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MICROSPONGE A NOVEL NEW DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT
The Microsponge Drug Delivery System (MDS) is a patented technology has been successively used for the controlled release of topical agents which consist of macro porous beads, typically 10-25 microns in a diameter, which are loaded with active agent. 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 The Microsponge shows time mode release when applied to the skin and they also response to other stimuli like rubbing, pH, etc. MDS technology is currently used in different dosage forms like cosmetics, over the counter (OTC) skin care, sunscreens and prescription products. Microsponge technology allows entrapment of ingredients and it also shows reduced side effects, more stability, increased elegance and enhanced formulation flexibility. In addition, various studies have showed that microsponge systems are non-irritating, non-mutagenic, non-allergenic, and non-toxic. Microspheres can be prepared by different methods using emulsion system or by suspension polymerization in liquid system.

KEYWORDS: Microsponge, Porous-beads, controlled-release, Quisi-emulsion-solvent-diffusion method, Liquid-liquid-suspension-method.

INTODUCTION[21]

Microsponges

A Microsponge drug delivery system (MDDS) is a patented, highly cross-linked, porous, polymeric microspheres polymeric system (10-30 µm in size), consisting of porous microspheric particles consisting of a myriad of inter connecting voids within non-collapsible structures, that can entrap wide range of actives like cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products etc.

MDS can then be incorporated into a formulated product such as a gel, cream, liquid or powder. MDS increases efficacy for topically active agents with enhanced safety, extended product stability and better aesthetic properties of the product.[26,43,44]

Microsponge based drug delivery system provides controlled released action. It also gives site specificity and targeted organ action. Microsponge (MDS) are mainly used for topical drug delivery of the actives as well as for oral controlled delivery system. The Microsponge system can prevent excessive drug concentration within the epidermis and the dermis of the skin. The Microsponge system significantly decreases the irritation of effective drugs without reducing their efficacy. Microsponges can entrap a wide range of active ingredients such as emollients, fragrances, essential oils, anti-fungal and anti-inflammatory agents.

Conventional preparations have many disadvantages like unpleasant odour, greasiness and skin irritation. These problems are overcome by microsponge delivery system.

The Microsponges are prepared by different methods using emulsion systems as well as by suspension polymerization in a liquid–liquid system. The most common emulsion system used is oil-in-water (o/w), with the microsponges which are produced by the emulsion solvent diffusion method.[1]

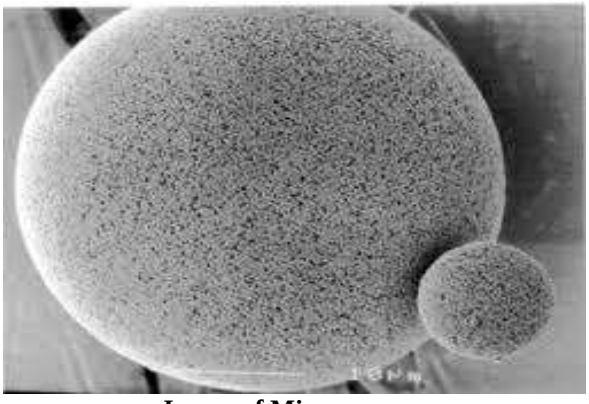

Image of Microsponge.

Characteristics of microsponges[3,21]

1. Microsponge formulations are stable over range of pH 1 to 11.
2. Microsponge formulations are stable at the temperature up to 130˚C.
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.

Advantages of Microsponge Drug Delivery[32,35]

1) Advanced oil control, absorb up to 6 times its weight without drying.
2) Improved product elegancy.
3) MDS allows the incorporation of immiscible products.
4) Extended release.
5) Reduced irritation.
6) Allows novel product form.
7) These are non-irritating, non-mutagenic, non-allergenic and non-toxic.
8) Improved product aesthetics.
9) Extended release.
10) Reduced irritation, better tolerance, broader consumer acceptance.
11) Improved product aesthetics, gives product an elegant feel.
12) Improves thermal, physical and chemical stability.
13) Allows incorporation of the immiscible products.
14) Improves material processing e.g. liquid can be converted to powders.
15) Improves efficacy in treatment.
16) Cure or control confirm more promptly.
17) Improve control of condition.
18) Improve bioavailability of drugs.

Actives that can be entrapped in microsponges 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.

Approaches to delivery the intact molecule to the colon

1. Coating with polymers

By coating of the drug molecule with the suitable polymers which gets degraded only in the colon site, we can deliver the intact drug molecule to the colonic site without absorbing at the upper part of the intest.[14]

2. Coating with pH-sensitive polymers

The pH of the human GIT increases from the stomach (pH 1-2) which increases to 4 during digestion, small intestine (pH 6-7) at the site of digestion and it increases to 7-8 in the distal ileum. By coating the tablets, capsules or pellets by the ph-sensitive polymers, we can provide delayed release and protect the active drug from gastric fluid.[29]

3. Coating with biodegradable polymers[7]

The human GIT consists of complex microflora, especially the colon that is rich in microorganisms that are involved in the process of reduction of dietary component or other materials. Polymer coated drugs Drugs which shows degradability due to the influence of colonic microorganisms, can be exploited in designing drugs for colon targeting.

Methods of preparation of microsponges

1) liquid liquid suspension method.
2) Quisi emulsion solvent diffusion.

Preparation of Microsponges[25,30]

Drug loading process in microsponges can take place in two ways, one-step process or by two-step process; depends on drug's physico- chemical properties. if the drug is an inert non-polar material, will create the porous structure, it is called **porogen**. porogen drug, which neither hinders the polymerization nor become activated by it and stable to free radicals is entrapped with one-step process when the drug is sensitive to the polymerization conditions.

1) Liquid-liquid suspension polymerization[5]

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

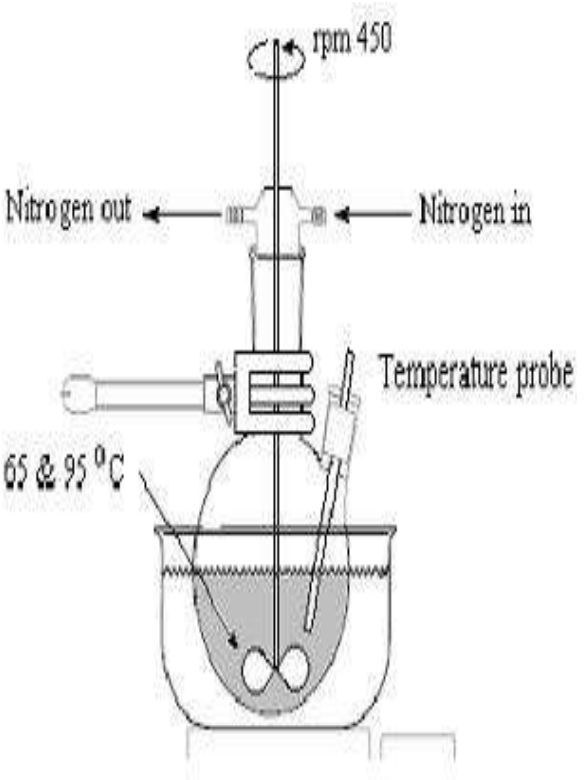

Figure: Reaction vessel for microsponge preparation by liquid- liquid suspension polymerization.

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.

2) Quasi-emulsion solvent diffusion[42]

The microsponges can also be prepared by quasi-emulsion solvent diffusion method using the different polymer amounts. Eudragit RS 100 was dissolved in ethyl alcohol/ Iso-propyl alcohol/ Dichloromethane. Then, drug can be then added to solution and dissolved under ultrasonication at 35˚C. The inner phase was poured into the PVA solution in water (external phase). Following 8 Hrs of stirring, the mixture is filtered to separate the microsponges. The microsponges are dried in an air-heated oven at 40˚C for 12 hr and weighed to determine production yield.

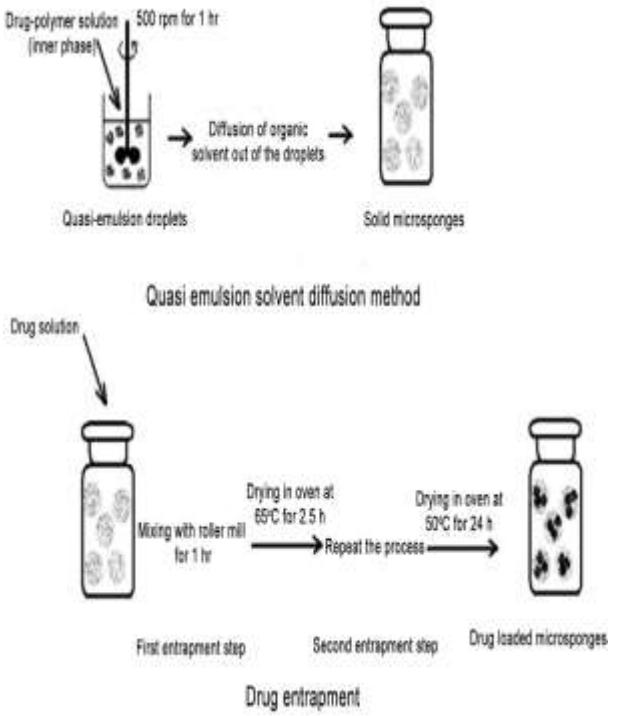

Figure: Preparation of Microsponges by Quasi Emulsion Solvent Diffusion Method.

Evaluation parameters of microsponges[40]

1) Particle size (Microscopy)
2) Morphology and Surface topography
3) Characterization of pore structure
4) Loading efficiency and production yield
5) Determination of true density
6) Drug release study
7) Compatibility studies

Particle size determination

Particle size analysis of drug loaded and unloaded microsponges can be performed by laser light diffractometry or any other suitable method. The values (d50) can be expressed for all formulations as mean 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.[10]

Morphology and Surface topography of microsponges

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 ultrastructure.[11]

Characterization of pore structure

Pore volume and diameter controls the intensity and duration of efficacy of the actives. Pore diameter also affects the migration of actives from microsponges into the vehicle in which the material is dispersed. Mercury intrusion porosimetry is used to study effect of pore diameter and volume with rate of drug release from microsponges.[23]

Determination of loading efficiency and production yield

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

$$\text{Loading Efficiency} = \frac{\text{Actual drug contect in microsponge}}{\text{Theoritical drug content}} \times 100$$

Determination of production yield[22]

The production yield of the microsponges is determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponge.

$$\text{Production Yield (PY)} = \frac{\text{Practical mass of microsponges}}{\text{Theoritical mass (Polymer + drug)}} \times 100$$

Determination of true density[20]

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

Dissolution studies[39]

Dissolution profile of microsponges can be studied by use of dissolution apparatus USP XXIII with a modified basket. 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.

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).

Different parameters and characterization methods for microsponges

1. Measurement of particle size, size.
2. distribution and polydispersity index.
3. Laser light diffractometry.
4. Scanning electron microscopy.
5. Determination of true density Ultra-pycnometer under helium gas (Displacement method)
6. Characterization of pore structure.
7. Total pore volume.
8. Material volume.
9. Material density.
10. Interstitial void volume.
11. Percent porosity.
12. Percent porosity filled.
13. Pore volume distribution by pore size.
14. Pore area, number of pores.
15. Pore tortuosity and tortuosity factor.
16. Mercury intrusion porosimetry.
17. FTIR study.
18. Differential scanning calorimetry.
19. X-ray diffraction (XRD) studies.
20. Thin layer chromatography (TLC)
21. Polymer / Monomer composition By plotting cumulative percent drug release against time.
22. Resiliency (viscoelastic properties) By considering release as a function of cross-linking with time.
23. Drug release studies.

Release mechanisms[1,7,41]

Microsponges can be designed to release given amount of active ingredients over time in response to one or more external triggers.

1. Pressure

Microsponge system releases the entrapped material when pressurized/rubbed; the amount released depends upon different characteristics of the sponge. By changing the type of material and different process variables, the microsponge can be optimized.

2. Temperature change

Some entrapped active ingredients can be too viscous at room temperature to flow spontaneously from microsponges onto the skin. Increased in skin temperature results in an increased flow rate and hence drug release. So it is possible to increase the drug release of actives from the microsponge by temperature change.

3. pH triggered systems

The pH-based release of the actives can be achieved by modifying the coating on the microsponge.

4. Solubility

Microsponges which are loaded with water-soluble ingredients like anti-prespirants and antiseptics will 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. Thus release of the actives is based on the ability of the external medium to dissolve the active, the concentration gradient or the swelling properties of the microspore network.

Various factors that are to be considered during development of such formulations includes

1. Physical and chemical properties of entrapped actives.
2. Physical properties of microsponge system like pore diameter, pore volume, resiliency etc.
3. Properties of vehicle in which the microsponges are finally dispersed. Particle size, pore characteristics, resiliency and monomer compositions can be considered as programmable parameters and microsponges can be designed for proper drug release in response to one or more external triggers.[28]

Formulation considerations

When formulating the vehicle, certain considerations are taken into consideration in order to achieve desired product characteristics.

1. The solubility of actives in the vehicle must be limited.
2. Not more than 10 to 12% w/w microsponges must be incorporated into the vehicle; To avoid cosmetic problems.
3. Polymer design and payload of the microsponges for the active must be optimized for required release rate for specific period.

There remains equilibrium between microsponge and vehicle and microsponge releases drug in response to the depletion of drug concentration in the vehicle. Drug concentration in the vehicle is depleted by absorption of the drug into skin. Hence continuous and steady release of actives onto the skin can be acheived with this system.[15]

Applications of microsponge systems[27]

1) Microsponges are porous, polymeric microspheres that are used mostly for topical and recently for oral administration (colon targeted).
2) It offers the formulator, a range of alternatives to develop drug and cosmetic products.
3) Microsponges are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects and modify drug release.

The microsponge system can have following applications.[16]

Table 1: The system can have following applications.

Sr 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-inflammatory e.g. hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatoses.
3	Anti-acne e.g. Benzoyl peroxide	Maintained efficacy with decreased skin irritation and sensitization.
4	Anti-fungals	Sustained release of the actives.
5	Anti-dandruffs e.g. zinc pyrithione, selenium sulfide	Reduced unpleasant odour with lowered 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 reduced irritancy greasiness and odour.

The Microsponge for oral delivery

A Microsponge system offers the potential to provide controlled oral drug delivery to the lower gastrointestinal (GI) tract, where it will be released into the colonic site upon exposure to specific enzymes in the colon. In oral applications, the Microsponge drug delivery system has been shown increased rate of solubilization of poorly water soluble drugs, by entrapping such drugs in the Microsponge system's pores. Because these pores are very small, there is significant increase in the surface area thus greatly increases the rate of solubilization of the drug. The time it takes the Microsponge system to traverse the small and large intestine is significantly increased thus maximizing the amount of absorbed drug.[21]

Bioerodible Systems based on new polymers, including proteins and peptides, for the delivery of small and large molecule drugs, can also be developed which, if successful can be used in systemic drug delivery areas.

Colon targeted drug delivery

Colon, as a site, has a near neutral pH, a much longer transit time, reduced digestive enzymatic activity and shows a much greater response to absorption enhancers.[3,4] Colon specific drug delivery systems can be used not only for local but also for systemic therapy, due to the importance of the different regions of the gastrointestinal tract. Generally, colonic drug delivery is used when a delay in drug absorption is required from a therapeutic point of view.

Conventional oral dosage forms are ineffective for the colon targeted drug delivery because of the absorption and/or degradation of the active ingredient in the upper gastrointestinal tract. Several triggering mechanisms can be used like the change in pH, bacterial concentration and pressure in the gastrointestinal tract to achieve colon specific drug delivery.[5]

Prodrugs approach and the microflora activated systems can be used for the colon targeted drug delivery systems. Use of non-starch polysaccharides are highly promising because the polysaccharides remain undigested in the stomach and the small intestine and can only be degraded by the anaerobic microflora of the colon. Furthermore, this strategy increases the bacteria population (400 distinct species of bacteria) and corresponding enzyme activities which ensures greater site-specificity of initial drug release.[6] The polysaccharides are also inexpensive, naturally occurring and abundantly available for colonic drug delivery, hence can be used.[17]

Marketed formulation using the MDS

Microsponge delivery systems are used to enhance the safety, efficacy and aesthetic quality of topical preparations, over-the-counter ("OTC") and personal care products. Products under development or in the marketplace utilize the topical Microsponge systems in three primary ways:[34]

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.

Which shows benefits such as extended efficacy, reduced skin irritation, formulation flexibility and improved product stability.

List of marketed formulation of microsponges[7,18]

Table2: Marketed formulation of microsponges.

S.N.	Drug	Formulation	Trade name	Dose
1	Mesalamine	Eudragit S coated tablets (dissolves at pH 7)	Asacol	0.8 -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	Entocort	9 mg/day

5-Fluorouracil (5-FU)[35]

5-FU is an effective chemotherapeutic agent used in the treating actinic keratosis, a precancerous, hardened-skin condition caused by excessive exposure to sunlight. However, it has a poor patient compliance, due to various side effects. Microsponge-enhanced topical formulation that potentially forms 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 leads to the premature aging of skin and has been used in skin cancer.

Cosmaceutical products retinol[36]

Retinol is a highly pure form of vitamin A which has showed a remarkable ability for maintaining the skin's 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, all while retaining an elegant feel on the skin's surface.[37] The technology is currently employed in almost number of products sold by major cosmetic products like skin cleansers, conditioners, oil control lotions, moisturizers, deodorants, lipstick, makeup, powders, and eye shadows; which offers several advantages, including improved physical and chemical

stability, controlled release of the active ingredients, reduced skin irritation.

Future impact

MDS offers different features like small size, efficient carrier characteristics enhanced product performance and elegancy, extended release, reduced irritation, improved thermal, physical, and chemical stability. Formulations can be developed with incompatible ingredients with prolonged stability without use of the 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.

Microsponges will be an ideal drug delivery system related to formulations like the transdermal delivery system. Unpleasant odor, irritation and hypersensitivity reactions can be decreased by using MDS technology. MDS increses the amount of time that an active ingredient is present either on the skin surface or within the epidermis.

peptides, proteins and DNA-based therapeutics are showing the rapid evolution of drug delivery technology. They can also be used for and Controlled oral delivery of drugs using different biodegradable polymers and tissue engineering can be acheived using MDS. Thus MDS is a very emerging field which is needed to be explored**.**

Summary and Conclusion

MDS is a unique technology for the controlled release of topical agents. It was originally developed for topical delivery of drugs can also be used for controlled oral drug delivery to the colon. Formulations can be developed even with incompatible ingredients with more 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 MDS entraps wide range of drugs and then release them onto the skin over a time and in response to trigger. Microsponge drug delivery has become highly competitive and rapidly emerging technology and more and more research are carrying out to optimize cost effectiveness and efficacy of therapy.

As formulators consider new and creative ways to deliver actives, they can realize the capabilities of these unique materials providing enhanced safety, improved stability, reduced side effects from actives, enhanced multi functionality and improved ingredient compatibility.

Microsponge delivery system can be a new strategy for a new generation of Pharmaceutical and Cosmetic industry. Microsponges have a distinct advantage over the existing conventional topical dosage forms for the treatment of tropical diseases; This shows advantageous over other products by non mutagenic, non toxic, non irritant. So microsponge drug delivery system has got a lot of potential and is a very emerging field which is needed to be explored in the future with most research study.

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