IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
May 2017 Vol.:9, Issue:2

An Overview of Microsponge as a Novel Tool in Drug Delivery

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submission: 5 May 2017
Accepted: 10 May 2017
Published: 25 May 2017

www.ijppr.humanjournals.com

Keywords: Microsponge, Porous Microspheres, Topical delivery etc.

ABSTRACT

Microsponges are polymeric delivery systems composed of porous microspheres. Microsponges are porous microspheres having myriad of interconnected voids of particle size ranging from 5-150 µm. Microsponge Drug Delivery System is a unique technology which provides controlled release of active ingredients. Microsponges formulations are stable over range of pH 1-11. Microsponges formulations are compatible with most vehicles and ingredients, these are self-sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate. Micro sponge's drug delivery system can be prepared in two ways, one-step process or by two-step process that is liquid-liquid suspension polymerization and quasi-emulsion solvent diffusion techniques that are based on physicochemical properties of drug to be loaded. Various method are used for the evaluation of the MDS they are following Particle size (Microscopy), Morphology and Surface topography, Characterization of pore structure, Determination of true density, Compatibility studies, Polymer/monomer composition Microsponges are used mostly for topical delivery and recently for oral as well as biopharmaceutical delivery.

INTRODUCTION[1-3]

Microsponges are porous microspheres having myriad of interconnected voids of particle size ranging from 5-150 μm. Microsponge Drug Delivery System (MDS) is a unique technology which provides controlled release of active ingredients. It offers numerous advantages over other technologies like reduced side effects, improved stability, increased elegance and enhanced formulation flexibility. Microsponges are porous, polymeric microspheres that are used mostly for topical and recently for oral administration. They can be incorporated into conventional dosage forms such as creams, lotions, gels, ointment, tablet and powder and share a broad package of benefits and thus provides formulation flexibility. They are tiny, sponge like spherical particles that consist of a myriad of interconnecting voids within a no collapsible structure with large porous surface MDS that can precisely control the release rates or target drugs to a specific body site have an enormous impact on the health care system. The MDS technology is widely applicable to the dermatological drug delivery products. But MDS also expands its application in oral drug delivery, bone and tissue engineering, in detecting the diseases and in RNAi silencing. New classes of pharmaceuticals, biopharmaceuticals (peptides, proteins and DNA-based therapeutics) are fueling the rapid evolution of drug delivery technology. Thus MDS is a very emerging field which is needed to be explored**.** Microsponges are porous, polymeric microspheres that are mostly used for prolonged topical administration. Microsponges are designed to deliver a pharmaceutically active ingredient efficiently at minimum dose and also to enhance stability, reduce side effects, and modify drug release profiles. It is a polymeric microsphere that acquires the flexibility to entrap a wide variety of active ingredients such as emollients, fragrances, sunscreens, essential oils, anti-infective, anti-fungal and anti-inflammatory agents etc. and is used as a topical carrier system. Resembling a true sponge, each microsphere consists of an innumerable of interconnecting voids within a non-collapsible structure with a large porous surface. MDS is "Patented, highly cross-linked, porous, polymeric microspheres, and polymeric system consisting of porous microspheres that can entrap wide range of actives and then release them into the skin over a time and in response to trigger". Micro-sponge polymers possess the versatility to load a wide range of actives providing the benefits of enhanced product efficacy, mildness, tolerability, and extended wear to a wide range of skin therapies. Several predictable and reliable systems were developed for systemic drugs under the heading of transdermal delivery system (TDDS) using the skin as portal of entry. It has

improved the efficacy and safety of many drugs. But TDDS is not practical for delivery of materials whose final target is skin itself. 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 in the body.

Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge-like spherical particles with a large porous surface. Moreover, they may enhance stability, reduce side effects and modify drug release favorably. Microsponges technology has many favorable characteristics, which make it a versatile drug delivery vehicle. Microsponges 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 efficacy for topically active agents with enhanced safety, extended product stability and improved aesthetic properties in an efficient manner.

Advantages of Micro sponges[3-4]

1. Microsponges offer better control of drug release than microcapsules. Microcapsules cannot usually control the release rate of the active pharmaceutical ingredients (API). Once the wall is ruptured, the API contained within the microcapsules will be released.

2. Microsponges show better chemical stability, higher payload and easier formulation as compared with liposomes.

3. In contrast to ointments, Microsponges have the ability to absorb skin secretions, therefore, reducing greasiness and shine from the skin. Ointments are often aesthetically unappealing, greasy and sticky, resulting in lack of patient compliance.

4. These formulations are stable over range of pH 1 to 11.

5. These formulations are stable at temperature up to 130ºC.

6. These formulations are compatible with most vehicles and ingredients.

7. These are self-sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate into it.

8. These formulations are free flowing and can be cost effective.

9. Microsponges are biologically safe and offer unique advantage of programmable release.

10. They offer entrapment of numerous ingredients and are believed to contribute elegance and enhanced formulation flexibility.

Release Mechanism of Micro Sponge[5-6]

As the Microsponges particles have an open structure (they do not have a continuous membrane surrounding them), the active is free to move in and out from the particles and into the vehicle until equilibrium is reached, when the vehicle becomes saturated. Once the finished product is applied to the skin, the active that is already in the vehicle will be absorbed into the skin, depleting the vehicle, which will become unsaturated, therefore, disturbing the equilibrium. This will start a flow of the active from the Microsponges particle into the vehicle, and from it to the skin until the vehicle is either dried or absorbed. Even after that, the Microsponges particles retained on the surface of the stratum corneum will continue to gradually release the active to the skin, providing prolonged release over time. This proposed mechanism of action highlights the importance of formulating vehicles for use with Microsponges entrapments. If the active is too soluble in the desired vehicle during compounding of the finished products, the products will not provide the desired benefits of gradual release.

Accelerated or Triggered by following mechanism:

- Pressure triggered systems
- Temperature triggered systems
- pH triggered systems
- Solubility triggered system

(i). Pressure triggered systems: Microsponges releases the entrapped material when pressurized or rubbed.

(ii).Temperature triggered systems: It is possible to modulate the release of substances Micrsponges by modulation of temperature. That is viscous sunscreens were show a higher release when exposed to higher temperatures.

(iii) pH triggered systems: Triggering the pH-based release of the active can be achieved by modifying the coating on the Microsponges.

(iv) Solubility triggered system: Microsponges loaded with water-soluble ingredients will release the ingredient in the presence of water. Perspiration can trigger the release rate of active ingredients.

Hypothetical Mechanism of Action[7]

The active ingredient is added to the vehicle in an entrapped form. As the Microsponges particles have an open structure (they do not have a continuous membrane surrounding them), the active is free to move in and out from the particles and into the vehicle until equilibrium is reached, when the vehicle becomes saturated. Once the finished product is applied to the skin, the active that is already in the vehicle will be absorbed into the skin, depleting the vehicle, which will become unsaturated, therefore, disturbing the equilibrium. This will start a flow of the active from the Microsponges particle into the vehicle, and from it to the skin until the vehicle is either dried or absorbed. Even after that, the Microsponges particles retained on the surface of the stratum corneum will continue to gradually release the active to the skin, providing prolonged release over time. This proposed mechanism of action highlights the importance of formulating vehicles for use with Microsponges entrapments. If the active is too soluble in the desired vehicle during compounding of the finished products, the products will not provide the desired benefits of gradual release. Instead, they will behave as if the active was added to the vehicle in a free form. Therefore, while formulating Microsponges entrapments, it is important to design a vehicle that has minimal solubilizing power for the actives. This principle is contrary to the conventional formulation principles usually applied to topical products. For these conventional systems, it is normally recommended to maximize the solubility of the active in the vehicle. When using

Microsponges 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 Microsponges is activated by the shift in equilibrium from the polymer into the carrier. Another way to avoid undesirable premature leaching of the active from the Microsponges 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 from the 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 diameter. Release can also be controlled through diffusion or other triggers such as moisture, pH, friction or temperature.

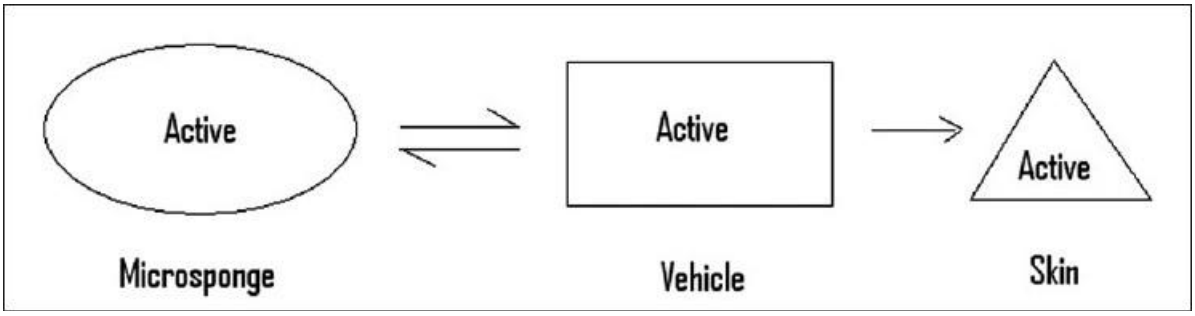

Figure 4: Schematic representation of the distribution of the loaded material (active) on skin

Characteristics of Micro Sponges[8-9]

1. Microsponges formulations are stable over range of pH 1 to 11;

2. Microsponges formulations are stable at the temperature up to 130^{o}C;

3. Microsponges formulations are compatible with most vehicles and ingredients.

4. Microsponges formulations are self-sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.

5. Microsponges formulations have higher payload (50 to 60%), still free flowing and can be cost effective

Active ingredients that are entrapped in Microsponges can then be incorporated into many products such as creams, gels, powders, lotions and soaps. Certain considerations are taken into account while, formulating the vehicle in order to achieve desired product characteristics:

1. It should be either fully miscible in monomer as well as capable of being made miscible by addition of small amount of a water immiscible solvent.

2. It should be inert to monomers and should not increase the viscosity of the mixture during formulation.

3. It should be water immiscible or nearly only slightly soluble.

4. It should not collapse spherical structure of the Microsponges.

5. It should be stable in contact with polymerization catalyst and also in conditions of polymerization.

6. The solubility of actives in the vehicle must be limited. If not, the vehicle will deplete the Microsponges before the application.

7. Not more than 10 to 12% w/w Microsponges must be incorporated into the vehicle in order to avoid cosmetic problems.

8. Payload and polymer design of the Microsponges for the active must be optimized for required release rate for given period of time.

Physical Characterization of Microsponges Drug Delivery System[8-9]

- **Particle size and shape:** 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 (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. Particle larger than 30 μm can impart gritty

feeling and hence particles of sizes between10 and 25 μm are preferred to use in final topical formulation.

- **Resiliency (viscoelastic properties):** Resiliency (viscoelastic properties) of Microsponges can be modified to produce beadlets that are softer or firmer according to the needs of the final formulation. Increased cross-linking tends to slow down the rate of release.

- **Drug release kinetics:** The dissolution profile of each formulation have been subjected to various models such as Zero order kinetics (percentage drug release against time), First order kinetics (log percentage drug unreleased against time), Higuchi (percentage drug released against square root of time) and Korsmeyer-Peppas (log percent drug released against log of time) were applied to assess the kinetics of drug release from prepared Microsponges.

- **Dissolution tests:** Dissolution release rate of Microsponges can be studied by using dissolution apparatus USP XXIII with a modified basket consisted of 5 μm stainless steel mesh. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. At various intervals, the samples from the dissolution medium were analyzed by suitable analytical methods.

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

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

Factor Affecting Mechanism of Drug Release[9-10]

- Physical and chemical properties of entrapped actives.

- Physical properties of Microsponges system like pore diameter, pore volume, resiliency etc.

- 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 to release given amount of actives in response to one or more external triggers like; pressure, temperature and solubility of actives.

- Pressure rubbing or pressure applied can release active ingredient from Microsponges onto skin.

- 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.

- Solubility of Microsponges loaded with water-soluble ingredients like antiperspirants 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

Drug used in microsponge delivery system[11-12]

Drug	Polymer	Offering Benefit
Mupirocin	Ethyl cellulose and dichloromethane as a solvent which contained PVA as emulsifying agent	Enhanced retention in the skin indicating better potential of the delivery system for treatment of primary and secondary skin infections.
Benzyl Peroxide	Ethyl cellulose and dichloromethane as a solvent.Suspension polymerization of styrene and methyl methacrylate	Reduce the side effect by reducing Percutaneous absorption and control the release BPO to the skin.
Fluconazole	liquid-liquid suspension polymerization of styrene and methyl methacrylate	Reduce the side effect and controlled the release.
Flurbiprofen	Eudragit RS 100 and pore plugging of Microsponges with pectin: HPMC mixture followed by tableting	Microsponges system containing flurbiprofen was formulated for the colonic delivery of the drug for targeted action.
Dicyclomine	Eudragit RS 100	System based on Microsponges that would reduce the GI side effects of the drug.
Hydroxyzine HCl	Eudragit RS-100 Microsponges	Controlled release of the drug from a delivery system to the skin could reduce the side effects while reducing percutaneous absorption.
Diclofenac Sodium	Xanthan gum-facilitated ethyl cellulose Microsponges	At the lowest drug/polymer ratio could be useful for controlled release of Diclofenac sodium to the skin.

Methods of Preparation[13-15]

Micro sponge's drug delivery system can be prepared in two ways, one-step process or by two-step process that is liquid-liquid suspension polymerization and quasi-emulsion solvent diffusion techniques based that is based on physicochemical properties of drug to be loaded.

1. Liquid-liquid suspension polymerization: The porous microspheres are prepared by suspension polymerization method in liquid-liquid systems. In this method the monomers which are immiscible are first dissolved along with active ingredients in a suitable solvent monomer

and are then dispersed in the aqueous phases which consist of additives like surfactants, suspending agents to facilitate formation of suspension. The polymerization is then activated by increasing temperature or irradiation or by addition of catalyst. The polymerization process continues the formation of a reservoir type of system with spherical structure. After the polymerization process, the solvent is removed, leaving the spherical structured porous microspheres, i.e. Microsponges.

2. Quasi-emulsion solvent diffusion: 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 ultrasonication at 35^{o}C and plasticizer such as triethyl citrate (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 h. Then, the 11 mixture was filtered to separate the Microsponges. The product (Microsponges) is then washed and dried in an air- heated oven at 40°C for 12 h.

Evaluation Parameters of Microsponges[16]

Various method used for the evaluation of the MDS are as follows:

1. Particle size (Microscopy)
2. Morphology and Surface topography
3. Characterization of pore structure
4. Determination of true density
5. Compatibility studies
6. Polymer/monomer composition

1. Particle size determination: Particle size analysis is performed by laser light diffractometry or any other suitable method. Free-flowing powders with fine aesthetic attributes are possible to obtain by controlling the size of particles during polymerization. The values (*d*50) 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. Particles larger than 30 μm can impart gritty feeling and hence particles of sizes between 10 and 25 μm are preferred to use in final topical formulation.

2. Scanning Electron Microscope (SEM) study: 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 Microsponges can be studied by SEM. SEM of a fractured Microsponges particle can also be taken to illustrate its ultrastructure.

3. 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.

4. Determination of true density: The true density of microparticles is measured using an ultra-pycnometer under helium gas and is calculated from a mean of repeated determinations.

5. Compatibility studies: Compatibility of drug with reaction adjuncts can be studied by thin layer chromatography (TLC) and Fourier Transform Infrared spectroscopy (FT-IR).

6. 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 Microsponges system and hence have direct influence on the release rate of entrapped drug. Release of drug from Microsponges systems of different polymer compositions can be studied by plotting cumulative percent drug release against time.

Application of Micro Sponges[17]

Microsponges are used mostly for topical delivery and recently for oral as well as biopharmaceutical delivery. It offers the formulator a range of alternatives to develop drug and cosmetic products. Microsponges are designed to deliver a pharmaceutically active ingredient

efficiently at the minimum dose and also to enhance stability, reduce side effects and modify drug release.

Active agents	Applications
Anti-inflammatory e.g. hydrocortisone	Long lasting activity with lessening of skin allergic response and dermatoses.
Anti-dandruffs e.g. zinc pyrithione, selenium sulfide	Reduced unpleasant odor with reduced irritation with extended efficacy and safety.
Skin depigmenting agents e.g. hydroquinone	Improved stabilization against oxidation with improved efficacy and aesthetic appeal.
Anti-fungals	Sustained release of actives.
Anti-acne e.g. Benzoyl peroxide	Maintained efficacy with reduced skin irritation and sensitization.
Antipruritics	Extended and improved activity.
Sunscreens	Long lasting product efficacy with improved protection against sunburns and sun related injuries even at elevated concentration and with reduced irritancy and sensitization.
Rubefacients	Prolonged activity with reduced irritancy, greasiness and odor.

CONCLUSION

Microsponge is porous microspheres that are recent advancement in drug delivery systems. On the basis of present review, it was concluded that microsponges mainly applied in topical applications. They can use orally also. Microsponges are beneficial for variety of drug. This technology needs to explore more as major consideration in research field.

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