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Review Article

A Review on Microsponges: A Novel Drug Delivery System.

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ABSTRACT
As pharmaceutical industry, moving ahead with different innovative techniques in various controlled released dosage forms like solid formulation, semi solid formulation and topical preparation due to efficacy and patient compliance. Conventional preparations of the topical drugs have some disadvantages like unpleasant odor and skin irritation and fail to reach the site of action in sufficient amounts in few cases. This problem overcomes by microsponge delivery system. Microsponge is a recent novel technique for control release and target specific drug delivery system. Microsponges are polymeric delivery system composed of porous microspheres. They are composed tiny sponge-like spherical particle with a large porous surface. Microsponge system reduced side effects, improved stability, increased appearance, and enhanced formulation flexibility and economic therapy. The present review introduces microsponge technology along with its properties, advantage, characteristics, method of preparation, evaluation, and application summery of various microsponge drugs of different category with various polymers and ratio and effectiveness over conventional dosage form.

KEYWORD
Microsponges, Controlled release, Microsponge dosage form.

1. INTRODUCTION

Microsponges are novel drug delivery system. They are porous, polymeric microspheres. They are composed tiny sponge-like spherical particles with a large porous surface having polymeric delivery system. Microsponges may improve stability, reduce side effects and modify drug release profiles favorably. Microsponges are polymeric delivery System so they based on microscopic, polymer-based microspheres that can entrap a wide variety of substances, and can then be incorporated into a formulated product such as a gel, cream, liquid or powder. Microsponge Delivery System can provide increased efficacy for topically active agents with enhanced safety, extended product stability and improved aesthetic properties in an efficient manner. In oral application, the microsponge has been shown to increase the of solubilization of poorly water soluble drug by entrapping such drugs in the microsponge system pores.[1, 2, 3] To control the delivery rate of active agents to a site of administration in the human body has been one of the biggest challenges faced by Pharmaceutical scientists. Several predictable and reliable systems have been developed for systemic delivery of drugs under the transdermal delivery system (TDS) using the skin as entrance of entry. It has improved the efficacy, stability and safety of many drugs that may be better administered through skin. But TDS is difficult for delivery of materials whose final target is skin itself. Controlled release of drugs onto the epidermis with certainty that the drug remains primarily localized and does not enter the systemic circulation in significant amounts is a challenging area of research.[4]Microsponges consist of non-collapsible structures with porous surface through which active ingredients are released in controlled manner. Depending upon the size, an internal pore structure equivalent to 10 ft in length and total pore volume of about 1 ml/g. When applied to the skin, the microsponge delivery system (MDS) releases its active ingredient on a predetermined time mode and also in reaction to other stimuli such as rubbing, temperature, and pH with increased efficacy. Microsponges have the capacity to load a high degree of active materials into the particle or onto its surface. Its large capacity for entrapment of actives up to 3 times its weight differentiates microsponges from other types of transdermal delivery systems. Mostly microsponge is use for topical drug delivery system. Recently microsponge drug delivery systems used in oral medications due to protected environment and provide the controlled delivery of drug at the lower GI tract, it has shown to increase the rate of solubilization of poorly water soluble drugs by the pores produced by microsponge systems.[5, 6]

1.1. Properties of Microsponges[7-9]

Microsponges when applied to the skin, its bioactive agent progressively release on the skin at a predetermined time mode and response to stimuli such as rubbing, temperature and pH effect with enhanced efficacy.

1. These formulations are stable over pH range of 1-11.
2. It is stable at up to 130°C.
3. They exhibit good compatible with most vehicles and ingredients.
4. Self-sterilizing as their average pore size is small about 0.25 μm, thus the bacteria cannot penetrate the pores.

5. They have pay load up to 50-60%
6. These particles are appropriated in size to absorb into the skin, therefore oiliness and shine from skin is reduced.
7. Microsponges formulation improved oil control as it can absorb oil up to 6 times its weight without drying.
8. They have extended release so provide continuous action upto 12 hrs.

1.2. Benefit of Microsponge Drug Delivery System

1. Microsponges have several advantages over topical preparations in being non-irritating, non-mutagenic, non-allergenic and non-toxic**.**
2. It can also improve efficacy in treatment, thus enhanced product performance.
3. Provide continuous action upto 12 hrs. i.e. extended release & improved product elegancy.
4. Lesser the irritation and better tolerance hence improved patient compliance.
5. Improved oil control as it can absorb oil up to 6 times its weight without drying.
6. They have superior formulation flexibility.
7. Microsponges are thermally, physically, and chemically stable.
8. Flexibility to develop novel product forms.[4, 10]

1.3. Characteristics of Actives Moieties that is Entrapped into Microsponges

a) Microsponges are polymeric delivery System so they based on microscopic, polymer-based microspheres that can entrap a wide variety of substances, and can then be incorporated into a formulated product such as a gel, cream, liquid or powder.
b) It should be either fully miscible in monomer or capable of being made miscible by addition of small amount of a water immiscible solvent.
c) It should be inert to monomers and polymers. It should not increase the viscosity of the mixture during formulation.
d) It should be water immiscible as well as most only slightly soluble.
e) The spherical structure of the microsponges should not collapse.
f) It should be stable in contact with polymerization catalyst and conditions of polymerization.
g) The solubility of actives in the vehicle must be limited.
h) If not, the vehicles will evacuate the microsponges before the application.
i) Not more than 10 to 12% w/w microsponges must be incorporated into the vehicle in order to avoid cosmetic problems.
j) High entrapment and polymer design of the microsponges for the active must be optimized for required release rate for given period of time. [11, 12]

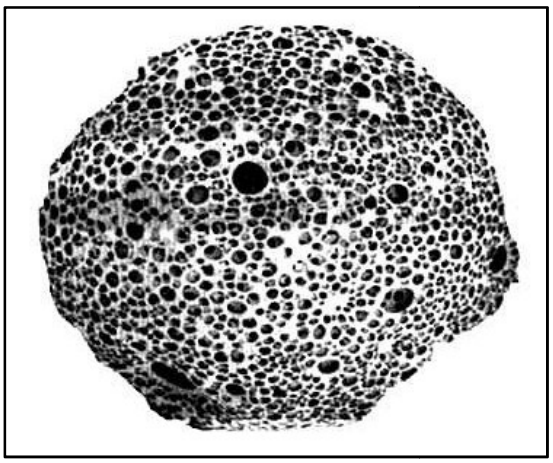

Fig. 1.Structure of microsponge

1.4. Preparation of Microsponge

Drug loading in Microsponges can take place in two different ways, one-step process or by two-step process which are based on physicochemical properties of drug to be loaded. Liquid liquid suspension polymerization is one step process and Quasi-emulsion solvent diffusion is two step process. If the drug is typically an inert non-polar material, will create the porous structure it is called Porogen. Porogen drug, which neither hinders the polymerization not become activated by it and stable to free radicals is entrapped with one-step process.[13]

1.4.1. Liquid-liquid suspension polymerization

Reaction vessel for microsponge preparation by liquid liquid suspension polymerization. By using suspension polymerization method in liquid-liquid systems prepared the porous microspheres. In that preparation, the monomers are first dissolved along with active ingredients in a suitable solvent solution of monomer and then dispersed in the aqueous phase, which consist of surfactant, suspending agents, etc.

The polymerization is then process to begin by adding catalyst or by increasing temperature or irradiation.

Preparation by liquid-liquid suspension method,

The various steps in the preparation of Microsponges are given as follows,

1. Selection of monomer or combination of monomers.
2. Formation of chain monomers as polymerization begins.
3. Formations of cross linking between chains as a ladder form.
4. Monomers.
5. Folding of monomer ladder to forms spherical particles Agglomeration of microspheres, which give rise to the formation of bunches of microspheres.
6. Binding of bunches to for microsponges.

The polymerization process starts to the formation of a reservoir type of system, which opens at the surface through pores. In a few cases an inert liquid immiscible with water but fully miscible with monomer is used during the polymerization to form the pore network. After the

polymerization the liquid is evacuated leaving the porous microspheres, i.e. Microsponges. Fertilizing them within preformed Microsponges then incorporates the functional substances. Frequently solvent may be used for faster and efficient incorporation of the active substances. The Microsponges act as not representative of a group carriers for variety of functional substances, e. g. Anti-acne, anti-inflammatory, antiquities, antifungal, rubefacients etc. When the drug is quick to detect the polymerization conditions, two-step processes used. The polymerization is performed using substitute Porogen and is replaced by the functional substance under mild experimental condition.[14]

1.4.2.Quasi-emulsion solvent diffusion

This is mostly used method for preparation of microsponge. In this method porous microspheres (microsponges) were also prepared by a quasi-emulsion solvent diffusion method (two-step process) using an internal phase containing polymer such as eudragit which is dissolved in ethyl alcohol. Then, the drug is slowly added to the polymer solution and dissolved under ultra-sonication at 35^0c and plasticizer such as triethylcitrate (TEC) was added in order to aid the plasticity. The inner phase is then poured into external phase containing polyvinyl alcohol and distilled water with continuous stirring for 2 hours. Then, the mixture was filtered for the separation of the microsponges. The product (microsponges) was washed and then dried in an air- heated oven at 40°C for 12 hr. and then weighed accurately for result.[15, 16]

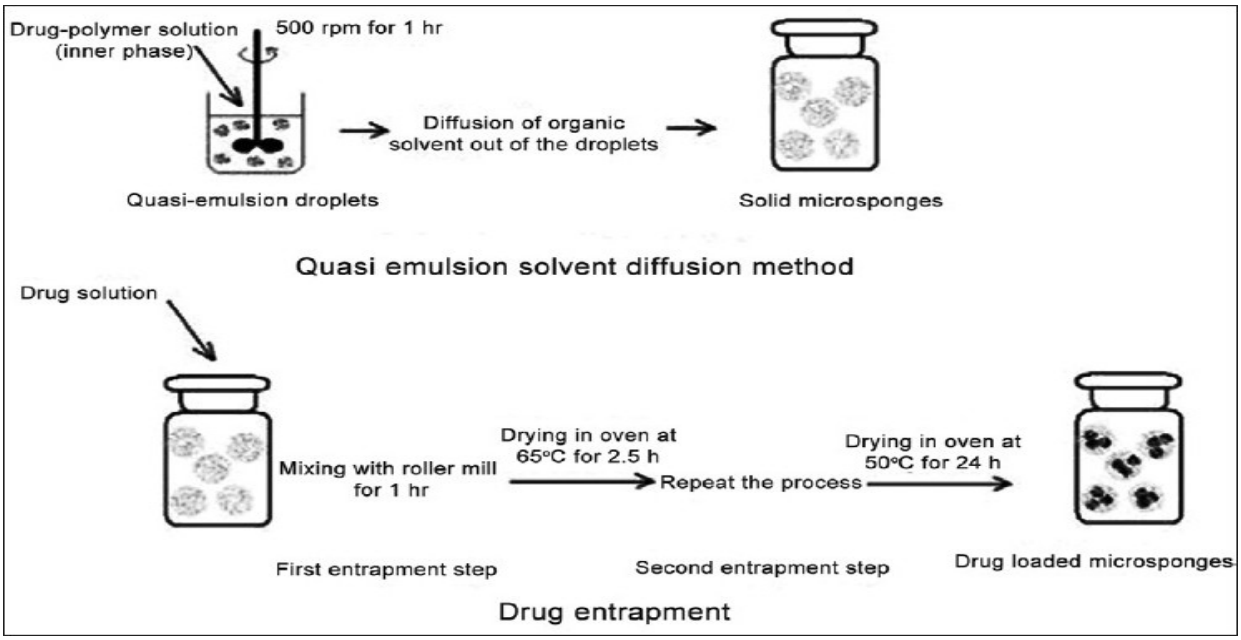

Fig. 2. Quasi-emulsion solvent diffusion method.

1.5. evaluation of microsponge

1.5.1. Particle size determination

Laser light diffractometry can be used for the particle size analysis of loaded and unloaded microsponges. 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 of sizes between 10 and 25µm are preferred to use in final topical formulation because particals larger than 30µmcan impart gritty feeling.

1.5.2. Morphology and surface topography of microsponges

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

1.5.3. Determination of loading efficiency and production yield

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

$$\text{Loading efficiency} = \frac{\text{Actual Drug Content in Microsponges}}{\text{Theoratical drug content}} \times 100$$

---Formula 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.

$$\text{Production Yield} = \frac{\text{Practical mass of Microsponges}}{\text{Theoratical mass(polymer+drug)}} \times 100$$

---Formula 2

1.5.4. Dissolution tests

Dissolution apparatus USP XXIII with a modified basket consisted of 5µm stainless steel mesh is use for the study of dissolution release rate of microsponges. The dissolution medium is selected while considering solubility of actives to protect sink conditions. At various intervals the samples from the dissolution medium was analysed by suitable analytical methods at different intervals.

1.5.5. 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 replicated determinations.

1.5.6. Resiliency (viscoelastic properties)

Resiliency (visco elastic properties) of microsponges can be converted to produce beadlets that is softer or firmer according to the needs of the final formulation. Increased cross-linking turn to slow down the rate of release. Hence resiliency of microsponges will be studied by considering release as a fuction of cross linking with time.[17-23]

Table 1. Drug Explored In Microsponge Delivery System.[24-44]

Sr. No.	Drug	Category	Method ofpreparation	Polymer Used	Ratio Drug:Polymer	Conclusion
1.	Paracetamol	NSAID	Quasi-emulsion solvent diffusion method	Eudragit RS 100	3:1, 6:1, 9:1, 12:1	Provide effective local action than convensional dasage form.
2.	Diclofenac Sodium	NSAID	Quasi-emulsion solvent diffusion method	Ethyl cellulose	1:1 to 1:10	Control the release rates or target drugs to a specific body site and release its active ingredient on a timer mode.
3.	Indomethacin	NSAID	Quasi-emulsion solvent diffusion method	Eudragit RS 100	3:1, 4:1, 5:1	More uniform maintainance of blood plasma level of active agent.
4.	Lornoxicam	NSAID	Quasi-emulsion solvent diffusion method	Eudragit RS 100	1:1, 3:1, 5:1, 7:1, 9:1.	Prolonged released characteristics and producing mechanically strong tablets.
5.	Rabamipide	Anti-ulcer drug	Quasi-emulsion solvent diffusion method	Eudragit L 100	1:1, 2:1, 3:1, 5:1, 10:1, 15:1	Enhanced the saturated solubility of rabapimide in HCL.

6.	Fluconazole	Anti-fungal	Quasi-emulsion solvent diffusion method	Eudragit S 100	1:1 to 1:6	Reduce application frequency, hypertensive reactions & to improve bioqavailability & safety.
7.	Acyclovir	Anti-viral	Quasi-emulsion solvent diffusion method	Ethyl cellulose	1:1, 2:3	No sign of bleeding, streaking, blooming for lipstick formulation.
8.	Mupirocin	Anti-bacterial	Quasi-emulsion solvent diffusion method	Eudragit RS 100	1:1, 2:1, 4:1, 6:1, 8:1, 10:1, 12:1, 14:1	Rapid, easy, reproducible & avoiding solvent toxicity.
9.	Prednisolone	Corticoste-roids	Quasi-emulsion solvent diffusion method	Eudragit RS 100	1:1, 3:1, 5:1, 7:1, 9:1, 11:1, 13:1, 15:1	Colon targeted, inhibits the release of drug in upper part of GIT.
10.	Mometasone Furoate	Corticoste-roids	Quasi-emulsion solvent diffusion method	Eudragit RS 100	1:1, 3:1, 5:1, 7:1, 9:1, 11:1, 13:1	Reduce the solubility of polymer in the droplets, since polymer is insoluble in water.
11.	Curcumin	Anti-inflamma-tory agent	Quasi-emulsion solvent diffusion method	Ethyl cellulose	1:1, 2:1, 3:1, 4:1, 5:1	Extended period of time, to reduce frequency of administration & improve bioavailabity.

12.	Valsertan	Anti-Hypertensive	Quasi-emulsion solvent diffusion method	Ethyl Cellulose	1:4, 1:5, 1:6	For extensive time period to reduce application frequency, hypertensive reactios and to improve bioavailability.
13.	Febuxostat	Hyperuri-cemia agent	Quasi-emulsion solvent diffusion method	Eudragit RS 100	1:1, 3:1, 5:1, 7:1, 9:1, 11:1, 13:1	Reduced dose related side effects.
14.	Nateglinide	Anti-diabetic agent	Quasi-emulsion solvent diffusion method	Eudragit RS 100	1:1, 1:2, 1:3, 1:4, 1:5	Maximise the therapeutic effect of the drug.
15.	Ketoconazole	Anti-fungal	Quasi-emulsion solvent diffusion method	Eudragit RS 100	2.5:1, 5:1, 10:1, 20:1	Drug polymer ratio increases partical size decreases.
16.	Oxybenzone	Photopro-tective agent	Quasi-emulsion solvent diffusion method	Ethyl cellulose	1:1, 1:2, 1:3	Enhanced sunscreening efficiency.
17.	Erythro-mycin	Antibiotic	Quasi-emulsion solvent diffusion method	Ethyl cellulose	0.3:1, 0.3:2, 0.3:3, 0.3:4, 0.3:6	Formulation shows good loading efficiency, production yield, particle size, drug content.

18.	Terbinafine HCL	Anti-fungal	Quasi-emulsion solvent diffusion method	Ethyl cellulose	2:1, 1.5:1, 1:1, 1:1.5	Polymer ratios, internal solvent volume & stirring speed greatly affected to partical size & active drug content of microsponges.
19.	Sertacona -zole nitrate	Anti-fungal	Quasi-emulsion solvent diffusion method	Eudragit RS 100	1:1, 4:1, 6:1, 8:1, 10:1	Drug polymer ratios enhanced the production yield, encapsulation efficiency & partical size upto certain limit beyond which no further enhancement obesreved.
20.	Roxythro -mycine	Antibiotic	Quasi-emulsion solvent diffusion method	Eudragit RL 100	1:0.5, 1:1, 1:1.5, 1:2, 1:2.5, 1:3, 1:3.5, 1:4, 1:4.5, 1:5	Control the release rates or target drug to specific body site.
21.	Miconazole Nitrate	Anti-Fungal	Quasi-emulsion solvent diffusion method	Eudragit RS 100	-----	Cut the dosing frequency & improve bioavailability.

1.6. Applications of Microsponge Systems

Microsponges are porous, polymeric microspheres that are used frequently for topical but recently used for oral administration. Microsponges are arranged to deliver the pharmaceutical active ingredient efficiently at the minimum dose. Microsponges are also to increase stability, reduce side effects and modify drug release.

1.6.1.Microsponge for topical delivery

Conventional formulations of topical drugs are proposed to work on the outer layers of the skin. The Microsponge systems are based on microscopic, polymer-based microspheres that can bind, suspend or entrap a wide variety of substances and then be incorporated into a formulated product, such as a gel, cream, liquid or powder.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. Comprehensive 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 rupture them down. Although they are microscopic in size, these systems are too large to pass through the stratum corneum when incorporated into topical products.[45-53]

1.6.2.Microsponge for oral delivery

In oral applications, the microsponge system has been shown to increase the rate of solubilisation of poorly watersoluble drugs by entrapping such drugs in the microsponge system 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.[45-53]

2. CONCLUSION

A Microsponge Delivery System can entrap wide range of actives and then release them at the site of action 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.The microsponge delivery system also use for oral as well as biopharmaceutical drug delivery. The microsponge delivery technology of controlled release system in which active pharmaceutical ingredient is loaded in the macro porous beads and process to begin reduction in side effects with improved therapeutic efficacy. Microsponge can be effectively incorporated into topical drug delivery system for retention of dosage form on skin, and also use for oral delivery of drugs using bio erodible polymers, especially for colon specific delivery and controlled release drug delivery system thus become better patient compliance by providing site specific drug delivery system and extend the duration of dosage intervals.

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