Journal of Scientific and Innovative Research 2013; 2 (6): 1097-1110
Available online at: www.jsirjournal.com

Review Article

ISSN 2320-4818
JSIR 2013; 2(6): 1097-1110

Received: 19-10-2013
Accepted: 27-12-2013

Namrata Jadhav, Vruti Patel
Department of Pharmaceutics, Bharti Vidyapeeth College of Pharmacy, Navi Mumbai-400614, India

Siddesh Mungekar, Gaurav Bhamare
Department of Pharmaceutics, Bharti Vidyapeeth College of Pharmacy, Navi Mumbai-400614, India

Manisha Karpe, Vilasrao Kadams
Department of Pharmaceutics, Bharti Vidyapeeth College of Pharmacy, Navi Mumbai-400614, India

Correspondence:
Namrata Jadhav
c/o, Department of Pharmaceutics, Bharti Vidyapeeth College of Pharmacy, Sector-8, CBD Belapur, Navi Mumbai-400614, India
Tel: +91-8097745056
Fax: +022 27571122
E-mail:
mail:namratajadhav18@gmail.com

Microsponge Delivery System: An updated review, current status and future prospects

Namrata Jadhav, Vruti Patel, Siddesh Mungekar, Gaurav Bhamare, Manisha Karpe, Vilasrao Kadams*

Abstract

Microsponges are at the forefront of the rapidly developing field of novel drug delivery technology. Microsponge drug delivery technology holds a great promise for reaching the goal of controlled and site-specific drug delivery and hence, has attracted wide attention of researchers. This article presents a broad review of Microsponges delivery system discussing the principles and preparation methods. Appropriate analytical techniques for characterization of Microsponges like Particle size and its distribution, surface morphology, porosity, density are covered. Advantages, limitations and their possible remedies of the microsponge drug delivery are also mentioned. These microsponges are used in the sunscreens, creams, ointments, over-the-counter skin care preparations, which are meant for topical application. Microsponge drug delivery can provide increased efficacy for topically active agents with enhanced safety, extended product stability and improved aesthetic properties in an efficient and novel manner. They are mostly used for topical use and have recently been used for oral administration.

Keywords: Microsponges, Controlled release, Porous microspheres, Solvent evaporation.

Introduction

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. New classes of pharmaceuticals, biopharmaceuticals (peptides, proteins and DNA-based therapeutics) are fuelling the rapid evolution of drug delivery technology. These new drugs typically cannot be effectively delivered by conventional mean. Drug delivery systems (DDS) that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the health care system.

In the current years the development of new drugs is not sufficient for the drug treatment. But it also involves the development of suitable drug delivery system at site of action. The in-vivo fate of the drug is not only determined by the properties of the drug, but it is also determined by the carrier system, which permits a controlled and localized release of the active drug according to the specific need of the therapy. The biggest challenge up to date is to control the delivery rate of the medicaments by various modern technologies met by extensive research.[1, 2]

However, TDS is not practical for delivery of materials whose final target is the skin

itself. The controlled release of drug from the formulation into the epidermis such that the drug remains primarily localized with only a restricted amount entering the systemic circulation, is a means of controlling side-effects. Thus, the need exists for delivery systems to maximize the period of time that an active ingredient is present, either on the skin surface or within the epidermis while minimizing its transdermal penetration into the body. Another potential problem in topical delivery of drugs relates to uncontrolled evaporation of the active ingredient, unpleasant odour, the use of unaesthetic vehicles which may be greasy, sticky and may cause discolorations, since this can result in the lack of patient compliance.[3-5]

Carrier technology is the potential solution to these challenges. Microparticles and nanoparticles have been increasingly researched to achieve targeted and sustained release of drugs. These include microspheres, liposomes, and nanoparticles etc. which alter the absorption and release characteristics of the drug. Microspheres are unable to control the release rate of drug from itself. Once the outer wall is ruptured the drug contained within microspheres will be released from it. Liposomes having demerits like lower drug entrapment, difficulty in preparing formulation, limited chemical stability and microbial stability so the preservatives are required. Solid lipid nanoparticles are having most of the benefits in the topical drug delivery. Nanomaterial can easily enter in to the systemic circulation by inhalation or ingestion, and possibly also via skin absorption, especially if the skin is damaged. Once in the blood stream, nanomaterials can be transported around the body and are taken up by organs and tissues including the brain, heart, liver, kidneys, spleen, bone marrow and nervous system.[6]

The microsponge-based polymeric microspheres uniquely overcome problems associate with above technologies. Microsponges are extremely small, inert, indestructible spheres that do not pass through the skin. Rather, they collect in the tiny nooks and crannies of the skin and slowly release the entrapped drug, as the skin needs it. They 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.

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. These products are typically presented to the consumer in conventional forms like creams, gels or lotions and they contain a relatively high concentration of active ingredients. Recently their use is also being investigated for oral drug delivery. This article provides concise information to the various aspects of the structure, development, applications and future of microsponges. It is to be introductory to the vast amount of research that has been done and the large number of opportunities that exist in the field of microsponges.[7]

Defining microsponges

The Microsponge Delivery System (MDS) is a patented polymeric system consisting of porous microspheres. They are tiny sponge like spherical particles that consist of a myriad of interconnecting voids within a non-collapsible structure with a large porous surface through which active ingredient are released in a controlled manner. The size of the microsponge's ranges from 5-300μm in diameter and a typical 25μm sphere can have up to 250000 pores and an internal pore structure equivalent to 10 feet in length, providing a total pore volume of about 1ml/g for extensive drug retention. The surface can be varied from 20 to 500 m2/g and pore volume range from 0.1 to 0.3cm3/g. This results in a large reservoir within each microsponge, which can be loaded with up to its own weight of active agent.[8, 9]

The microsponge technology was developed by Won in 1987, and the original patents were assigned to Advanced Polymer Systems, Inc.[10] This Company developed a large number of variations of the procedures and those are applied to the cosmetic as well as over-the-counter (OTC) and prescription pharmaceutical products. At the current time, this interesting technology has been licensed to Cardinal Health, Inc., for use in topical products.

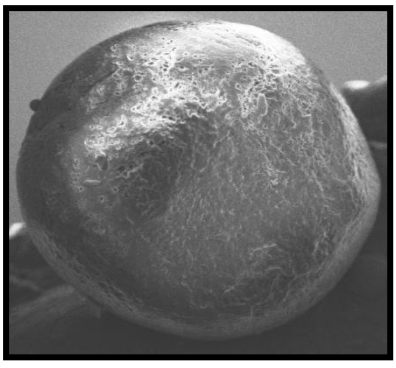

Figure 1: A typical diagram of Microsponge

The scanning electron microscopy of the microsponge particle reveals that its internal structure as the "bag of marbles". The porosity is due to the interstitial spaces between the marbles. The interstitial pores can entrap

many wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, anti-infective and anti-inflammatory agents. These entrapped microsponges may then integrated or formulated into product forms, such as creams, lotions, powders, soaps, capsules and tablets. When these products are applied the entrapped material gets delivered to the skin in a controlled time release pattern or a pre-programmed manner through the use of several different 'triggers', rubbing or pressing the Microsponge after it has been applied to the skin, elevates skin surface temperature introducing solvents for the entrapped materials such as water, alcohol or even perspiration and controlling the rate of evaporation. Active ingredients entrapped in the porous polymeric structure display altered behavior, with respect to their release, which is restricted and prolonged.[11]

Characteristics of microsponges

When these are applied to the skin, the microsponge releases its active ingredient gradually to the skin on a time mode and also in response to stimuli such as rubbing, temperature and pH effect etc. with excellent efficacy and minimal irritation. Characteristics of microsponges are as follows: [10, 12-14]

1. Microsponge formulations are stable over range of pH 1 to 11.

2. Microsponge formulations are stable at the temperature up to 130^0C.

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

4. Microsponge formulations are self- sterilizing as their average pore size is about 0.25μm where the bacteria cannot penetrate the pores.

5. Microsponge formulations have high entrapment upto 50 to 60%.

6. Microsponge formulations are free flowing and can be cost effective.

7. Microsponge particles themselves are too large so they are difficult to be absorbed into the skin and this adds a measure of safety to these microsponge materials by avoiding the side effects of the microsponge adjutants.

8. Microsponges formulations can be cost effective even for the cosmetic mass market use where the cost of the materials is important.

9. Microsponges can absorb oil up to 6 times its weight without drying.

10. It provides continuous action up to 12 hours i.e. extended release.

11. They have superior formulation flexibility.

Methods of preparation of microsponges

The selection of a particular encapsulation method is primarily determined by the solubility characteristics of the drug and polymer. A popular method for the encapsulation of water-insoluble drugs within water insoluble polymers is the diffusion solvent method. This method can be both readily performed in the laboratory but has scale up potential such that large volumes of water can be handled. When finally developing a microencapsulation procedure then finally selected method should ideally produce.[15]

- High yields of microparticles and free of extensive agglomeration,
- Higher encapsulation of the core material,
- A reproducible release profile from batch to batch, and
- An ability to modify in vitro release rates by varying process parameters in order to prepare microparticles with the desired in vivo release characteristics.

Properties of the actives for the entrapment into the microsponge

- 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 and should not increase the viscosity of the mixture during formulation.
- It should be stable when in contact with polymerization catalyst and under conditions of polymerization.
- The spherical structure of the microsponges should not collapse.[15-19]

Various polymers like Eudragit RS100, Ethyl Cellulose, Polystyrene and PHEMA can form a microsponge 'cage'. In addition to actives; some microsponges contain plasticizers like Triethylcitrate (TEC) that help to stabilize their structure.

Free Radical Suspension Polymerization: (Bottom up approach)

This is Bottom-up approach starting with monomer. Microsponges were conveniently prepared by free radical suspension polymerization in an emulsified liquid-liquid system. Particles forming polymerization mixtures are usually two phase systems. The monomers are referred to as 'monomer phase' or 'dispersed Phase'; the immiscible liquid phase containing the dispensed (or dissolved) monomer is defined as "Polymerization medium."

In addition to the monomers and polymerization medium, another liquid (miscible with the monomer and immiscible with the medium) may also be added to the monomer to form a pore network. This liquid is known as 'monomer diluent' or 'porogen' and belongs to the category of inert, nonpolar organic solvents when added to the polymerization reaction, polymeric beads with open, porous structures can be obtained and they look just like sponges under SEM, hence the name 'microsponges'.[20] For preparing Microsponge, the requirements are monomer namely Styrene, PHEMA, Cross linking Agents is Divinyl Benzene and Porogen is Toluene.[21]

It is important to maintain the temperature for most efficient operation. Temperature of the reaction mix dictates the rate of decomposition, the initiation into free radicals and hence affecting the rate of polymerization.

Once the suspension is established with discrete droplets of the desired size, polymerization is affected by activating the monomers either by catalysis, increased temperature or irradiation. The result is a series of polymer ladders wrapping around one another into solid Microspheres. As the Polymerization process continues, a spherical structure is produced containing thousands of Microspheres bunched together like grapes, forming interconnecting reservoirs in which the porogen is entrapped. These reservoirs open onto the surface of the spheres through which active ingredient can be released when triggered.

Once polymerization is complete the solid particles that result from the process are recovered from the suspension. The particles are then washed and processed until they are substantially ready for use. Particle formation and incorporation of the functional substance is thus performed as a single step. This may be termed as one step process. When the material is sensitive to the polymerization conditions, polymerization is performed using substitute porogen. The porogen is then removed and replaced by contact absorption assisted by solvents to enhance absorption rate.[11, 22]

Quasi-emulsion solvent diffusion method: (Top down approach)

This is top-down approach starting with preformed polymer. This process involved formation of quasi-emulsion of two different phases' i.e. internal phase and external phase similar to emulsions. The internal phase of drug--polymer solution made in a volatile solvent like ethanol or acetone or dichloromethane was added to external phase comprising the aqueous polyvinyl alcohol (PVA) solution with vigorous stirring. Triethylcitrate (TEC), which was added at an adequate amount in order to facilitate plasticity. Stirring lead to the formation of discrete emulsion globules called quasi-emulsion globules. Solvent was then extracted out from these globules to form insoluble, rigid microparticles i.e. microsponges. Following sufficient stirring, the mixture was then filtered to separate the microsponges. The microsponges were then dried in an air heated oven. Conceptually, the finely dispersed droplets of the polymeric solution of the drug (dispersed phase) get solidified in aqueous phase via counter diffusion of organic solvent and water out of and into the droplets. The diffused aqueous phase within the droplets decreased the drug and polymer solubility resulting in the co-precipitation of both the components and continued diffusion of the organic phase results in further solidification, producing matrix-type porous microspheres. In comparison with liquid--liquid suspension polymerization method, this method offered the advantage of less exposure of the drug to the ambient conditions, low solvent residues in the product because the solvent get extracted out due to its solubility in aqueous media or due to its volatile nature.[15, 16, 23]

In another method that is drug entrapment method, drug loading is done after the formation of microsponges. In this method, blank microsponges and drug solution in ethanol is added. Bottles are arranged on roller mill and mixed for 1hr. The mixture is dried in an oven at 65 °C for 2.5 h. This process is repeated for a second entrapment step and the drying process is held at 50 °C for 24h.[24]

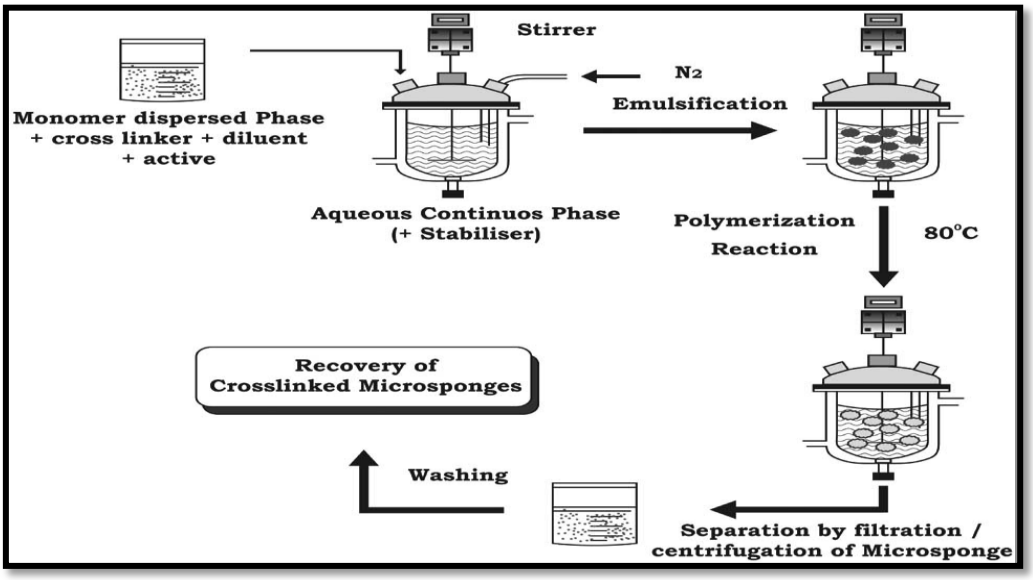

Figure 2: Suspension polymerization- system set up method

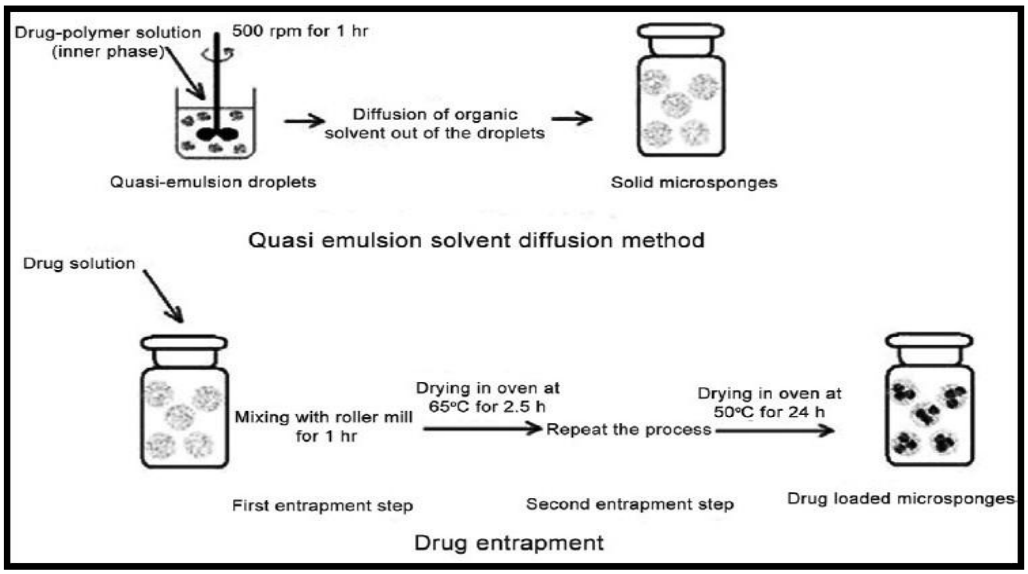

Figure 3: Preparation of microsponges by quasi emulsion solvent diffusion

Formulation considerations

Actives entrapped in MDS can then be incorporated into many products such as creams, gels, lotions, powders and soaps or can be compressed into tablets. When formulating the vehicle, certain considerations are taken into account in order to achieve desired product characteristics.[8]

- 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.

Hypothetical mechanism of action

The active ingredient is added to the vehicle in an entrapped form. As the microsponge 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 microsponge particle into the vehicle, and from it to the skin, until the vehicle is either dried or absorbed. Even after that the microsponge 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 microsponge 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 microsponge 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 microsponge 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 microsponge 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 microsponge 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.[7]

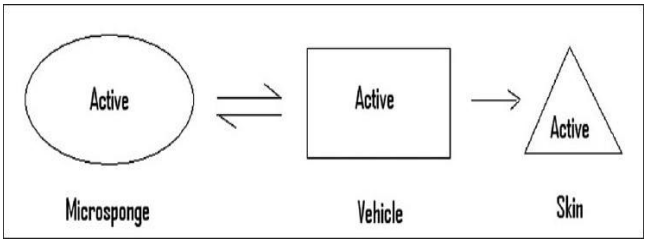

Figure 4: schematic representation of the distribution of the loaded material (active) on skin

Release mechanisms

The mentioned programmable parameters can be effectively manipulated to design Microsponge delivery system for the release of functional substance over a period of time in response to one or more external stimuli. The release mechanism of this system is mainly:-

A. Sustained or Time Release

In the development of a sustained release Microsponge, different physical and chemical parameters of the entrapped active substance such as volatility, viscosity and solubility will be studied while in case of polymeric microsponge pore diameter, volume, and resiliency of the polymeric microsponge are evaluated to give necessary sustained release effects.[7]

B. Release on Command

Microsponges can be designed to release the given amounts of active ingredients over time in response to one or more external triggers.

1. Pressure Release

Microsponge system releases fluid or active ingredient when it is pressed or squeezed, thereby replenishing the level of entrapped active ingredient onto the skin. The amount released may also depend upon the release of the sponge and the resiliency of the Microsponges.[25]

2. Temperature Release

The release of active ingredients from microsponges can be activated by temperature.

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.[26]

3. pH

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.[25]

4. 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.[27]

Characterization of microsponges

1. Particle size and size distribution

Particle size and size distribution are evaluated using either an optical microscope or an electron microscope. This is an extremely crucial step, as the size of the particles greatly affects the texture of the formulation and its stability. 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.[28]

2. Morphology and Surface topography of SPM

For morphology and surface topography, various techniques have been used like photon correlation spectroscopy (PCS), Scanning electron microscopy (SEM), transmission electron microscopy (TEM) etc. SEM is used widely for which prepared Microsponges are coated with gold–palladium under an argon atmosphere at room temperature and then the surface morphology of the Microsponges is studied.[29]

3. Determination of loading efficiency and production yield

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

$$\%\text{loading efficiency} = \frac{\text{actual drug content in microsponges}}{\text{theoretical drug content}} \times 100$$

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 SPM obtained.[30]

$$\%\text{Production yield} = \frac{\text{Production yield}}{\text{theoretical mass (polymer + drug)}} \times 100$$

4. Determination of true density

The true density of Microsponges can be measured using an ultra-pycnometer under helium gas and is calculated from a mean of repeated determinations.[29]

5. 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 include 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. Incremental intrusion volume scan be plotted against pore diameters that represented pore size distributions. The pore diameter of Microsponges can be calculated by using Washburn equation:

$$D = \frac{-4\gamma\cos\Theta}{P}$$

Where D is the pore diameter (μm); γ the surface tension of mercury (485 dyn cm^{-1}); θ he contact angle (130°); and P is the pressure (psia).

Total pore area (Atot) was calculated by using equation,

$$A_{tot} = \frac{1}{\gamma cos\theta}\int_0^{V_{tot}} P.dV$$

Where P is the pressure (psia); V volume (mL g^{-1}); V_{tot} is the total specific intrusion volume (mL g^{-1}).The average pore diameter (Dm) was calculated by using equation,

$$Dm = \frac{4V_{tot}}{A_{tot}}$$

Envelope (bulk) density (ρse) of the Microsponges was calculated by using equation,

$$\rho_{se} = \frac{W_s}{V_p - V_{Hg}}$$

Where Ws is the weight of the SPM sample (g); Vp the empty penetrometer (mL); V_{Hg} is the volume of mercury (mL).

Absolute (skeletal) density (ñsa) of Microsponges was calculated by using equation,

$$\rho_{se} = \frac{W_s}{V_{se} - V_{tot}}$$

Where Vse is the volume of the penetrometer minus the volume of the mercury (mL).

Finally, the % porosity of the sample was found from equation,

$$\text{Porosity}\,(\%) = (1 - \frac{P_{se}}{P_{sa}}) \times 100$$

Pore morphology can be characterized from the intrusion–extrusion profiles of mercury in the Microsponges.[31, 32]

6. Compatibility studies

The drug-excipients compatibility studies are carried out in order to ensure that there is no inadvertent reaction between the two when formulated into a dosage form. These studies are commonly carried out by recording the differential scanning Calorimetry (DSC) of the chemicals viz., API and excipients individually and also together and checking for any addition or deletion of any peaks or troughs. For DSC approximately 5 mg samples can be accurately weighed into aluminium pans and sealed and can be run at a heating rate of 15oC/min over a temperature range 25–430oC in atmosphere of nitrogen.[33, 34] Infrared (IR) spectroscopy can also reveal the incompatibilities between the chemical moieties. Compatibility of drug with reaction adjuncts can also be studied by thin layer chromatography (TLC) and FT-IR.[35] Effect of polymerization on crystallinity of the drug can be studied by powder X-ray diffraction (XRD) and Differential Scanning Colorimetry (DSC).[36]

7. Polymer/ Monomer composition

Factors such as particle size, drug loading, and polymer composition govern the drug release from Microsponges. Polymer composition of the Microsponges Drug Delivery system 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 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.[37]

8. Resiliency

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 is studied and optimized as per the requirement by considering release as a function of cross linking with time.[38]

9. Drug Release

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 analyzed by suitable analytical method at various intervals.[39]

Kinetics of release

To determine the drug release mechanism and to compare the release profile differences among microsponges, the drug released amount versus time was used. The release data were analyzed with the following mathematical models:

$$Q = k_1 t^n \quad \text{or} \quad \log Q = \log k_1 + n \log t \qquad \text{……Equation (1)}$$

Where Q is the amount of the released at time (h), n is a diffusion exponent which indicates the release mechanism, and k1 is a constant characteristic of the drug–polymer interaction. From the slope and intercept of the plot of log Q versus log t, kinetic parameters n and k1 were calculated

For comparison purposes, the data was also subjected to Equation (2), which may be considered a simple, Higuchi type equation.

$$Q = k_2 t^{0.5} + C \qquad \text{…… Equation (2)}$$

Equation (2), for release data dependent on the square root of time, would give a straight line release profile, with k2 presented as a root time dissolution rate constant and C as a constant.[40]

Safety Considerations

Safety studies of microsponges can be confirmed by;

- Allergenicity in guinea pigs
- Eye irritation studies in rabbits
- Mutagenicity in bacteria
- Oral toxicity studies in rats
- Skin irritation studies in rabbits.[26, 30, 41]

Limitations

Use of organic solvents poses threats, such as toxicity and flammability. Traces of residual monomers in bottom- up approach can be toxic and dangerous to health. But these limitations can be overcome by proper quality control measures coupled with optimization and standardization of procedures e. g, post manufacture washing.[42, 43]

Applications of microsponges

Microsponge delivery systems are used to enhance the safety, effectiveness and aesthetic quality of topical prescription, over-the-counter and personal care products.

Microsponges can be used in variety of applications. It is used mostly for topical and recently for oral administration. Several patents have reported that it can be used as excipients due to its high loading capacity and sustained release ability. 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. Over-the-counter products that incorporate microsponge drug delivery system include numerous moisturizers, specialized rejuvenative products, and sunscreens.

Applications of microsponges with respect to their advantages

Table 1: Applications of microsponges with respect to their advantages

S. No.	Application	Advantages
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.
3	Anti-inflammatory e.g. hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatoses.
4	Anti-dandruffs e.g. zinc pyrithione, selenium sulfide	Reduced unpleasant odour with lowered irritation with extended safety and efficacy.
5	Antipruritics	Extended and improved activity.
6	Skin depigmenting agents e.g. hydroquinone	Improved stabilization against oxidation with improved efficacy and aesthetic appeal.

Examples of microsponge drug delivery with their formulations[40-50, 53]

Table 2: Examples of microsponge drug delivery with their formulations

Microsponge Delivery Systems	Drug	Disease
Gels	Benzoyl peroxide	Anti-Acne Treatment
	Fluconazole	Inflammation
	Mupirocin	Antibacterial activity
	Diclofenac sodium	Inflammation
	Acyclovir	Viral infections
	Hydroxyzine HCl	Urticaria and atopic dermatitis
	Terbinafine HCl	Anti-fungal
Lotions	Benzoyl peroxide	Anti-Acne Treatment
Creams	Hydroquinone and Retinol	Melanoma

Tablets	Indomethacin	Inflammation
	Paracetamol	Anti-pyretic
	Chlorpheniramine maleate	Hay Fever
	Ketoprofen	Musculoskeletal pain
	Fenofibrate	Gout
	Flurbiprofen	Metabolic ratio
	Dicyclomine	Anticholinergic
	Meloxicam	Arthritis
	Paracetamol	Colon targeting
Implants	Poly (DL-lactic-co-glycolic acid)	Skin tissue engineering
Grafts	Poly (lactic-co glycolic acid)	Cardiovascular surgery
Injection	Basic fibroblast growth facto	Growth factor
Others	Benzoylperoxide	Anti-Acne Treatment
	Mefenamic acid	Rheumatoid arthritis
	Ibuprofen	NSAID

List of Marketed Products based on Microsponges[7, 42, 43]

Table 3: List of Marketed Products based on Microsponges

Product Name	Pharmaceutical Uses	Manufacturer
Glycolic Acid Moisturizer w/SPF 15	Anti-Wrinkles, soothing	AMCOL Health & Beauty Solution
Retin A Micro	Acne vulgaris	Ortho-McNeil Pharmaceutical, Inc.
Carac Cream, 0.5%	Actinic keratoses	Dermik Laboratories, Inc.
Line Eliminator Dual Retinol Facial Treatment	Anti-wrinkle	Avon
Retinol 15 Night cream	Anti-wrinkles	Sothys
Retinol cream	Helps maintain healthy skin	Biomedic
EpiQuin Micro	Hyper pigmentation	SkinMedica Inc
Sports cream RS and XS	Anti-inflammatory	Embil Pharmaceutical Co. Ltd.
Salicylic Peel 20	Excellent exfoliation	Biophora
Oil free matte block SPF 20	Sunscreen	Dermalogica
Lactrex™ 12% Moisturizing Cream	Moisturizer	SDR Pharmaceuticals, Inc
Dermalogica Oil Control Lotion	Skin protectant	John and Ginger Dermalogica Skin Care Products
Ultra Guard	Protects baby's skin	Scott Paper Company

Patents Filed Related to Microsponges[53]

Table 4: Patents Filed Related to Microsponges

Patent no	Inventors	Publication Date
US4690825	Won, Richard	1987
US4863856	Dean RC Jr *et al.*	1989
US5292512	Schaefer *et al*	1989
US5135740	Katz *et al.*	1992
US5679374	Fanchon; Chantal *et al*	1994
US5316774	Eury, Robert P *et al.*	1994
US5725869	Lo; Ray J. R.	1996
US6395300	Straub *et al*.	1999
US6211250	Tomlinson *et al*	2001
US20030232091	Shefer *et al.*	2002

US20040247632	Cattaneo, Maurizio	2004
US20050271702	Wright, Steven G *et al.*	2005

Recent advances in microsponge drug delivery system

Various advances were made by modifying the methods to form nanosponges, nanoferrosponges and porous microbeads.

β-CD nanosponges were also developed that can be used for hydrophobic as well as hydrophilic drugs, in contrast to polymeric micro or nanosponges. These advanced systems were studied for oral administration of dexamethasone, flurbiprofen, doxorubicin hydrochloride, itraconazole and serum albumin as model drug. These nanosponges were developed by cross-linking the β-CD molecule by re-acting the β-CD with diphenyl carbonate.

Some researchers also observed the nanosponges as good carrier for the delivery of gases. Researchers also observed that incorporating a cytotoxic in a nanosponge carrier system can increase the potency of the drug suggesting that these carriers can be potentially used for targeting the cancerous cells.[54]

Nanoferrosponge, a novel approach constituted the self-performing carriers having better penetration to the targeted site due to the external magnetic trigger which enforces the carriers to penetrate to the deeper tissue and then causing the removal of magnetic material from the particle leaving a porous system.[55]

Due to the improved characteristics of porous microspheres, process was developed to produce the porous micro beads. This method (High internal phase emulsion, HIPE) consisted of the monomer containing continuous oil phase, cross linking agent and aqueous internal phase.[56] They also observed an improved stability of RNA and the relatively effective encapsulation process of siRNA. The approach could lead to novel therapeutic routes for siRNA delivery.[57]

Future prospects

Microsponge drug delivery system holds a promising opportunity in various pharmaceutical applications in the upcoming future as 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. As these porous systems have also been studied for the drug delivery through pulmonary route which shows that these system can show effective drug release even in the scarce of the dissolution fluid thus colon is an effective site for targeting for drug release. 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. Due to their elegance, these carrier systems have also found their application in cosmetics. These developments enabled researchers to utilize them variably. These novelties in formulation also open new ways for drug deliver.[43]

Conclusion

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.

Acknowledgement

Authors are grateful To Mr. Abhishek Anil Bhondave for his technical support and advice.

References

1. Shaha V., Jain H., Jethva K., Patel P. Microsponge drug delivery: A Review. Int. J. Res. Pharm. Sci. 2010; Vol-1, Issue-2: 212-218.

2. Kydonieus A.F., Berner B. Transdermal Delivery of Drugs. CRC Press, Raton: 1987.

3. Madgassi S., Touitou E. Novel cosmetic delivery systems. In: Cosmetic science and technology series. Vol. 19.Marcel Dekker Inc.: USA, 1999.

4. Benita S. Microencapsulation: Methods and Industrial applications. In:Drugs and Pharmaceutical Sciences Series, Vol. 73. Marcel Dekker:N.Y., 1996.

5. Osborne O.W., Amann A.H. Topical Drug Delivery Formulation, 308-309. Marcel Dekker Inc.: New York and Basel, 1990.

6. Miller G. Cosmetics, nanotoxicity and skin penetration – a brief summary of the toxicological and skin penetration literature. Friends of the Earth. 2006; 1-8.

7. Kaity S., Maiti S.,Ghosh A.,Pal D.,Banerjee A. Microsponges: A novel strategy for drug delivery system. J Adv Pharm Technol Res. 2010; 1(3): 283-90.

8. Embil K.,Nacht S. The Microsponge Delivery System (MDS): A topical delivery system with reduced irritancy incorporating multiple triggering mechanisms for the release of actives. J. Microencapsul.1996; 3(5), 575-588

9. Nacht S, Kantz M. The microsponge: A novel topical programmable delivery system. Top Drug Deliv Syst. 1992; 42:299-325.

10. Won R: Method for delivering an active ingredient by controlled time release utilizing a novel delivery vehicle which can be prepared by a process utilizing the active ingredients as a Porogen. 1987; US Patent No. 4690825.

11. Chadawar V., Shaji J. Microsponge Delivery System. Current Drug Delivery. 2007 ; 4: 123-129.

12. Aritomi H., Yamasaki Y., Yamada K., Honda H, Koshi M. Development of sustained release formulation of chlorpheniramine maleate using powder coated microsponges prepared by dry impact blending method. Journal of Pharmaceutical Sciences and Technology. 1996; 56(1): 49-56.

13. D'souza J.I., Masvekar R.R., Pattekari P.P., Pudi S.R., More H.N. Microspongic delivery of fluconazole for topical application. Indo-Japanese Int. Conference on Adv. Pharm. Res. and Tech. 2004;76.

14. Parthiban K.G., Manivannan R., Krishnarajan D., Chandra S., Nidhin R. Microsponge role in novel drug delivery system. Intl. J. Pharm. Res. Devel., 2011; 3(4): 117-125.

15. Jelvehgari M, Siahi-Shadbad MR, Azarmi S, Gary P, Martin, Nokhodchi A: The microsponge delivery system of benzoyl peroxide: Preparation, characterization and release studies. International Journal of Pharmaceutics .2006; 308:124-132.

16. Kawashima Y, Niwa T, Takeuchi H, Hino T, Ito Y. Control of Prolonged Drug Release and Compression Properties of Ibuprofen Microsponges with Acrylic Polymer, Eudragit RS, by Changing Their Intraparticle Porosity. Chemical and pharmaceutical bulletin. 1992; 40(1):196-201.

17. Vyas L.K., Tapar K.K., Laddha B.H., Lahoti A.O. , Nema R.K.Formulation and development of anti-blemish preparation using microsponge technology. J. Chem. Pharm. Res. 2010; 2(5):562-571.

18. Ruckenstein E, Hong L. Concentrated emulsion polymerization pathway to hydrophobic and hydrophilic microsponge molecular reservoirs. Chem. Mater. 1992; 4:1032-1037

19. Zaki Rizkalla C.M., Latif Aziz R,Soliman I.I. In vitro and in vivo evaluation of hydroxyzine hydrochloride microsponges for topical delivery. AAPS PharmSciTech .2011; 12(3):989-1001

20. Patrick B., Deasy ed. Microencapsulation and related drug processes.In: Drugs and Pharmaceutical sciences series. Vol. No. 20. Marcel Dekker Inc.: N.Y. 1984; 195.

21. Friedrich H. Ion Exchange. McGraw Hill book, Inc.: USA, 1962; 60-61.

22. Grochowicz M, Bartnicki A, Gawdzik B. Preparation and characterization of porous polymeric microspheres obtained from multifunctional methacrylate monomers. J Polymer Sci.2008; 46: 6165-74

23. Comoglu T, Gonul N, Baykara T. Preparation and in vitro evaluation of modified release ketoprofen microsponges. ll Farmaco. 2003; 58: 101-6

24. D'souza J.I., More H.N. Topicalanti-inflammatory gels of flucinolone acetonide entrapped in eudragit basedmicrosponge delivery system. Res JPharm Technol. 2008; 1(4): 502-6

25. Christensen M.S., Hargens C.W., Nacht S., Gans, E.H.Viscoelastic properties of intact human skin instrumentations, hydration effects and contribution of the stratum corneum. J Invest Dermatol. 1977; 69: 282–286.

26. Sato T., Kanke M., Schroeder G., Deluca P. Porous biodegradable microspheres for controlled drug delivery. Assessment of processing conditions and solvent removal techniques. Pharm Res. 1988; 5:21- 30.

27. Guyot M. and Fawaz F, "Microspheres- Preparation and physical characteristics". Int. J. Pharmaceutics 1998; 175:61-74.

28. Martin A., Swarbrick J., Cammarrata A. In:Physical Pharmacy- Physical Chemical Principles in Pharmaceutical Sciences. 3rd Ed.1991; 527.

29. Emanuele A.D., Dinarvand R. Preparation, characterization and drug release from thermo responsive microspheres. Int.Journal of Pharmaceutics. 1995; 237-242.

30. Kilicarslan M, Baykara T. The effect of the drug/polymer ratio on the properties of Verapamil HCl loaded microspheres. Int. J. Pharm. 2003; 252:99–109.

31. Washburn E.W.Note on a method of determining the distribution of pore sizes in a porous material. Proc Natl Acad Sci .1921; 7(4):115-116.

32. Orr Jr.Application of mercury penetration to material analysis. Powder.Technol. (1969);3:117–123

33. Jones D.S., Pearce K.J. Investigation of the effects of some process variables on microencapsulation of propranolol HCl by solvent evaporation method. Int J. Pharm .1995; 118:99-205.

34. Kawashima Y, Niwa T, Takeuchi H, Hino T, Itoh Y, Furuyama S. Characterization of polymorphs of tranilast anhydrate and tranilast monohydrate when crystallized by two solvent change spherical crystallization techniques. J. Pharm. Sci. 1991; 81:472-478.

35. Anderson D.L., Cheng C.H., Nacht S .Flow characteristics of loosely compacted macroporous microsponge polymeric systems. Powder technology. 1994; 78:15-18.

36. Ford J.L., Timmins P. Pharmaceutical Thermal Analysis- Techniques and Applications. Ellis Horwood Ltd.: Chichester .1989.

37. Chowdary KPR, Rao Y.S. Mucoadhesive Microspheres for Controlled Drug Delivery. Biol. Pharm. Bull .2004; 27(11):1717- 1724.

38. Barkai A, Pathak V, Benita S.Polyacrylate (Eudragit retard) microspheres for oral controlled release of nifedipine. I.Formulation design and process optimization. Drug Dev. Ind. Pharm. 1990; 16:2057-2075.

39. Jayaweera D.M. Medicinal Plants (Indigenous and exotic) used in Ceylon. Part-II. A Publication of the Natural Sciences Council of Sri Lanka:Colombo .1980.

40. Peppas N.A., Analysis of Fickian and non-Fickian drug release from polymers. Pharm. Acta Helv. 1985; 60: 110–111.

41. Draize J.H., Woodard G., Calvery H.O. Methods for the study of irritation and toxicity of substance es applied topically to the Skin and Mucous Membranes. J Pharmacol Exp Ther .1944; 82:377-389.

42. Shyam S. M., Vedavathi T. Novel approach: microsponge drug delivery system. Int. J. Pharm. Sci.Res.2012; 3(4): 967-980.

43. Srivastava R, Pathak K. Microsponges: a futuristic approach for oral drug delivery. Expert Opin. Drug Deliv., 2012; 9(7): 863-878.

44. Patravale V.B. , Mandawgade S.D. Novel cosmetic delivery systems: an application update. Int.J.Cosmetic Sci.2008; 30:19-33.

45. Leyden J.J., Tanghetti E.A., Miller B., Ung M.,.Berson D., Lee J. Once-daily tazarotene 0.1% gel versus once-daily tretinoin 0.1%microsponge gel for the treatment of facial acne vulgaris: a double-blind randomized trial. Cutis. 2002;69:12-19

46. Wester R., Patel R., Natch S., Leyden J., Melendres J., Maibach H. Controlled release of benzoyl peroxide from a porousmicrosphere polymeric system can reduce topical irritancy. J. Am. Acad.Derm.1991; 24:720-726.

47. D'souza J.I. In vitro antibacterial and skin irritation studies of microsponges of benzoyl peroxide. Indian Drugs.2001;38(7): 361-362.

48. D'souza J.I.,Masvekar R.R., Pattekari, P.P., Pudi S.R., More H.N. Pharmaceutical Research and Technology. Microspongic delivery of fluconazole for topical application. In: Proceedings of the 1st Indo-Japanese International Conference on Advances in Pharmaceutical Research and Technology. Mumbai, India. November; 2005; 25-9.

49. Shigemitsu I. , Yoshiki S.,Hajime I., Satoshi T., Eiichiro U., Guoping C., Masayuki H., Jun M, Hikaru M.Biodegradable polymer with collagen microsponge serves as a new bioengineered cardiovascular prosthesis.Journal of Thoracic and Cardiovascular Surgery.2004;128(3):472-479.

50. Guoping C., Takashi S., Hajime O., Takashi U., Tetsuya T., Junzo T. Culturing of skin fibroblasts in a thin PLGA–collagen hybrid mesh.Biomaterials.2005; 26:2559–2566.

51. Beruto D.T., Botter R., Fini M. The effect of water in inorganic microsponges of calcium phosphates on the porosity and permeability of composites made with polymethylmethacrylate. Biomaterials. 2002; 23(12): 2509.

52. Sarat C. P. M., Ajay M., Nagendra B.B., Prathyusha P., Audinarayana N., Bhaskar R.K. Microsponge Drug Delivery System . A Review. J. Pharm. Res.2011; 4(5): 1381-1384.

53. Gangadharappa H.V., Gupta V., Sarat C.P.M., Shivakumar H.G. Current Trends in Microsponge Drug Delivery System. Current Drug Delivery. 2013;10: 453-465.

54. Trotta F, Cavalli R, Tumiatti W. Cyclodextrin-based nanosponges for drugdelivery. J Incl PhenomMacrocyclic Chem. 2006;56:209-13.

55. Hu S.H., Liu T.Y., Liu D.M.,Nano-ferrosponges for controlled drugrelease. J Control Release. 2007; 121(3):181-9.

56. Ll NH., Benson JR.,Kitagawa N .Polymeric microbeads and method of preparation. International publication number. WO1995033553; 2003.

57. Lee JB, Hong J, Bonner DK,.Self-assembled RNA interference microsponges for efficient siRNA delivery. Nat Mater. 2012; 11(4): 316-22.