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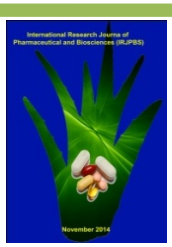

Microsponges: A Novel Drug Delivery System

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Abstract

Microsponge is recent novel technique for control release and target specific drug delivery system. Microsponges are polymeric delivery system composed of porous microspheres. They are tiny sponge-like spherical particle with a large porous surface. Microsponge system offers entrapment of ingredient and is believed to contribute towards reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility. Microsponge systems are based on microscopic, polymer-based microspheres that can suspend or entrap a wide variety of substances, and can then be incorporated into a formulated product such as gel, cream, liquid or powder and have recently been used for oral administration. Microsponge systems are non-irritating, non-mutagenic, non-allergenic and non-toxic. 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.

Keywords: Microsponges, polymer-based, Active ingredient, Enhance stability

INTRODUCTION

Drug delivery systems (DDS) that can acutately control the release rates or target drugs to a specific body site have a massive effect on the health care system. Carrier technology offers an insightful approach for drug delivery by coupling the drug to a carrier particle such as microsponges, nanoparticles, liposomes, *etc.* which regulates the release and absorption characteristics of the drug. Microsponges are important part of DDS because of their small size and efficient carrier characteristics [1]. The biggest challenge faced by drug industry nowadays is to control the delivery rate of active agents to a predetermined site in human body. Controlled release of drugs onto the epidermis with assurance that the drug does not enter the systemic circulation and remains primary localized has only recently been

addressed with success. Application of topical drugs suffers many problems that often results into lack of patient compliance [2]. These vehicles require high concentrations of active agents for effective therapy because of their low efficiency of delivery system, resulting into irritation and allergic reactions. Other drawbacks of topical formulations are uncontrolled evaporation of active ingredient, unpleasant odour and potential incompatibility of drugs with the vehicles. Thus the need exists for system to maximize amount of time that an active ingredient is present either on skin surface or within the epidermis, while minimizing its transdermal penetration into the body. The microsponge delivery system fulfills these requirements.

The microsponge technology was developed by Won in 1987 and the original patents were assigned to Advanced Polymer Systems, Inc. Microsponges are composed of tiny sponge like spherical particles with large porous surface having polymeric delivery system composed of porous microspheres. Microsponge technology has many beneficial features, which make it a multifaceted drug delivery vehicle, they may enhance stability, reduce side effects and modify drug release favorably. Microsponge Systems are based on microscopic, polymer-based microspheres that can suspend or entrap a wide variety of substances, and can then be incorporated into a formulated product such as a gel, cream, liquid or powder. MDS can provide increased effectiveness for topically active agents with enhanced safety, extended product stability and improved aesthetic properties in an efficient and novel manner. A typical 25 µm sphere can have up to 250000 pores and an internal pore structure equivalent to 10 ft in length, providing a total pore volume of about 1 ml/g. This results in a large reservoir within each microsponge, which can be loaded with up to its own weight of active agent. The microsponge particles themselves are too large to be absorbed into the skin and this adds a measure of safety to these microsponge materials [3].

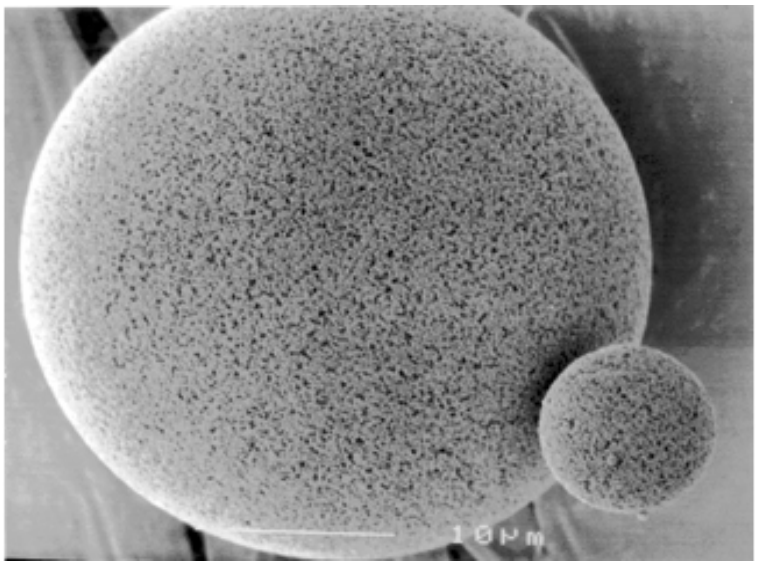

Figure 1: Microsponge

Advantages of Microsponges [4-7]

1. Microsponges are biologically safe and offer unique advantage of programmable release.
2. They offer entrapment of numerous ingredients and are believed to contribute elegance and enhanced formulation flexibility.
3. They have the capacity to absorb or load a high degree of active materials into the particle or
unto its surface.
4. Microsponges are stable over a ph range of 1- 11 and upto temperature of 130ºC
5. They are self sterilizing as average pore size is 0.25 µm where bacteria cannot penetrate.
6. Microsponges are capable of absorbing skin secretions so reducing the oiliness of the skin upto 6 times of its weight.
7. With size 10-25 microns in diameter it is capable of entrapping the various ingredients in a single microsphere.
8. The drug releases in microsponges by the external stimuli like ph, temperature, and rubbing.
9. Microsponges have several advantages over topical preparations in being non-allergic, non-toxic, non-irritant and non-mutagenic.
10. Microsponges are thermal, physical and chemically stable.
11. These are compatible with the majority of vehicles and ingredients.
12. These systems have higher payload up to 50 to 60%.
13. Provides continuous action upto 12 hrs ie. extended release & improved product elegancy.
15. It can amend bioavailability of same drugs & efficacy in treatment.

Characteristics of Materials to be Entrapped in Microsponges [8]

Actives that can be entrapped in microsponges must meet 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.
- It should be inert to monomers.
- The solubility of actives in the vehicle must be limited to avoid cosmetic problems; not more than 10 to 12% w/w microsponges must be incorporated into the vehicle. Otherwise the vehicle will deplete the microsponges before the application.
- The spherical structure of microsponges should not collapse.
- Polymer design and payload of the microsponges for the active must be optimized for required release rate for given time period.
- It should be stable in contact with polymerization catalyst and conditions of polymerization.

Microsponge Preparation [9-13]

Drug loading in microsponges is mainly take place in two ways depending upon the physicochemical properties of drug. If the drug is typically an inert non-polar material which

will generate the porous structure then, it is known as porogen. A Porogen drug neither hinders the polymerization process nor become activated by it and also it is stable to free radicals. Microsponges are suitably prepared by the following methods:

Liquid-liquid suspension polymerization

Microsponges are prepared in liquid-liquid systems by suspension polymerization process (one-step process). Firstly, the monomers are dissolved along with active ingredients (non-polar drug) in an appropriate solvent solution of monomer, which are then dispersed in the aqueous phase with agitation. Aqueous phase typically consist of additives such as surfactants and dispersants (suspending agents) etc in order to facilitate the formation of suspension. Once the suspension is established with distinct droplets of the preferred size then, polymerization is initiated by the addition of catalyst or by increasing temperature as well as irradiation. The polymerization method leads to the development of a reservoir type of system that opens at the surface through pores. During the polymerization, an inert liquid immiscible with water however completely miscible with monomer is used to form the pore network in some cases. Once the polymerization process is complete, the liquid is removed leaving the microsponges which is permeate within preformed microsponges then, incorporates the variety of active substances like anti fungal, rubefacients, anti acne, anti inflammatory etc and act as a topical carriers. In some cases, solvent can be used for efficient and faster inclusion of the functional substances. If the drug is susceptible to the condition of polymerization then, two-step process is used and the polymerization is performed by means of alternate porogen and it is replaced by the functional substance under mild conditions.

The various steps involved in the preparation of microsponges are summarized as follows:
Step 1: Selection of monomer as well as combination of monomers.
Step 2: Formation of chain monomers as polymerization starts.
Step 3: Formations of ladders as a result of cross-linking between chain monomers.
Step 4: Folding of monomer ladder to form spherical particles.
Step 5: Agglomeration of microspheres leads to the production of bunches of microspheres.
Step 6: Binding of bunches to produce microsponges.

Quasi-Emulsion Solvent Diffusion Method

Microsponges are also prepared by a quasi-emulsion solvent diffusion method (two-step process) using an internal phase containing polymer such as Eudragit RS 100 which is dissolved in ethyl alcohol. Then, the drug is slowly added to the polymer solution and dissolved under ultrasonication at 35º C 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 11. Then, the mixture was filtered to separate the microsponges. The product (microsponges) was washed and dried in an air heated oven at 40°C for 12 hrs.

Mechanism of action [14]

The porous microspheres contain a complex network of interconnecting voids with a non-collapsible structure. These systems can absorb a wide range of active ingredients such as emollients, volatile oils, sunscreens, perfumes, and anti-infective and antifungal agents. The release rate of the active ingredients can be determined before they are entrapped in the microspheres. Depending on several factors, such as pore diameter, extent of cross-linking of the polymers, concentration difference of the active ingredient between the microspheres and the vehicle in which these spheres resides.

The topical agent formulation with this system can be prepared in many different forms such as a gel, cream, or lotion. The active ingredients diffuse out of the spheres into the vehicle and then onto the skin, while applying the formulation topically to the desired area of the skin. The release can be initiated by many release triggers, including pressure and temperature changes and moisture. The microsponges cannot pass through to the stratus corneum because of their size, so they retained on the skin surface, releasing slowly the active ingredients over a period of time. The rate of release associated with MDS provides more control, which potentially has an impact on the intensity of skin irritancy provoked by the topical agent. However, the MDS technology is limited in that it can only entrap active ingredients with certain characteristics.

Mechanism of Drug Release

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

Temperature Change

At room temperature, few entrapped active ingredients can be too viscous to flow suddenly from microsponges onto the skin. With increase in skin temperature, flow rate is also increased and therefore release is also enhanced [15].

Pressure: Rubbing or pressure applied can release the active ingredient from microsponges onto skin [16].

Solubility

Microsponges loaded with water miscible ingredients like antiseptics and antiperspirants will release the ingredient in the presence of water. The release can also be activated by diffusion but taking into consideration, the partition coefficient of the ingredient between the microsponges and the external system [17].

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 [18].

Review of Literature

Microsponge of diclofenac diethylamine for arthritis therapy was evaluated by Osmani et al. Quasi emulsion solvent diffusion method was implied using Eudragit RS-100. Microsponges were characterized by SEM, DSC, FT-IR, XRPD. Invitro drug release results showed that

microsponges with 1:2 drug : polymer ratio were more efficient to give extended drug release of 75-88% [19].

The microsponge of ketoconazole by quasi emulsion solvent technique using different types of Eudragits as Eudragit E100, Eudragit RS was evaluated by **Hussien et al**. Microsponges were characterized by FT-IR, DSC. The results revealed the physibility of preparing fast release ketoconazole as microsponges in oral capsule dosage form [20]. Acyclovir loaded microsponges by quasi emulsion solvent diffusion method was developed by **Rao et al**. The microsponges were characterized by FT-IR and dissolution behavior. The gel formulation GF2 was selected as the best gel formulation because the polymer has 10% of functional quaternary ammonium groups which was responsible for high permeability and sustained release [21].

The hydroxyzine hydrochloride microsponges for anti-histamine drug was designed by **Gade et al**. Microsponges of drug was prepared by using polymer Methocel 1000 cps and in combination with Eudragit-S 100, Eudragit L-100, Eudragit RL 100 and Eudragit RS 100 by using emulsion solvent diffusion method. Compatability of drug with adjuncts was studied by FT-IR. The microsponge tablet formulation showed controlled release of hydroxyzine hydrochloride [22]. Microsponge containing ketotifen drug using quasi emulsion solvent difussin methodwas obtained by **Kumar et al**. The microsponge gel formulation was studied for various parameters & characterized by HPLC and SEM analysis. The formulation was able to release drug upto 8 hrs [23]. The microsponge of Lornoxicam for the treatment of inflammatory diseases was studied by **Kartika et al**. Microsponges containing Lornoxicam and Eudragit RS100 were prepared by quasi emulsion solvent diffusion method. The compatability of drug with adjuncts was studied by FT-IR. The study presents a new approach based on microsponge drug delivery system [24]. The controlled release formulation of indomethacin microsponges prepared by Eudragit RS 100 was studied by **Mahajan et al**. Microsponges were evaluated by micrometric properties, drug content, encapsulation efficiency. Indomethacin microsponges were characterized by FT-IR, DSC, X-ray diffractometry & SEM. Indomethacin microsponges were more promising than conventional formulation therapy [25]. Mometasone furoate microsponges for topical drug delivery using an emulsion solvent diffusion method was prepared by **Rekha et al**. Microsponges were characterized by FT-IR. The results showed that an increase in the ratio of drug : polymer resulted in a reduction in the release rate of mometasone furoate from microsponges [26]. Paracetamol loaded Eudragit based microsponges uing quasi emulsion solvent diffusion method was prepared by **Jain et al**. Microsponges were characterized by SEM. The colon specific tablets were prepared by comprising microsponges followed by coating with pectin : hydroxypropyl methyl cellulose mixture. The study represents the new approach for colon specific drug delivery [27].

Advantages of microsponges over other formulations

Microsponges have several other advantages over other preparations available in the market.

Comparison between some of them is given below as such;

1. **Advantages over conventional formulations**: Conventional formulations of topical drugs are intended to work on the outer layers of the skin. Such products release their active ingredients upon application, producing a highly concentrated layer of active ingredient that is rapidly adsorbed. When compared to the conventional system. Microsponge system can prevent excessive accumulation of ingredient within the epidermis and the dermis. Potentially, the MDDS can reduce significantly the irritation of effective drugs without reducing their efficacy.

2. **Advantages over microencapsulations and liposomes**: Microcapsules cannot usually control the release rate of actives. Once the wall is ruptured, the actives contained within microcapsules will be released. Liposomes suffer from lower payload, difficult formulation, limited chemical stability and microbial instability, while microsponges system in contrast to the above system has several advantages like stable over a ph range of 1-11 and upto temperature of 130 ^{o}C, stable thermally, physicaly and chemically, have higher payload up to 50 to 60%, have average pore size is 0.25 µm whwre bacteria cannot penetrate [28].

3. **Advantages over ointments**: Ointments are often aesthetically unappealing, greasiness; stickiness etc. That often results into lack of patient compliance. These vehicles require high concentrations of active agents for effective therapy because of their low efficiency of delivery system, resulting into irritation and allergic reactions in significant users. Other drawbacks of topical formulations are uncontrolled evaporation of active ingredient, unpleasant odor and potential incompatibility of drugs with the vehicles, when microsponge system maximize amount of time that an active ingredient is present either on skin surface or within the epidermis, while minimizing its transdermal penetration into the body [29].

APPLICATIONS

Microsponges are used mostly for topical and recently for oral administration as well as biopharmaceutical delivery. It offers the formulator a range of alternatives to develop drug and cosmetic products. These are developed to deliver an active ingredient efficiently at the low dose and also to enhance stability, reduce side effects and modify drug release 20 (Various applications are shown in **table 1**.

Table 1: [30]

Sr. No	Actives	Application
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 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 lowered irritation with extended safety and efficacy.
6	Antipruritics	Extended and improved activity
7	Skin depigmenting Agents	Improved stabilization against oxidation with improved efficacy and aesthetic appeal.
8	Rubefacients	Prolonged activity with reduced irritancy greasiness and odour

Marketed Formulation of Microsponges: [31]

Product Name	Manufacturer	Advantages
Retinol cream	Biomedic	Microspongesystem helps to maximize retinol dosage while reducing the possibility of irritation. Retinol is a topical vitamin A derivative which helps maintain healthy skin, hair and mucous membranes.
Dermalogica oil control lotion	John & Ginger Dermalogica skin care products	Microsponge technology has exclusive skin response complex soothes and purifies, provides effective skin hydration, without adding excess oil.
Oil free matte block spf 20	Dermalogica	Microsponge technology absorbs oil, maintaining an all-day matte finish and preventing shine without any powdery residue. Oil free formula contains soothing Green Tea to help calm inflammation caused by breakouts. Contains no artificial fragrance or color.

FUTURE PROSPECTS

Microsponge drug delivery system holds a promising opportunity in various pharmaceutical applications in the upcoming future. It has unique properties like enhanced product performance and elegancy, extended release, improved drug release profile, reduced irritation, improved physical, chemical and thermal stability which makes it flexible to develop novel product forms. The real challenge in future is the development of the delivery system for the oral peptide delivery by varying ratio of polymers. The use of bioerodible and biodegradable polymers for the drug delivery is enabling it for the safe delivery of the active

material. These porous systems have also been studied for the drug delivery through pulmonary route. These carriers also require to be developed for alternative drug administration routes like parenteral and pulmonary route. These particles can also be used as the cell culture media and thus can also be employed for stem cell culture and cellular regeneration in the body. These carrier systems have also found their application in cosmetics. These developments enabled researchers to utilize them variably [32].

CONCLUSION

Microsponge drug delivery has become highly competitive and rapidly evolving technology and more and more research are carrying out to optimize cost effectiveness and efficacy of therapy. With demand for innovative and highly efficient Pharmaceutical as well as Cosmetic products, the market holds considerable potential for Microsponge technology and the versatility they offer. As formulators consider new and creative ways to deliver actives, they can realize the full capabilities of these unique materials providing enhanced safety, improved stability, reduced side effects from actives, enhanced multifuntionality and improved ingredient compatibility. Complemented by novel development approaches and creative formulation techniques, Microsponge delivery system can be a winning 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; it is a unique technology for the controlled release of topical agents also use for oral as well as biopharmaceutical drug delivery. 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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