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MICROSPONGES: A NOVEL DRUG DELIVERY SYSTEM FOR CONTROLLED DELIVERY OF TOPICAL DRUGS

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ABSTRACT

Even though possess several advantages topical formulations have some drawbacks such as the need to contain high concentrations of active agents for effective therapy due to the 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 in-compatibility of drugs with the vehicles. These drawbacks are overcome by microsponge drug delivery system. Microsponge delivery system consists of a polymeric bead having network of pores held with an active ingredient which maximizes the retention time of an active ingredient either on skin surface or within the epidermis thereby providing controlled release of drugs. Microsponge possess the versatility to load a wide range of actives providing the benefits of enhanced product efficacy, mildness, tolerability, and extended over to a wide range of skin therapies. 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. This review covers the advantages of microsponges, their formulation and applications in pharmaceutical field.

Keywords: Topical, Microsponge, polymers, Vehicle, Epidermis.

INTRODUCTION

Controlled release of drugs onto the epidermis with assurance that the drug remains primarily localized and does not enter the systemic circulation in significant quantities is an area of research that has only recently been addressed with achievement. No efficient vehicles have been discovered for controlled and localized delivery of drugs into the stratum corneum and underlying skin layers and not beyond the epidermis. Application of drugs topically has many problems such as with the ointments, which are often aesthetically unappealing, greasy and sticky. The vehicles of topical formulations need to contain high concentrations of active agents for effective therapy because of the 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 in-compatibility of drugs with the vehicles. Thus there is a need 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 [1].

Microsponge delivery system consisting of a polymeric bead having network of pores with an active ingredient held within was developed to provide controlled release of the active ingredients whose final target is skin itself. The system was employed for the improvement of performance of topically applied drugs. The common method of formulation remains same; the incorporation of the active substance at its maximum thermodynamic activity in an optimized vehicle and reduction of the resistance to diffusion from stratum corneum. Microsponge consists of noncollapsible structures with porous surface

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through which 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. Microsponges are porous microspheres having interconnected voids of particle size range 5-300µm. Microsponges are uniform, spherical polymer particles (as shown in figure No. 1, 2, 3). 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 absorb 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 [2].

Microsponges are microscopic spheres capable of absorbing skin secretions, therefore reducing oiliness and shine from the skin. Spherical particles composed of clusters of even tinier spheres are capable of holding four times their weight in skin secretions. Microsponge 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 [3]. MDS technology is being used in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products.

ADVANTAGES OF MICROSPONGE DELIVERY SYSTEMS [4]

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 absorbed. When compared to these, the Microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Apart from this, the Microsponge system can reduce the irritation of effective drugs without reducing their efficacy. For example, by delivering the active ingredient gradually to the skin like MDS-Benzoyl peroxide formulations have excellent efficacy with minimal irritation.

Advantages over microencapsulation and liposomes

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

Advantages over ointments

Ointments are often aesthetically unappealing, greasy and sticky 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, 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.

FORMULATION CONSIDERATIONS [5,6]

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.

REQUIREMENT OF DRUGS TO BE ENTRAPPED INTO MICROSPONGES [7,8]

Most liquid or soluble ingredients can be entrapped in the particles. Actives that can be entrapped into the microsponges must meet following requirements,

1. It should be either fully miscible in monomer or capable of being made miscible by addition of small amount of a water immiscible solvent.
2. It should be water immiscible or at most only slightly soluble.
3. It should be inert to monomers.
4. It should be stable in contact with polymerization catalyst and conditions of polymerization.
5. The solubility of actives in the vehicle must be limited to avoid cosmetic problems. Not more than 10-12 % w/w microsponges must be incorporated into vehicle. Otherwise vehicle will deplete microsponges before the application.
6. Polymer design and payload of the microsponges for the active must be optimized for required release rate for given time period.

Active following these criteria serves as porogen or pore forming agent. Such drugs can be entrapped while polymerization takes place by one-step process. When the material is sensitive to the polymerizing conditions, polymerization is performed using substitute porogen. The porogen is then removed and replaced by contact absorption assisted by solvents to enhance absorption rate [9].

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.

BENEFITS OF MICROSPONGE DRUG DELIVERY SYSTEM [10]

1. Advanced oil control- absorb up to 6 times its weight without drying.
2. Extended release-continuous action up to 12 hours.
3. Reduced irritation-better tolerance means broader consumer acceptance.
4. Improved product aesthetics- gives product an elegant feel.
5. Improved stability- thermal, physical and chemical.
6. Allows incorporation of immiscible substances.
7. Improves material processing-liquid can be converted to powders.
8. Allows for novel product forms.

Method of Preparation of Microsponges

Drug loading in microsponges can take place in two ways, one-step process or by two-step process; based on physicochemical properties of drug to be loaded. If the drug is typically an inert non-polar material, it will create the porous structure and it is called porogen. Porogen drug, which neither hinders the polymerization nor becomes activated by it and stable to free radicals is entrapped with one-step process.

Liquid-liquid suspension polymerization

Microsponges are conveniently prepared by liquid-liquid suspension polymerization method. Polymerization of styrene or methyl methacrylate is carried out in round bottom flask. In their preparation, the monomers are first dissolved along with non-polar active ingredients in a suitable solvent and then dispersed into the aqueous phase, which consist of additives such as surfactant, suspending agents etc. which aid in formation of suspension. Once suspension with the discrete droplets of the desired size is established, polymerization is effected by activating the monomers either by catalysis or increased temperature or irradiation. The various steps in the preparation of microsponges are summarized as [11]

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

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 [12]. After the completion of polymerization, the liquid is removed leaving the porous microspheres, i.e., microsponges (Shown in figure No. 5). 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 .

Quasi-emulsion solvent diffusion

When the drug is sensitive to the polymerization conditions, two-step process is used. Microsponges were prepared by a quasi-emulsion solvent diffusion method using the different polymer amounts. In this, the external phase consists of 200 ml distilled water and 40 mg polyvinyl alcohol (PVA). The internal phase consists of drug, ethyl alcohol, polymer and triethylcitrate (TEC), which was added at an amount of 20%, of the polymer in order to facilitate the plasticity. The drug can be then added to solution and dissolved under ultrasonication at 35^{o}C. 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 [13].

DRUG RELEASE MECHANISM

The topical agent formulation with the MDS can be prepared in many different forms, such as a gel, cream, or lotion. Once the formulation is topically applied to the desired area of the skin, the active ingredients diffuse out of the spheres into the vehicle and then onto the skin (Figure 7).

While the rate of release of the active ingredient from the formulation can be predetermined, the release can be initiated or accelerated by many release triggers as given below,

(i) Pressure: Rubbing/ pressure applied can release active ingredient from microsponges onto the skin.

(ii) Solubility: Microsponges loaded with water-soluble ingredients like anti-prespirants and antiseptics will release the ingredient in the presence of water. The release can also be activated by diffusion taking into consideration the partition coefficient of the ingredient between the microsponges and the outside system.

(iii) Temperature change: Some entrapped active ingredients can be too viscous at room temperature to flow spontaneously from microsponges onto the skin. Increase in skin temperature can result in an increased flow rate and hence drug release. Drug release from the topical semisolid formulation can be studied by using Franz-type static diffusion cells [14].

Figure 1. Microsponges

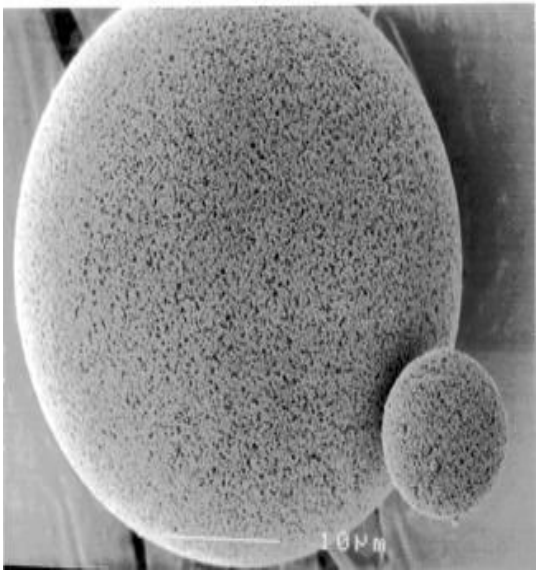

Figure 2. Microsponges

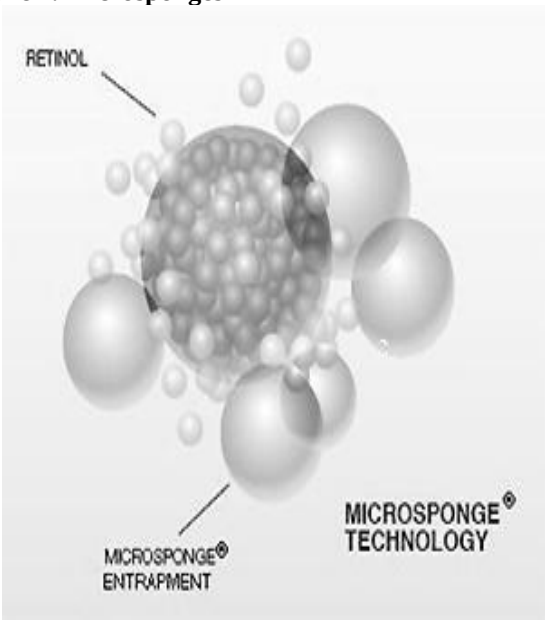

Figure 3. Porous structure of microsponge

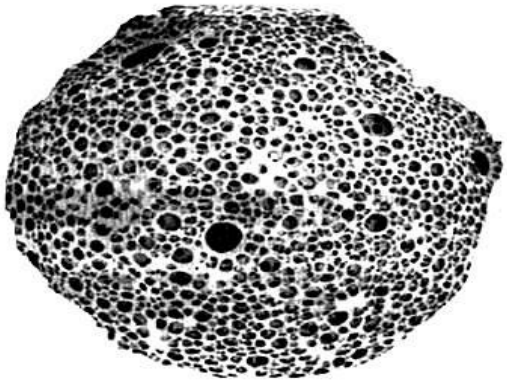

Figure 4. Liquid-liquid suspension polymerization technique

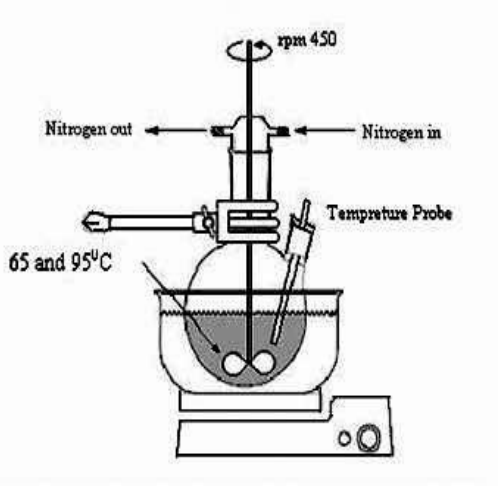

Figure 5. Steps involved in formation of microsponges in liquid-liquid suspension polymerization method

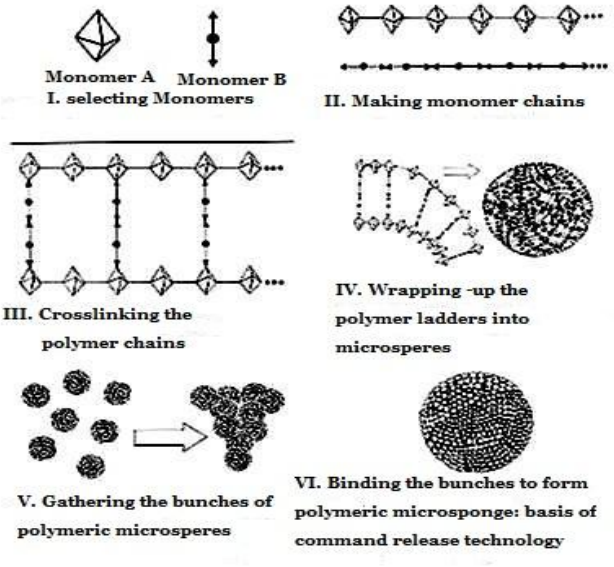

Figure 6. Steps involved in Quasi-emulsion solvent diffusion method

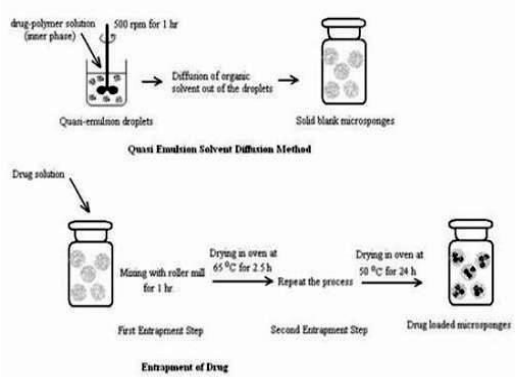

Figure 7. Release mechanism of active ingredient from microsponges

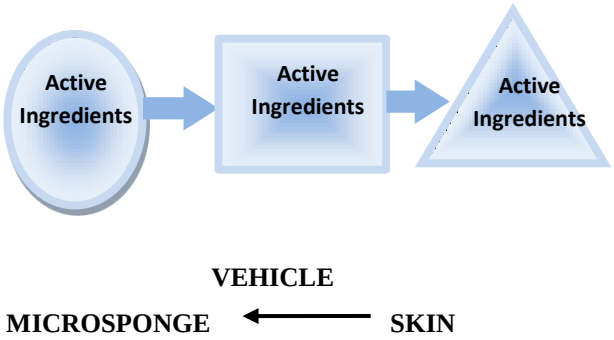

Table 1. Applications of microsponges [18

S. No.	ACTIVE AGENTS	APPLICATIONS
1.	Sunscreens	Long lasting product efficacy, with improved protection against sunburns and sun related injuries 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,	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.

Table 2. Marketed products based on MDS [19-21]

PRODUCT NAME	ADVANTAGES	MANUFACTURER
Retin-A-Micro	0.1 And 0.04% tretinoin entrapped in MDS, for topical treatment of acne vulgaris. This formulation uses patented methyl methacrylate / glycol+8 dimethacrylate cross-polymer porous microspheres.	Ortho-McNeil Pharmaceutical,Inc.
Carac cream, 0.5%	Carac cream contains 0.5% fluorouracil, with 0.35% being incorporated into a patented porous microsphere (Microsponge) composed of methyl methacrylate / glycol dimethacrylate cross-polymer and dimethicone.	Dermik Laboratories, Inc.Berwyn,PA19312 USA
Line eliminator dual retinol facial treatment	Lightweight cream with a retinol (Vitamin A) in MDS, delivers both immediate and time-released wrinkle-fighting action.	Avon
Retinol cream	The retinol molecule is kept in the microsponge system to protect the potency of vitamin A. This helps to maximize the retinol dosage, while reducing the possibility of irritation. Retinol is a topical vitamin A derivative, which helps maintain healthy skin, hair, and mucous membranes.	Biomedic
Retinol 15 nightcream	A night time treatment cream with Microsponge system. The formula contain of pure retinol. Continuous use of Retinol 15 will result in the visible diminishment of fine lines and wrinkles, and improve in skin discolorations.	Biomedic,sothys
EpiQuin micro	The Microsponge® system entrap hydroquinone and retinol. The microsponges release these ingredients into the skin gradually throughout the day, which may minimize skin irritation	Skin Medica Inc

Sports cream RS and XS	Topical analgesic-anti-inflammatory and counterirritant actives in a Microsponge® Delivery System (MDS) for the management of musculoskeletal conditions	Embil Pharmaceutical.
Salicylic peel 20 and 30	Deep BHA peeling agent: Salicylic acid 20% and 30%, 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.	Biophora
Micro peel plus	The MicroPeel® Plus,stimulates cell turnover through the application of salicylic acid in the form of microcrystals using Microsponge® technology.The MicroPeel® Plus aggressively outperforms other superficial chemical peels by freeing the skin of all dead cells, while doing no damage to the skin.	Biomedic
Oil free matte block spf-20	This sunscreen provides a shield for the skin from damaging UV rays and controls oil production. Microsponge technology absorbs the oil, maintaining an all-day matte finish. Oil-free formula contains soothing Green Tea to help calm inflammation caused by breakouts. Cornstarch and Vinyl Dimethicone / Methicone Silsesquioxane Cross-polymer act as microsponges to absorb excess surface oils on skin.	Dermalogica
Oil control lotion	Feature-light lotion microsponges that absorb oil on the skin's surface during the day, for a matte finish.Eliminate shine for hours with this feature-weight lotion. The natural-antibiotic Skin Response Complex soothes inflammation and tightness to promote healing, Acne-Prone, oily skin conditions	Fountain Cosmetics
Lactrex™ 12% moisturizing cream	It contains 12% lactic acid as the neutral ammonium salt and ammonium lactate. Lactrex™ also contains water and glycerin, a natural humectant, to soften and help moisturize dry, flaky, cracked skin.	SDR Pharmaceuticals, Inc., Andover, NJ, .S.A. 07821
Dermalogica oil control lotion	It 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.	John and Ginger Dermalogica skin care products
Aramis fragrances	24-Hour high performance antiperspirant spray sustained release of fragrance in the microsponge.The microsponge comes in the form of an ultra light powder, and because it is micro in size, it can absorb fragrant oil easily, while maintaining a free-flowing powder characteristic where release is controlled due to moisture and temperature.	Aramis Inc
Ultra guard	Microsponge system that contains dimethicone to help protect a baby's skin from diaper rash	Scott Paper

PHYSICAL CHARACTERIZATION OF MICROSPONGES

(i) Particle size determination

Particle size analysis of loaded and unloaded microsponges can be performed by laser light diffractometer or any other suitable method. The values can be expressed for all formulations as mean size range. Cumulative percentage drug release from microsponges of different particle size must be plotted against time to study effect of particle size on drug release. Particles larger than 30μm can impart gritty feeling and hence particles of sizes between 10 and 25μm are preferred to use in final topical formulation.

(ii) Morphology and surface topography of microsponges

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 scanning electron microscopy (SEM). SEM of a fractured microsponge particle can also be taken to illustrate its ultra structure.

(iii) Determination of loading efficiency and production yield

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

$$\text{Loading efficiency} = \left(\frac{\text{Actual drug in microsphers}}{\text{Theoretical drug concentration}}\right) 100$$

The production yield of the microparticles can be determined by following equation:

$$\textbf{Production yield} = \left(\frac{\textbf{Practicalmass}}{\textbf{Theoriticalmass}}\right)\textbf{100}$$

(iv) 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 [15].

(v) 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. Porosity parameters of microsponges such as intrusion–extrusion isotherms pore size distribution, total pore surface area, average pore diameters, shape and morphology of the pores, bulk and apparent density can be determined by using mercury intrusion porosimetry.

(vi) Compatibility studies

Compatibility of drug with reaction adjuncts can be studied by thin layer chromatography (TLC) and Fourier Transform Infra-red spectroscopy (FT-IR). Effect of polymerization on crystallinity of the drug can be studied by powder X-ray diffraction (XRD) and Differential Scanning Colorimetry (DSC). For DSC, approximately 5mg samples can be accurately weighed into aluminum pans and sealed and can be run at a heating rate of 15 ^{o}C/min over a temperature range 25–430 ^{o}C in atmosphere of nitrogen.

(viii) Resiliency (Viscoelastic properties)

Resiliency 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.

(ix) Dissolution studies

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 [16].

APPLICATIONS OF MICROSPONGE DRUG DELIVERY 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.

CONCLUSION

Microsponge drug delivery system is advantageous over the conventional topical drug delivery due to its properties like Ease manufacturing, simple ingredients and wide range drugs can be entrapped. MDS is originally developed for topical delivery of drugs like anti-acne, anti-inflammatory, anti-fungal, anti-dandruffs, antipruritics, rubefacients etc. MDS have a hopeful prospect in various pharmaceutical applications in the coming years by virtue of their exclusive properties like small size, efficient carrier characteristics enhanced product performance and elegancy, extended release, reduced irritation, improved thermal, physical, and chemical stability so flexible to develop novel product forms. Microsponge delivery system can further be incorporated into conventional dosage forms such as creams, lotions, gels, ointments, and powder. Thus microsponges represent a promising approach for controlled delivery of drugs.

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