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Review Article

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Microsponges: A Novel Strategy for Drug Delivery

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ABSTRACT

Microsponge technology has been introduced in topical drug products to facilitate the controlled release of active drug into the skin in order to reduce systemic exposure and minimize local cutaneous reactions to active drugs. Microsponge consists of macroporous beads, typically 10-25 micron in diameter, loaded with active agent. When applied to the skin, the microsponge releases its active ingredients on a time mode and also in response to other stimuli. 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. 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*: Microsponge, controlled release, Topical drug delivery,solvent diffusion method, Quasi-emulsion.*

INTRODUCTION

Now a day the major challenge to the pharmaceutical industry is to control the delivery rate of active pharmaceutical ingredient to a pre-determined site in human body. So researcher focused on designing different controlled release drug delivery systems to improve efficacy and patient compliance[1].

Topical formulations are most useful drug delivery systems for both local and systemic treatment. 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[2].

The aplication of topical drugs has manyproblems, such as, ointments that are often aesthetically unappealing, greasiness, stickiness, and so on, that often results in lack of patient compliance. These vehicles require a high concentrations of active agents for effective therapy because of their low efficiency of delivery system, resulting in irritation and allergic reactions in significant users. Other drawbacks of topical formulations are uncontrolled evaporation of the active ingredient, unpleasant odor, and the potential incompatibility of the drugs with the vehicles. 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.

Thus the need exists for a system to maximize the amount 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[3].

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. 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(4) 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. Further, these porous microspheres with active ingredients can be incorporated in to formulations such as creams, lotions and powders. Release of drug into the skin is initiated by a variety of triggers, including rubbing and higher than ambient skin temperature[5].

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 particles 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. The microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Potentially, the microsponge system can significantly reduce the irritation of effective drugs withoutn reducing their efficacy. The empty spheres are then washed away with the next cleansing. The microsponge deliverysystem fulfills these requirements and has resulted in a new generation of very well-tolerated and highly efficacious, novel products. 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[6].

Microsponge Delivery System MDS is a unique technology for controlled delivery of drug. MDS technology has been introduced in topical drug products to facilitate the controlled release of active drug into the skin in order to reduce the systemic exposure and minimize local cutaneous reactions to active drugs. A Microsponge delivery system is patented, highly cross-linked, porous, polymeric microspheres polymeric system consisting of porous microspheres that can entrap wide range of actives and then release them onto the skin over a time and in response to trigger[7].

It is a unique technology for the controlled release of topical agents and consists of microporous beads, typically 10-25 microns in diameter, loaded with active agent. When applied to the skin, the MDS releases its active ingredient on a time mode and also in response to other stimuli (rubbing, temperature, pH, etc). MDS technology is being used in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products. Delivery system comprised 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[8].

Characterstics of Microsponges[9]

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

Characteristics of actives that is entrapped into microsponges[10]

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

1. It should be either fully miscible in monomer as well as capable of being made miscible by addition of small amount of a water immiscible solvent.
2. It should be inert to monomers and should not increase the viscosity of the mixture during formulation.
3. It should be water immiscible or nearly only slightly soluble.
4. It should not collapse spherical structure of themicrosponges.
5. It should be stable in contact with polymerization catalyst and also in conditions of polymerization.
6. The solubility of actives in the vehicle must be limited. If not, the vehicle will deplete the microsponges before the application.
7. Not more than 10 to 12% w/w microsponges must be incorporated into the vehicle in order to avoid cosmetic problems.
8. Payload and polymer design of the microsponges for the active must be optimized for required release rate for given period of time.

Drug Explored In Microsponges[10-16]

- Ketoprofen
- Benzyl Peroxide
- Retinol
- Fluconazol
- Ibuprofen
- Tretinoin
- Trolamine
- Tioconazcole
- Prednisolone
- Acyclovir sodium

Advantages[17]

1) Advance oil control,absorb up to 6times its weight without drying
2) Improved product elegancy
3) MDS allows the incorporation of immiscible products
4) Improved product asthetics
5) Improves stability,thermal,physical and chemical stability
6) Improves material processing e.g. liquid can be converted to powder
7) Extended release,continuous action up to 12 hours
8) Reduced irritation, better tolerance means broader consumer acceptance

Advantages over conventional formulation[18,19]

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 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. 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[18,20]

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 1300C; compatible with most vehicles and ingredients; self sterilizing as 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[20,21]

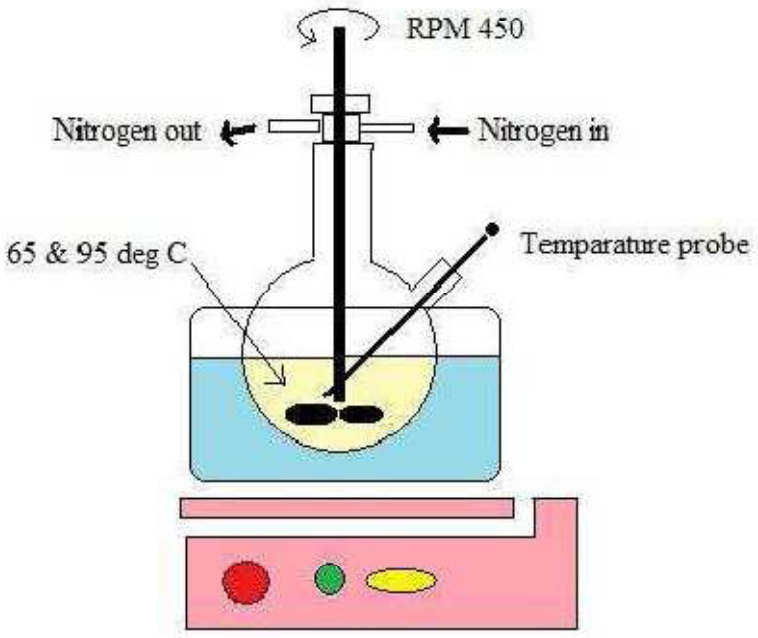
Ointments are often aesthetically unappealing, greasiness; stickiness etc. That often results into lack of patient compliance. These vehicles require high concentrations of active agents for effective therapy because of their low efficiency of delivery system, resulting into irritation and allergic reactions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

MEHODS OF PREPARATION OF MICROSPONGES

1) Liquid-Liquid suspension polymerization-

In this method of polymerization the monomer is dissolved along with the active ingriendts in suitable solvent and then added in aqueous phase containing additives i.e. surfactant, suspending agents etc. The polymerization is then initiated by adding catalyst or by increasing temperature or irritation. Polymerization of styrene or methyl methacrylate is carried out in round bottom flask. A solution of non-polar drug is made in the monomer, to which aqueous phase, usually containing surfactant and dispersant to promote suspension is added. Polymerization is effected, once suspension with the discrete doplets of the desired size is established, b activating the monomers either by catalysis or increased temperature.(Reaction vessel shown in fig.) When the drug is sensitive to the polymerization conditions, two step process is used[22]. The polymerization is performed using substitute porogen and is replaced by the functional substance under mild experimental conditions.

Fig. 1: Reaction vessel for Micropsaonge



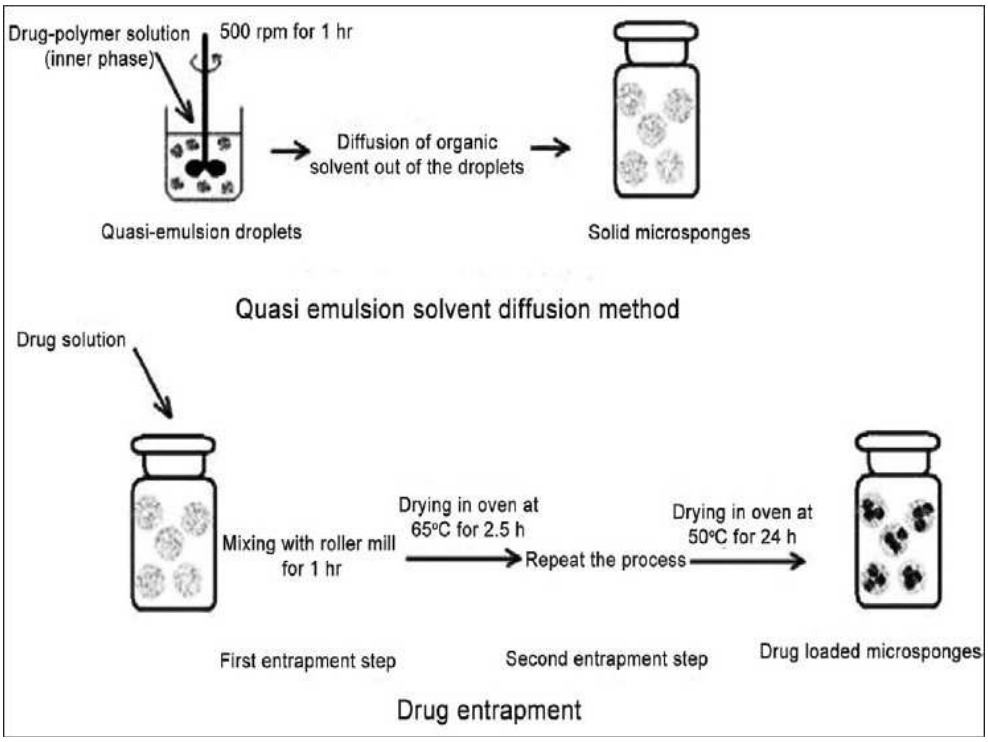
The various steps in the preparation of microsponges are summarized as follows[23,24]

- Selection of monomer or combination of the monomer
- Formation of chain monomer as polymerization begins
- Formation of monomer ladder as result of cross linkage between chain monomer
- Folding of monomer ladder to form spherical particles
- Agglomeration of microsphere lead to formation of bunches of microsphere Binding of bunches lead to formation of microsponge.

2) Quasi-emulsion solvent diffusion-

To prepare the inner organic phase, Eudragit RS 100 is dissolved in ethyl alcohol. Next, the drug is added to the solution and dissolved under ultrasonication at 35°C. The inner phase is poured into the polyvinyl alcohol solution in water (outer phase). Following 60 minutes of stirring, the mixture is filtered, to separate the microsponges. The microsponges are dried in an air-heated oven at 40ºC for 12 hours (25)

Fig. 2: Quasi-emulsion solvent diffusion methods



Drug Release Mechanism:

Microsponges can be intended to release given amount of active ingriendts over time in response to one or more following external triggers i,e. pressure,temperature change and solubility etc which are described as follows

1. Temperature change:At room temperature, few entrapped active ingredients can be too viscous to flow suddenly from microsponges onto the skin. With increase in skin temperature, flow rate is also increased and therefore release is also enhanced14.
2. Pressure**:** Rubbing or pressure applied can release the active ingredient from microsponges onto skin14.
3. Solubility**:** Microsponges loaded with water miscible ingredients like antiseptics and anti-perspirants 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

Safety consideration

Safety studies of microsponges can be established by:

- Eye irritation studies in rabbits.
- Skin irritation studies in rabbits.
- Mutagenicity in bacteria.
- Oral toxicity studies in rats.
- Allergenicity in guinea pigs[27,28]

Characterization of microsponges:

1. **Particle size analysis:** Particle size determination of loaded as well as blank microsponges can be carried out by laser light diffractometry or any other appropriate method. Values can be expressed for all the formulations in terms of mean size range. It can be studied by plotting cumulative % drug release from microsponges of different particle size against time to study effect of particle size on drug release. Particles having sizes bigger than 30 μm can impart grittiness and thus particles having sizes between 10 and 25 μm are favored to be use in final topical formulation[29].
2. **Determination of entrapment efficiency and production yield**[30]: The entrapment efficiency (%) of the microsponges can be calculated according to the following equation:

Entrapment efficiency (%) = [Actual drug content/Theoretical drug content] X 100

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

Production yield = [Practical mass of microsponges/Theoretical mass (polymer + drug)] X 100

3. **Morphology and surface topography of microsponges:** The internal and external morphology and surface topography can be studied by scanning electron microscopy (SEM). Prepared microsponges can be coated with gold–palladium under an argon atmosphere at room temperature and then SEM images of microsponges were recorded at the required magnification. SEM of afractured microsponge particle can also be taken toillustrate its ultra structure[31].
4. **Characterization of pore structure:** Pore volume and pore ndiameter are critical in controlling the intensity as well as duration of effectiveness of the active ingredient. Pore diameter can also affects the passage of active ingredients from microsponges into the vehicle in which the material is dispersed. The effect of pore diameter as well as volume with rate of drug release from microsponges can be studied by mercury intrusion porosimetry. Porosity parameters of microsponges such as intrusion–extrusion isotherms, total pore surface area, pore size distribution, average pore diameters, shape and morphology of the pores, bulk and apparent density can also be determined by using mercury intrusion Porosimetry[31].
5. **Determination of true density:** The true density of microsponges was measured by an ultra-pycnometer under helium gas and was calculated from a mean of repeated determinations[32].
6. **Polymer/ Monomer composition:** Various factors such as microsphere size, polymer composition and drug loading govern the drug release from microspheres. Polymer composition can also influence the partition coefficient of the entrapped drug between the microsponge system and the vehicle and thus have direct affect on the rate of release of entrapped drug. Drug release from microsponge systems of different polymer compositions can be studied by plotting cumulative % drug release against time. The choice of monomer is dictated both by the vehicle into which it will be dispersed and characteristics of active ingredient to be entrapped. Polymers with varying degrees of hydrophobicity or lipophilicity or electrical charges may be prepared to give flexibility in the release of active ingredients. A variety of probable monomer combinations will be screened for their appropriateness with drugs by studying their drug release profile[32].
7. **Compatibility studies:** Fourier Transform Infra-red spectroscopy (FT-IR) and thin layer chromatography (TLC) was performed to study the compatibility of drug with reaction adjuncts.

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 weighed accurately into aluminum pans, then sealed and can be run at a heating rate of 15°C/min over a temperature range 25–430°C in atmosphere of nitrogen[33].

8. **Resiliency (viscoelastic properties) :**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[34,35].
9. ***In-vitro* release studies**: *In-vitro* release studies have been carried out using dissolution apparatus USP XXIII equipped with a modified basket consisted of 5µm stainless steel mesh. Dissolution rates were measured at 37°C under 150 rpm rotor speed. The dissolution medium is selected while considering solubility of active ingredients to ensure sink conditions. Sample aliquots were withdrawn from the dissolution medium and analyzed by suitable analytical method (UV spectrophotometer) at regular intervals of time[36].
10. **Stability studies:** In pharmaceutical sense, stability is technically defined as the capacity of particular formulation in a specific container or closure system, to remain within its physical, chemical, microbiological, therapeutic and toxicological specification. Durability of a product may be defined as the capability of a particular formulation in a specific container to remain with the physical, chemical, microbiological, therapeutic and toxicological specification. Stability of Microsponge gel formulation on storage is of a great concern as it is the major resistance in the development of marketed preparations. The prepared formulation was tested for stability on storing them at 4 ± 1ºC, 25 ± 2ºC and 37 ± 5ºC & RH (Relative Humidity) 75 %. After one month and the three months they were evaluated for the following parameters-Appearance, pH, Drug content analysis, Drug release profiles, Rheological properties etc[37,38].

Applications

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[39,40,41]

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 Paracetamol Chlorpheniramine maleate Ketoprofen Fenofibrate Meloxicam	Inflammation Anti-pyretic Hay Feve Musculoskeletal pain Gout Arthritis
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

List of Marketed Products based on Microsponges[42,43,44]

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.
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[45]

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	2005
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[46].

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[47].

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[48].

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[49].

CONCLUSION

Microsponge drug delivery has become highly competitive and rapidly evolving technology and more and more research are carrying out to optimize cost effectiveness and efficacy of therapy. With demand for innovative and highly efficient Pharmaceutical as well as Cosmetic products, the market holds considerable potential for Microsponge technology and the versatility they offer. As formulators consider new and creative ways to deliver actives, they can realize the full capabilities of these unique materials providing enhanced safety, improved stability, reduced side effects from actives, enhanced multifuntionality and improved ingredient compatibility. Complemented by novel development approaches and creative formulation techniques, Microsponge delivery system can be a winning strategy for a new generation of Pharmaceutical and Cosmetic industry. Microsponges have a distinct advantage over the existing conventional topical dosage forms for the treatment of tropical diseases; it is a unique technology for the controlled release of topical agents also use for oral as well as biopharmaceutical drug delivery. This shows advantageous over other products by non mutagenic, non toxic, non irritant. So microsponge drug delivery system has got a lot of potential and is a very emerging field which is needed to be explored in the future with most research study.

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