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Review Article

Microsponge drug delivery: A Review

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ABSTRACT

The drug delivery technology landscape has become highly competitive and rapidly evolving. More and more developments in delivery systems are being integrated to optimize the efficacy and cost-effectiveness of the therapy. Peptides, proteins and DNA-based therapeutics cannot be effectively delivered by conventional means. To control the delivery rate of active agents to a predetermined site in human body has been one of the biggest challenges faced by drug industry. Controlled release of drugs onto the epidermis with assurance that the drug remains primarily localized and does not enter the systemic circulation in significant amounts is an area of research that is successively done by the microsponge delivery system. The Microsponge Delivery System (MDS) is a unique technology for the controlled release of topical agents and consists of macroporous beads, typically 10-25 microns in diameter, loaded with active agent. When applied to the skin, the microsponge releases its active ingredient on a time mode and also in response to other stimuli (rubbing, temperature, pH, etc). Microsponge technology offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility. In addition, numerous studies have confirmed that microsponge systems are non-irritating, non-mutagenic, non-allergenic, and non-toxic. MDS technology is being used currently in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products.

Keywords: Microsponge; transdermal delivery; proteins and peptides.

INTRODUCTION

Several predictable and reliable systems were developed for systemic drugs under the heading of transdermal delivery system (TDS) using the skin as portal of entry. It has improved the efficacy and safety of many drugs that may be better administered through skin. But TDS is not practical for delivery of materials whose final target is skin itself. (Kydonieus et al. 1987)

Controlled release of drugs onto the epidermis with assurance that the drug remains primarily localized and does not enter the systemic circulation in significant amounts is an area of research that has only recently been addressed with success. No efficient vehicles have been developed for controlled and localized delivery of drugs into the stratum corneum and underlying skin layers and not beyond the epidermis. (Chowdary K.P.R. et al. 2004) Application of topical drugs suffers many problems such as ointments, which 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 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. Microsponge delivery systems are uniform, spherical polymer particles. Their high degree of cross-linking results in particles that are insoluble, inert and of sufficient strength to stand up to the high shear commonly used in manufacturing of creams, lotions, and powders. Their characteristic feature is the capacity to adsorb or “load” a high degree of active materials into the particle and on to its surface. Its large capacity for entrapment of actives, up to three times its weight, differentiates microsponge products from other types of dermatological delivery systems. While the active payload is protected in the formulation by the microsponge particle, it is delivered to skin via controlled diffusion. This sustained release of actives to skin over time is an extremely valuable tool to extend the efficacy and lessen the irritation commonly associated with powerful therapeutic agents such as Retinoids or Benzoyl Peroxide. Microsponge polymers possess the versatility to load a wide

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range of actives providing the benefits of enhanced product efficacy, mildness, tolerability, and extended wear to a wide range of skin therapies. (Delattre L. et al. 1995)

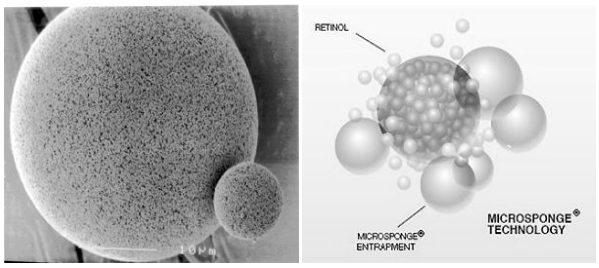

Figure 1: View of Microsponge

CHARACTERISTICS OF MICROSPONGES (Aritomi H. et al. 1996)

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

CHARACTERISTICS OF MATERIALS THAT IS ENTRAPED IN MICROSPONGES (Kawashima Y. et al. 1992)

Most liquid or soluble ingredients can be entrapped in the particles. 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 water immiscible or at most only slightly soluble.
- It should be inert to monomers.
- It should be stable in contact with polymerization catalyst and conditions of polymerization. (Aritomi et al. 1996)

PREPARATION OF MICROSPONGES

Drug loading in microsponges can take place in two ways,
one-step process or by two-step process as discussed in liquid-liquid suspension polymerization and quasi emulsion solvent diffusion techniques which are based on physico-chemical properties of drug to be loaded. 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 nor become activated by it and stable to free radicals is entrapped with one-step process.

Liquid-liquid suspension polymerization (Tansel C. et al. 2002, Vyas S.P. et al. 2002)

The porous microspheres are prepared by suspension polymerization method in liquid-liquid systems. In their preparation, the monomers are first dissolved along with active ingredients in a suitable solvent solution of monomer and are then dispersed in the aqueous phase, which consist of additives (surfactant, suspending agents, etc. to aid in formation of suspension). The polymerization is then initiated by adding catalyst or by increasing temperature or irradiation. The various steps in the preparation of microsponges are summarized as (Won et al. 1987, 1992):

- Selection of monomer or combination of monomers
- Formation of chain monomers as polymerization begins
- Formation of ladders as a result of cross linking between chain monomers
- Folding of monomer ladder to form spherical particles - Agglomeration of microspheres, which give rise to formation of bunches of microspheres
- Binding of bunches to form microsponges.

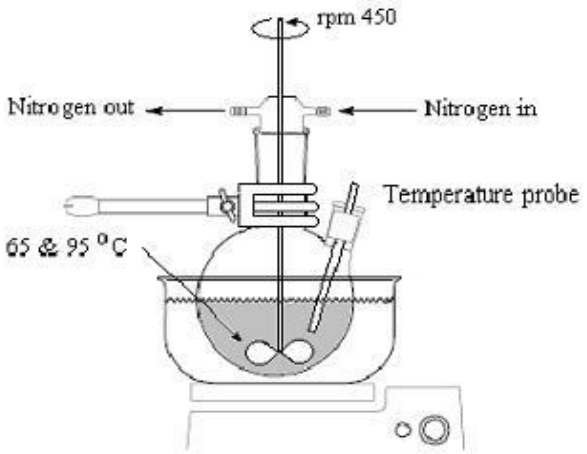

Figure 2: Reaction vessel for microsponge preparation by liquid-liquid suspension polymerization

The polymerization process leads to the formation of a reservoir type of system, which opens at the surface through pores. In some cases an inert liquid immiscible with water but completely miscible with monomer is used during the polymerization to form the pore network. After the polymerization the liquid is removed leaving the porous microspheres, i.e., microsponges. Impregnating them within preformed microsponges then incorporates the functional substances. Sometimes solvent may be used for faster and efficient incorporation of the active substances. The microsponges act as a topical carriers for variety of functional substances, e.g. anti acne, anti inflammatory, anti purities, anti fungal, rubefacients, etc. (Vyas et al. 2002)

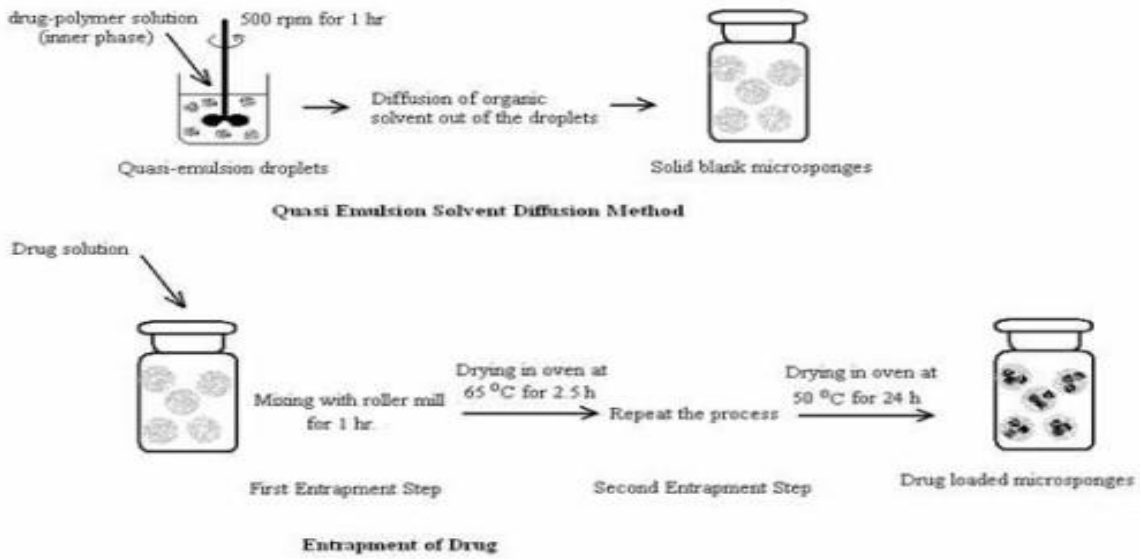

Figure 3: Method of Quasi-emulsion solvent diffusion

Quasi-emulsion solvent diffusion

All microsponges were prepared by a quasi-emulsion solvent diffusion method using an external phase of containing 200 ml distilled water and 40 mg polyvinyl alcohol (PVA) 72 000. The internal phase consisted of ketoprofen, ethyl alcohol, polymer and triethylcitrate (TEC), which was added at an amount of 20% of the polymer in order to facilitate the plasticity. At first, the internal phase was prepared at 60°C and added to the external phase at room temperature. After emulsification, the mixture was continuously stirred for 2 hours. Then the mixture was filtered to separate the microsponges. The product was washed and dried by vacuum oven at 40°C for 24 hours. (Tansel et al. 2003)

DRUG USED IN MICROSPONGE DELIVERY (Geeta Patel et al. 2006)

Drugs explored in Microsponge delivery system (MDS)

Dicyclomine, an anticholinergic drug, has direct smooth muscle relaxant action, and in addition to being a weak anticholinergic, it exerts antispasmodic action. Its plasma half life is 4 - 6 h. Dicyclomine causes gastrointestinal (GI) side effects like other antispasmodic drugs. The study was designed to formulate a delivery system based on microsponges that would reduce the GI side effects of the drug.

Flurbiprofen, Microsponge system containing flubiprofen was formulated for the colonic delivery of the drug for targeted action.

Benzylperoxide, Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne and athletes foot. Skin irritation is a common side effect, and it has been shown that controlled release of BPO from a delivery system to the skin could reduce the side effect while reducing percutaneous absorption. Therefore, the ethylcellulose microsponge system was formulated containing BPO which were able to control the release of BPO to the skin.

Fluocinolone acetonide, (FA) is a corticosteroid primarily used in dermatology to reduce skin inflammation and relieve itching. The percutaneous absorption increases risk associated with systemic absorption of topically applied formulation. Controlled release of drug to the skin could reduce the side effect while reducing percutaneous absorption. Therefore, FA entrapped microporous microparticles (microsponges) were formulated to control the release of drug to the skin.

Retinol, the use of vitamins like tocopherol, retinol in cosmetic formulations like creams, gels is limited due to high instability so oil and water soluble microsponge delivery of the retinol has been developed.

EVALUATION METHODOLOGY OF MICROSPONGE

Particle size determination (Martin et al. 1991)

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 unloade microsponges can be performed by laser light diffractometry or any other suitable method. 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.

Morphology and Surface topography of microsponges (Emanuele et al. 1995)

For morphology and surface topography, prepared microsponges can be coated with gold–palladium un-

der 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 microsponge particle can also be taken to illustrate its ultra structure.

Determination of loading efficiency and production yield (Kilicarslan et al. 2003)

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

Loading efficiency =

$$\frac{\text{Actual Drug Content in Microsponges}}{\text{Theorotical DrugContent}} \text{ X } 100$$

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

Production Yield (PY) =

$$\frac{\text{Practical Mass of Microsponges}}{\text{Therotical Mass (polymer + drug)}} \text{ X } 100$$

Determination of true density (Barkai et al. 1990)

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.

Polymer/ Monomer composition (Barkai et al. 1990)

Factors such as microsphere size, drug loading, and polymer composition govern the drug release from microspheres. Polymer composition of the MDS can affect partition coefficient of the entrapped drug between the vehicle and the microsponge system and hence have direct influence on the release rate of entrapped drug. Release of drug from microsponge systems of different polymer compositions can be studied by plotting cumulative % drug release against time. Release rate and total amount of drug released from the system composed of methyl methacrylate/ ethylene glycol dimethacrylate is slower than styrene/ divinyl benzene system. Selection of monomer is dictated both by characteristics of active ingredient ultimately to be entrapped and by the vehicle into which it will be dispersed. Polymers with varying electrical charges or degrees of hydrophobicity or lipophilicity may be prepared to provide flexibility in the release of active ingredients. Various monomer combinations will be screened for their suitability with the drugs by studying their drug release profile.

Resiliency (D'souza et al. 2008)

Resiliency (viscoelastic properties) of microsponges can be modified to produce beadlets that is softer or firmer according to the needs of the final formulation. Increased cross-linking tends to slow down the rate of release. Hence resiliency of microsponges will be studied and optimized as per the requirement by considering release as a function of cross-linking with time.

Release evaluations (D'souza et al. 2008)

Release mechanism of microsponges: Release can be controlled through diffusion or other triggers such as moisture, pH, friction, or temperature. This release technology is available for absorbent materials or to enhance product aesthetics. Microsponge delivery system can be incorporated into conventional dosage forms such as creams, lotions, gels, ointments, and powder and share a broad package of benefits. Systems can and improve its formulation flexibility.

Dissolution tests (D'souza et al. 2001)

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

FORMULATION CONSIDERATIONS

Actives entrapped in MDS can then be incorporated into many products such as creams, lotions, powders and soaps. When formulating the vehicle, certain considerations are taken into account in order to achieve desired product characteristics. The solubility of actives in the vehicle must be limited. Otherwise the vehicle will deplete the microsponges before the application. To avoid cosmetic problems; not more than 10 to 12% w/w microsponges must be incorporated into the vehicle. Polymer design and payload of the microsponges for the active must be optimized for required release rate for given time period.

ADVANTAGES OF MICROSPONGE

The MDS has advantages over other technologies like microencapsulation 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

- Oil control: Microsponge can absorb oil up to 6 times its weight without drying.
- Extended release
- Reduced irritation and hence improved patient compliance
- Improved product elegancy
- Improved thermal, physical, and chemical stability
- Incorporation of immiscibles
- Liquids can be converted in to powders improving material processing
- Flexibility to develop novel product forms . (D'souza et al. 2004)

APPLICATIONS OF MICROSPONGE SYSTEMS

Microsponges are porous, polymeric microspheres that are used mostly for topical and recently for oral administration. It offers the formulator a range of alternatives to develop drug and cosmetic products. 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.

Table 1: Applications of Microsponge system (Khopade et al.1996)

S.No.	Active agents	Applications
1.	Sunscreens	Long lasting product efficacy, with improved protection against sunburns and sun related injuries even atelevated concentration and with reduced irritancy and sensitization.
2.	Anti-acne e.g. Benzoyl peroxide	Maintained efficacy with decreased skin irritation and sensitization.
3.	Anti-inflammatory e.g. hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatoses.
4.	Anti-fungals	Sustained release of actives.
5.	Anti-dandruffs e.g. zinc pyrithione, selenium sulfide	Reduced unpleasant odour with 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 AS TOPICAL DELIVERY

Conventional formulations of topical drugs are intended to work on the outer layers of the skin. Typically, such products release their active ingredients upon application, producing a highly concentrated layer of active ingredient that is rapidly absorbed. The Microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Potentially, the Microsponge system can reduce significantly the irritation of effective drugs without reducing their efficacy. Further these porous microspheres with active ingredients can be incorporated in to formulations such as creams, lotions and powders. Microsponges consisting of non-collapsible structures with porous surface through active ingredients are released in a controlled manner. Depending upon the size the total pore length may range up to 10 ft and pore volume up to 1 ml/g. (Geeta Patel, 2006)

Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne and athletes foot. Skin irritation is a common side effect, and it has been shown that controlled release of BPO from a delivery system to the skin could reduce the side effect while reducing percutaneous absorption. Therefore, the aim of the present study was to produce ethylcellulose microparticles containing BPO which were able to control the release of BPO to the skin.

In order to optimize the microparticle formulation, factors affecting the physical properties of microparticles were also investigated. Benzoyl peroxide microparticles were prepared using an emulsion solvent diffusion method by adding an organic internal phase containing benzoyl peroxide, ethyl cellulose and dichloromethane into a stirred aqueous phase containing polyvinyl alcohol. Drug content, particle size analysis and loading yield were determined in the prepared microparticles.

BPO microparticles were then incorporated into standard vehicles for release studies. Scanning electron microscopy was used to study the shape and morphology of the microsponges. The micrograph of microsponges showed that they were spherical in shape and contained pores. These pores resulted from the diffusion of solvent from the surface of the microparticles and thus the particles were designated as microsponges. It was shown that the drug : polymer ratio, stirring rate, volume of dispersed phase influenced the particle size and drug release behavior of the formed microsponges and that the presence of emulsifier was essential for microsponge formation. The results showed that, generally, an increase in the ratio of drug : polymer resulted in a reduction in the release rate of BPO from microsponges which was attributed to a decreased internal porosity of the microsponges. (D'souza et al. 2001)

Ketoprofen was used as a model drug for systemic drug delivery of microsponges in the study.This study concerns the use of this polymer; Eudragit† RS 100 to prepare modified release of microsponges. Ketoprofen was used as a model drug. Of containing 200 ml distilled water and 40 mg polyvinyl alcohol (PVA) 72 000. The internal phase was consisted of ketoprofen, ethyl alcohol, polymer and triethylcitrate (TEC) which was added at an amount of 20% of the polymer in order to facilitate the plasticity. At first, the internal phase was prepared at 60 8C and added to the external phase at room temperature. After emulsification, the mixture was continuously stirred for 2 h. Then the mixture was filtered to separate the microsponges. The product was washed and dried by vacuum oven at 40 8C for 24 h. and afterwards. The effects of pressure and direct compression on tabletting of microsponges are

Table 2: Marketed formulations of Microsponge

Product name	Manufacturer	Advantages
Retinol cream	Biomedic	The retinol molecule is kept in the microspongesystem to protect the potency of the vitamin A. This 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.
Salicylic Peel 20	Biophora	Deep BHA peeling agent for (professional use only): Salicylic acid 20%, Microsponge Technology, Excellent exfoliation and stimulation of the skin for more resistant skin types or for faster results. Will dramatically improve fine lines, pigmentation, and acne concerns.
Dermalogica Oil Control Lotion	John and Ginger Dermalogica Skin Care Products	Exclusive skin response complex soothes and purifies, provides effective skin hydration, without adding excess oil; eliminate shine for hours with Dermalogica Oil Control Lotion. Oil Control Lotion is a feather-light lotion, formulated with oil absorbing Microsponge technology and hydrating botanicals. The naturally antiseptic Skin Response Complex helps soothe and purify the skin.
Oil free matte block spf20	Dermalogica	Shield skin from damaging UV rays and control oil production with this invisible sunscreen. 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. Cornstarch and Vinyl Dimethicone/ Methicone Silsesquioxane Cross-polymer act as microsponges to absorb excess surface oils on skin.

checked so for that tablets of microsponges were prepared by direct compression method. Different pressure values were applied to the tablet powder mass in order to determine the optimum pressure value for compression of the tablets. Results indicated that compressibility was much improved over the physical mixture of the drug and polymer; due to the plastic deformation of sponge-like structure microsponges produce mechanically strong tablets. (Yamasaki Y and Tansel et al. 2003).

CONCLUSION

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

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