. Microsponge formulations are self sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate;
5. Microsponge formulations have higher payload (50 to 60%), still free flowing and can be cost effective.

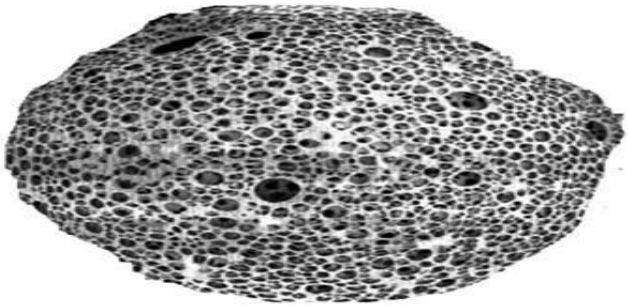


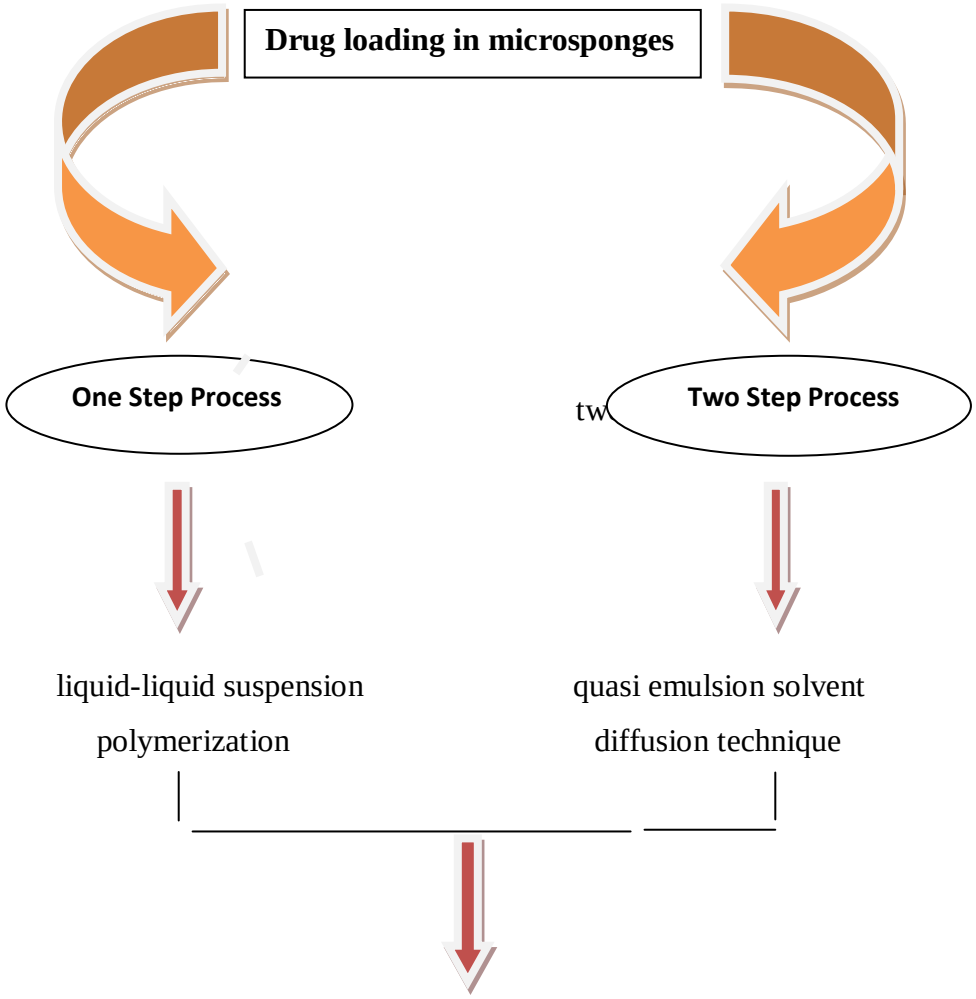
**Fig. 1.1: Highly porous nature of a Microsponge**

### Characteristics of Materials That Is Entraped in Microsponges [5]

Most liquid or soluble ingredients can be entrapped in the particles. Actives that can be entrapped in micro-sponges must meet following requirements,

1. It should be either fully miscible in monomer or capable of being made miscible by addition of small amount of a water immiscible solvent.
2. It should be water immiscible or at most only slightly soluble.
3. It should be inert to monomers.
4. It should be stable in contact with polymerization catalyst and conditions of polymerization.

**Preparation of Microsponges**




**Liquid-liquid Suspension Polymerization** [6]

In liquid-liquid systems the porous microspheres are prepared by suspension polymerization method. The various steps in the preparation of microsponges are-

1. The monomers are first dissolved along with active ingredients in a suitable solvent
2. Solution of monomer and are then dispersed in the aqueous phase, which consist of additives (surfactant, suspend-ing agents, etc. to aid in formation of suspension).
3. The polymerization is then initiated by adding catalyst or by increasing temperature or irradiation.

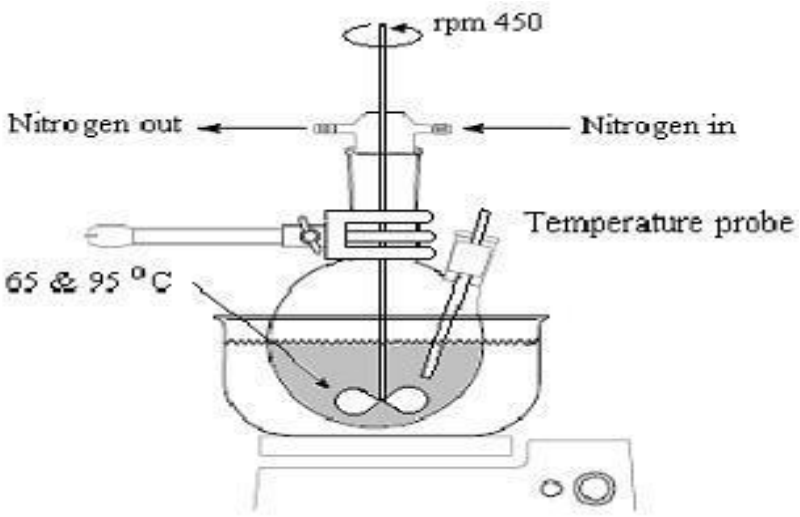



**Figure 2: Reaction vessel for microsponge preparation by liquid-liquid suspension polymerization**

The polymerization process leads to the formation of a reservoir type of system, which opens at the surface through pores. In some cases an inert liquid immiscible with water but completely miscible with monomer is used during the polymerization to form the pore net-work. After the polymerization the liquid is removed leaving the porous microspheres, i.e., microsponges. Impregnating them within preformed microsponges then incorporates the functional substances. Some-times solvent may be used for faster and efficient in-corporation of the active substances. The micro-sponges act as a topical carriers for variety of function-al substances, e.g. anti acne, anti inflammatory, anti purities, anti fungal, rubefacients, etc.

**Quasi-emulsion Solvent Diffusion** [7]

All microsponges were prepared by a quasi-emulsion solvent diffusion method using an external phase of containing 200 ml distilled water and 40 mg polyvinyl alcohol (PVA) 72 000. The internal phase consisted of ketoprofen, ethyl alcohol, polymer and triethylcitrate (TEC), which was added at an amount of 20% of the polymer in order to facilitate the plasticity. At first, the internal phase was prepared at 60°C and added to the external phase at room temperature. After emulsifica-tion, the mixture was continuously stirred for 2 hours. Then the mixture was filtered to separate the micro-sponges. The product was washed and dried by va-cuum oven at 40°C for 24 hours.

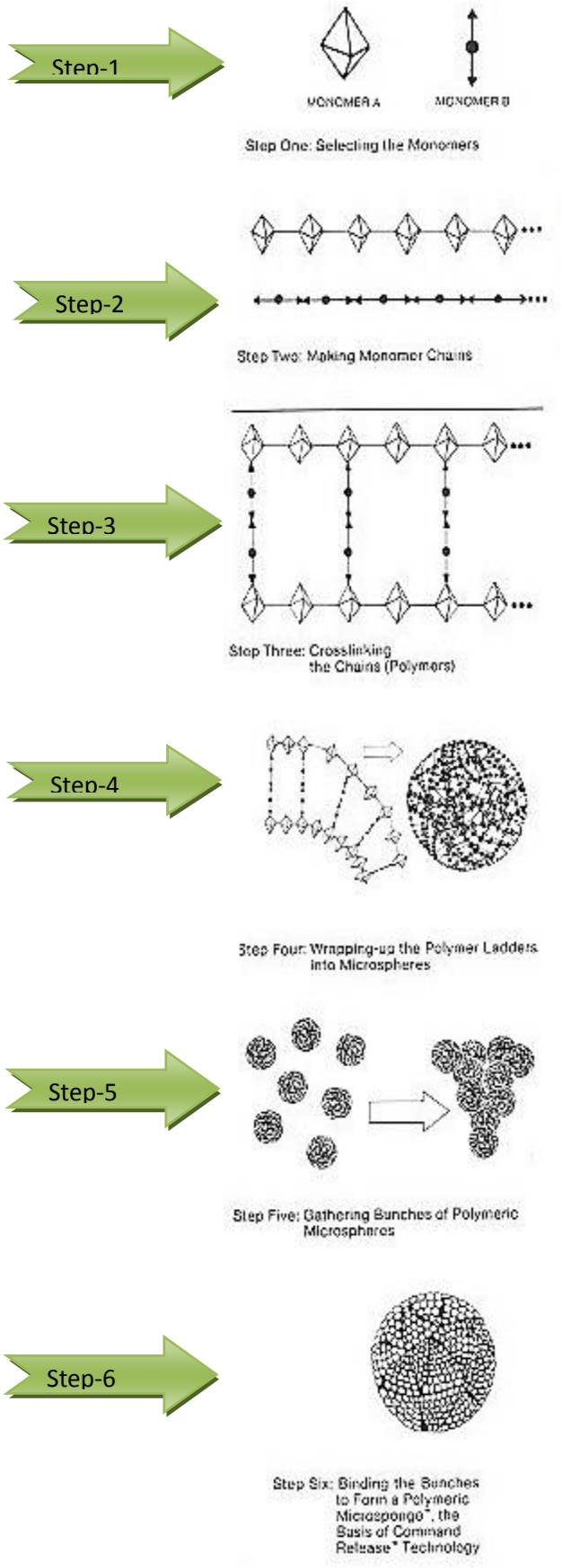



**Figure 3: Microsponges Synthesis by Suspension Polymerization.**

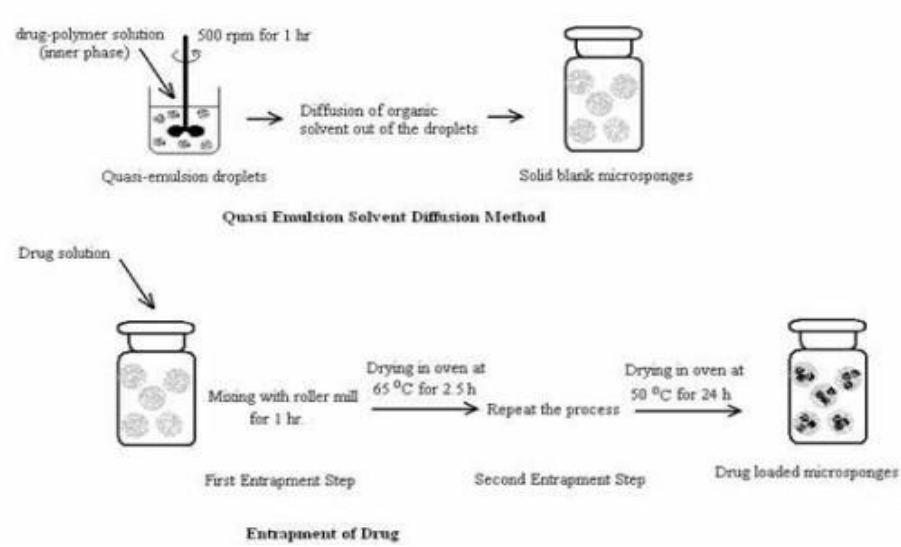



**Figure 4: Method of Quasi-Emulsion Solvent Diffusion.**

**Release Modulation**

In general, microsponges retard the release of the drug. Various groups have studied the release of actives from such systems19- 24. Some studies have shown an improvedrate of release by increasing theactive/polymer ratio and lowering the polymer wall thickness; however these results are not supported by another set ofstudies. Thus, there seem to be many other factors affecting the release of the drug from the microsponges. Another important parameter that governs the release seems to be the pore diameter5 however; another study 13 has shown that even the overall porosity (including the pore diameter and the number of pores) also affects the drug release. [8] The microsponge particles have an open structure and the active is free to move in and out from the particles and into the vehicle until equilibrium is reached. 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 it to the skin until the vehicle is either dried absorbed. Even after that the microsponge particles retained on the surface of 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 too soluble in the desired vehicle during compounding of 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 minimal solubilizing power for the actives. The principle is contrary to the

conventional formulation principles usually applied to the topical products. For these conventional systems it is normally recommended to maximize the solubility of the active in the vehicle. When using microsponge entrapments some solubility of the active in the vehicle is acceptable because the vehicle can provide the initial loading dose of the active until release from the microsponge. Another way to avoid undesirable premature leaching of the active from the microsponge polymer is to formulate the product with some free and some entrapped active, so the vehicle is pre saturated. In this case there will not be any leaching of the active form of polymer during compounding. The rate of active release will ultimately depend not only on the partition coefficient of the active ingredient between the polymer and the vehicle (or the skin), but also on some of the parameters that characterize the beads. Examples of these include surface area and primarily, mean pore diameter5. Release can also be controlled through diffusion or other triggers such as moisture, pH, friction or temperature[9].

**Programmable Release** [10, 11, 12]

**(i)Pressure triggered systems**
Microsponge system releases the entrapped material when pressurized/rubbed; the amount released depends upon various characteristics of the sponge. By varying the type of material and different process variables, the microsponge best suited for a given application may be optimized. When compared with mineral oil containing microcapsules, mineral oil containing microsponge showed much more softening effect. The duration of emolliency was also much more for the microsponge systems.

**(ii)Temperature triggered systems**
Some entrapped active ingredients can be too viscous at room temperature to flow spontaneously from microsponges onto the skin. Increased in skin temperature can result in an increased flow rate and hence release. So it is possible to modulate the release of substances from the microsponge by modulation of temperature. For example, viscous sunscreens were found to show a higher release from microsponges when exposed to higher temperatures; thus a sunscreen would be released from a microsponge only upon exposure to the heat from the sun.

**(iii)pH triggered systems**
Triggering the pH-based release of the active can be achieved by modifying the coating on the microsponge. This has many applications in drug delivery.

**(iv)Solubility triggered system**
Microsponges loaded with water-soluble ingredients like anti-prespirants and antiseptics will release the ingredient in the presence of water. Presence of an aqueous medium such as perspiration can trigger the release rate of active ingredients. Thus release may be achieved based on the ability of the external medium to dissolve the active, the concentration gradient or the ability to swell the microspore network.

**Physical Characterizatio of Microspoges** [13]

**1. Particle Size Determination**

Free-flowing powders with fine aesthetic attributes are possible to obtain by controlling the size of particles during polymerization. Particle size analysis of loaded and unloaded microsponges can be performed by laser light diffractometry or any other suitable method. The values (*d*50) can be expressedfor all formulations as mean size range. Cumulative percentage drug release from microsponges ofdifferent particle size will be plotted against time to study effect of particle size on drug release.Particles larger than 30 μm can impart gritty feeling and hence particles of sizes between 10 and 25 μmare preferred to use in final topical formulation.

**2. Morphology And Surface Topography of Microsponges**

For morphology and surface topography, prepared microsponges can be coated with gold–palladium under an argon atmosphere at room temperature and then the surface morphology of the microspongescan be studied by scanning electron microscopy (SEM). SEM of a fractured microsponge particle canalso be taken to illustrate its ultrastructure.

**3. Determination of Loading Efficiency And Production Yield**

The loading efficiency (%) of the microsponges can be calculated according to the following equation:

$$\text{Loading efficiency} = \frac{\text{Actual Drug Content In Microsponges}}{\text{Therotical Drug Content}} \times 100 \text{-Eqn no.(1)}$$

The production yield of the microparticles can be determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponge obtained.

$$\text{Production Yield (PY)} = \frac{\text{Practical Mass of Microsponges}}{\text{Therotical Mass (polymer+ drug)}} \times 100 \text{-Eqn no.(2)}$$

**4. Determination of True Density**

The true density of microparticles and BPO was measured using an ultra-pycnometer under helium gasand was calculated from a mean of repeated determinations.

**5. 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, shape and morphology of the pores, bulk and apparent density can be determined by using mercury intrusion porosimetry. Incremental intrusion volumes can be plotted against pore diameters that represented pore size distributions.

**6. Compatibility studies**

Compatibility of drug with reaction adjuncts can be studied by thin layer chromatography (TLC) and Fourier Transform Infra-red spectroscopy (FT-IR). Effect of polymerization on crystallinity of the drug can be studied by powder X-ray diffraction (XRD) and Differential Scanning Colorimetry (DSC). For DSC approximately 5 mg samples can be accurately weighed into aluminum pans and sealed andcan be run at a heating rate of 15oC/min over a temperature range 25–430oC in atmosphere of nitrogen.

**7. Polymer/ Monomer Composition**

Factors such as microsphere size, drug loading, and polymer composition govern the drug release from microspheres. Polymer composition of the MDS can affect partition coefficient of the entrapped drug between the vehicle and the microsponge system and hence have direct influence on the release rate of entrapped drug. Release of drug from microsponge systems of different polymer compositions can be studied by plotting cumulative % drug release against time. Release rate and total amount of drug released from the system composed of methyl methacrylate/ethylene glycol di-methacrylate is slower than styrene/ divinyl benzene system.Selection of monomer is dictated both by characteristics of active ingredient ultimately to be entrapped and by the vehicle into which it will be dispersed.

**8. Resiliency**

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. Hence resiliency of microsponges will be studied and optimized as per the requirement by considering release as a function of cross-linking with time.

**RELEASE EVALUATIOS** [14]

**1. Dissolution Tests**

Dissolution profile of microsponges can be studied by use of dissolution apparatus USP XXIII with a modified basket consisted of 5µm stainless steel mesh. The speed of the rotation is 150 rpm. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. Samples from the dissolution medium can be analysed by suitable analytical method at various intervals.

**2. Release mechanisms** [15]

By proper manipulation of the aforementioned programmable parameters, microsponges can be designed to release given amount of active ingredients over time in response to one or more external triggers.

1. **Pressure**: Rubbing/ pressure applied can release active ingredient from microsponges onto skin.
2. **Temperature change**: Some entrapped actives can be too viscous at room temperature to flow spontaneously from microsponges onto the skin. Increased in skin temperature can result in an increased flow rate and hence release.
3. **Solubility**: Microsponges loaded with water-soluble ingredients like anti-prespirants and antisepticswill release the ingredient in the presence of water. The release can also be activated by diffusion taking into consideration the partition coefficient of the ingredient between the microsponges and the outside system.

- **Safety considerations**

Safety substantiation of microsponges can be confirmed by skin irritation studies in rabbits; eye irritation studies in rabbits; oral toxicity studies in rats; mutagenicity in bacteria and allergenicity in guinea pigs.

**Applications of Microspoge Systems** [16]

Microsponges are porous, polymeric micro spheres that are used mostly for topical and recently for oral administration. It offers the formulator a range of alternatives to develop drug and cosmetic products. Microsponge delivery systems are used to enhance the safety, effectiveness and aesthetic quality of topical prescription, over-the-counter and personal care products. Products under development or in the market place utilize the topical microsponge systems in three primary ways: [17]

1. As reservoirs releasing active ingredients over an extended period of time,
2. As receptacles for absorbing undesirable substances, such as excess skin oils, or
3. As closed containers holding ingredients away from the skin for superficial action.

**Table no: 1 Applications of microsponge drug delivery system** [18]

| S. No | Active agents | Applications |
|---|---|---|
| 1. | Sunscreens | Long lasting product efficacy, with improved protection against sunburns and sun related injuries even at elevated concentration and with reduced irritancy and sensitization. |
| 2. | Anti-acne e.g. Benzoyl peroxide | Maintained efficacy with decreased skin irritation and sensitization. |
| 3. | Anti-inflammatory e.g. hydrocortisone | Long lasting activity with reduction of skin allergic response and dermatoses. |
| 4. | Anti-fungals | Sustained release of actives. |
| 5. | Anti-dandruffs e.g. zinc pyrithione, selenium sulfide | Reduced unpleasant odour with lowere irritation with extended safety and efficacy. |
| 6. | Antipruritics | Extended and improved activity. |
| 7. | Skin depigmenting Agents e.g. hydroquinone | Improved stabilization against oxidation with improved efficacy and aesthetic appeal. |
| 8. | Rubefacients | Prolonged activity with reduce irritancy greasiness and odour. |

**Marketed Formulation Using the MDS**

Microsponge delivery systems are used to enhance the safety, effectiveness and aesthetic quality of topical prescription, over-the-counter ("OTC") and personal care products.[19]Products under development or in the marketplace utilize the Topical Microsponge systems in three primary ways [20].

1. As reservoirs releasing active ingredients over an extended period of time,
2. As receptacles for absorbing undesirable substances, such as excess skin oils.
3. As closed containers holding ingredients away from the skin for superficial action.

The resulting benefits include extended efficacy, reduced skin irritation, cosmetic elegance, formulation flexibility and improved product stability.

**Table2: Marketed Formulation of Microsponges.**

| S.N. | Drug | Formulation | Trade name | Dose |
|---|---|---|---|---|
| 1. | Mesalamine) 0.8 | Eudragit-S coated tablets(dissolves at pH 7 | Asacol | -2.4 g/day |
| 2. | Mesalamine | Eudragit-L coated tablets (dissolves at pH 6) | Salofac | 1.0-4.0 g/day |
| 3. | Mesalamine | Eudragit-L coated tablets | Claversal mesazal Calitoflak | 1.0-2.0 g/day |
| 4. | Budesonide | Eudragit-L coated beads 9 mg/ | day Entocort | 9 mg/day |

**5-Fluorouracil (5-FU)**: [21]

5-FU is an effective chemotherapeutic agent for treating actinic keratosis, a precancerous, hardened-skin condition caused by excessive exposure to sunlight. However, patient compliance with the treatment regimen is poor, due to significant, adverse side effects. Microsponge-enhanced topical formulation that potentially offers a less irritating solution for treating actinic keratosis is sold under the brand of Carac.

**Tretinoin Photo-damage Treatment**

Microsponge system product for the treatment of photo-damage, which contributes to the premature aging of skin and has been implicated in skin cancer.

**Cosmaceutical Products Retinol**: [22]

Retinol is a highly pure form of vitamin A which has demonstrated a remarkable ability for maintaining the skin's youthful appearance. However, it has been available only on a limited basis because it becomes unstable when mixed with other ingredients. Stabilized retinol in a formulation which is cosmetically elegant and which has a low potential for skin irritation were successfully developed and marketed.

**Personal Care and OTC Products**

MDS is ideal for skin and personal care products. They can retain several times their weight in liquids, respond to a variety of release stimuli, and absorb large amounts of excess skin oil, allwhile retaining an elegant feel on the skin's surface.[23] The technology is currently employed in almost number of products sold by major cosmetic and toiletry companies worldwide. Among these products are skin cleansers, conditioners, oil control lotions, moisturizers, deodorants, razors, lipstick, makeup, powders, and eye shadows; which offers several advantages, including improved physical and chemical stability, greater available concentrations, controlled release of the active ingredients, reduced skin irritation and sensitization, and unique tactile qualities. APS developed microsphere precursors to the microsponge for use as a testing standard for gauging the purity of municipal drinking water. Marketed nationwide, these microspheres are suspended in pure water to form an accurate, stable, reproducible turbidity standard for the calibration of turbid meters used to test water purity. The technology can have much broader applications than testing the turbidity of water and can even be used for the calibration of spectrophotometers and colorimeters [24]

**Benefits of Microsponge Technology**

1. Advanced oil control, absorb up to 6 times its weight without drying.
2. Extended release.
3. Reduced irritation formulas.
4. Allows novel product form.
5. Improved product aesthetics.
6. Extended release, continuous action up to 12 hours
7. Reduced irritation, better tolerance means broader consumer acceptance
8. Improved product aesthetics, gives product an elegant feel
9. Improves stability, thermal, physical and chemical stability
10. Allows incorporation of immiscible products.
11. Improves material processing eg. Liquid can be converted to powders
12. Allows for novel product forms.
13. Improves efficacy in treatment.
14. Cure or control confirm more promptly.
15. Improve control of condition.
16. Improve bioavailability of same drugs.

**Future Impact**

MDS holds a promising future invarious pharmaceutical applications in the coming years by virtue of their unique properties like small size, efficient carrier characteristics enhanced product performance and elegancy, extended release, reduced irritation, improved thermal, physical, and chemical stability soft exible to develop novel product form .It provides a wide range of formulating advantages. Liquids can be transformed into free flowing powders. Formulations can be developed with otherwise incompatible ingredients with prolonged stability without use of preservatives. [25] Safety of the irritating and sensitizing drugs can be increased and programmed release can control the amount of drug release to the targeted site. New classes of pharmaceuticals, biopharmaceuticals (peptides, proteins and DNA-based therapeutics) are fueling therapid evolution of drug delivery technology. Thus MDS is a very emerging field which is needed to be explored**.** They can also be used for tissue engineering and controlled oral delivery of drugs using biodegradable polymers. It provides a wide range of formulating advantages. Formulations can be developed with otherwise incompatible ingredients, with prolonged stability, without the use of preservatives. Therefore, microsponges will be an ideal drug delivery system related to formulations like the

transdermal delivery system. As it requires vehicles at a higher concentration in order to dissolve the API for effective therapy, it causes irritation and hypersensitivity reactions in significant users. Another demerit of topical formulations is uncontrolled evaporation of the cactive ingredient, unpleasant odor, and the potential incompatibility of drugs with the vehicles.26 Conventional formulations of topical drugs are intended to work on the outer layers of the skin. Typically, such products release their active ingredients upon application, producing a highly concentrated layer of an active ingredient that is rapidly absorbed. Thus, the need exists for a system to maximize the amount of time that an active ingredient is present either on the skin surface or within the epidermis. [27]

## CONCLUSION

The MDS which was originally developed for topical delivery of drugs can also be used for controlled oral delivery of drugs using bio erodible polymers, especially for colon specific delivery. It provides a wide range of formulating advantages. Liquids can be transformed into free flowing powders. Formulations can be developed with otherwise incompatible ingredients with prolonged stability without use of preservatives. Safety of the irritating and sensitizing drugs can be increased and programmed release can control the amount of drug release to the targeted site.

A Microsponge Delivery System can entrap wide range of actives and then release them onto the skin over a time and in response to trigger. It is a unique technology for the controlled release of topical agents and consists of microporous beads loaded with active agent and also use for oral as well as biopharmaceutical drug delivery. A Microsponge Delivery System can release its active ingredient on a time mode and also in response to other stimuli. Thus microsponge has got a lot of potential and is a very emerging field which is needed to be explored.

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