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MICROSPONGES – A COMPREHENSIVE REVIEW: SUCCESS AND CHALLENGES

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ABSTRACT

Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge-like spherical particles with a large porous surface. Moreover, they may enhance stability, reduce side effects and modify drug release favorably. Microsponge is current novel technique for control release and target specific drug delivery system. Microsponge technology has been introduced in topical drug products to facilitate the controlled active drug release into the skin in order to decrease the systemic exposure and minimize local cutaneous reactions to active drugs. This review focus on a microsponge's delivery system discussing the preparation methods, evaluation methods, mechanism of drug release and Physical characterization of microsponges. Microsponge delivery system technology is being used at present in skin care, sunscreens, cosmetics, over-the-counter (OTC) and prescription products. One of the most excellent features of the microsponge is it is self-sterilizing.

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INTRODUCTION

The microsponge technology was developed in 1987 by Won and the original patents were assigned to advance polymer systems, Inc[1]. This company developed a large number of variations of the technique. It is a patented, porous, highly cross linked, polymeric microspheres polymeric system (10-25 µm) consists porous microspheres particles consisting of a many of inter connecting space within non collapsible structures with a large porous surface that can entrap large range of actives (sunscreens, cosmetics, over the counter (OTC) skin care and prescription products) and then release them on to the skin over a time and in response to trigger[2]. At present, this microsponge technology has been licensed to cardinal health, Inc., for use in the topical products. 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.

Some of reliable and predictable systems were developed for systemic drugs under the heading of transdermal delivery system (TDS) using the skin as portal of entry[3]. It has improved the safety and efficacy of many drugs that may be superior administered through the skin. But transdermal drug delivery system is not practical for materials delivery whose final target is skin itself. Further these porous microspheres with active ingredients can be incorporated into formulations such as lotions, creams and powders. Drug release into the skin is initiated by a variety of triggers, including rubbing and higher than ambient skin temperature[4].

Microsponges are polymeric delivery systems consisting of porous microspheres that can entrap a wide range of active ingredients such as fragrances, essential oils, sunscreens, emollients and anti fungal, anti inflammatory and anti fungal agents[5].

The microsponge delivery system has advantages over other technologies like liposomes and microencapsulation. Microcapsules cannot generally control the release rate of actives. Once the wall is ruptured the actives contained within microcapsules will be released. Liposomes suffer from difficult formulation, lower pay load, limited microbial instability and chemical stability[6].

Figure 1: Structure of Microsponge.

HYPOTHETICAL MECHANISM OF MICRO SPONGE[7, 8]

The active ingredient is added to the vehicle in an entrapped form. As the microsponge particle has an open structure (i.e., they do not have a continuous membrane surrounding them), the active ingredient moves freely 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 on the skin, the active is already in the vehicle will be absorbed into the skin, depleting the vehicle, which will become unsaturated, therefore, disturbing the equilibrium. This will begins a flow of the microsponge particle into the vehicle, and then it to the skin, until the vehicle is either absorbed or dried.

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 continue to have on the stratum corneum surface and continue to gradually release the active to the skin and providing prolonged release over time.

This proposed mechanism of action highlights the significance of formulating vehicles for use with microsponge entrapments. During the compounding of finished productsif the active is very soluble in the preferred vehicle, the products will not offers the preferred 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 significant to design a vehicle that has least solubilizing power for the actives. This principle is opposite to the conventional formulation principles generally applied to the topical products. For these conventional systems it is usually recommended to maximize the solubility of the active in the vehicle. When using microsponge entrapments, a few of the active in the vehicle is acceptable, because the vehicle can give the initial loading dose of the active until release from the microsponge is activated by the shift in equilibrium into the carrier from the polymer. Another method to avoid undesirable premature leaching of active from the microsponge polymer is to formulate the product with some entrapped active and some free, so the vehicle is pre saturated. In this case there will not be any leaching of the active from the polymer during compounding process. The rate of active release will finally not only depends on the partition coefficient of the active ingredient between the vehicle (or the skin) and the polymer, but also on a few of the parameters that characterize the bead. Example for these includes surface area and primarily, means diameter of pore. Release can also be controlled through diffusion or any other triggers such as pH, temperature, friction or moisture.

Characteristics of microsponges:[9-13]

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

Advantages of Microsponges[14, 15]**:**

✓Microsponge delivery system allows the incorporation of immiscible products
✓It shows extended drug release, continuous action up to 12 hours
✓It reduced formulas of irritation
✓Advanced oil control, without drying it absorb up to six times its weight
✓Improved product elegancy
✓It allows novel product form
✓These microsponges are non toxic, non mutagenic, non irritating, non allergenic
✓Microsponges improves bio availability of the same drugs
✓It improves control of condition
✓It improves efficacy in treatment
✓It improves processing of materials Eg: liquid can be converted to powders
✓Improved product aesthetics, it gives product an elegant feel
✓Reduced irritation, improved tolerance means highly consumer acceptance
✓It improves stability, like physical, chemical and thermal stability.

Characteristics of materials that is entrapped in microsponges[16]**:**

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

- It should be immiscible in water or at most only soluble slightly in water
- It should be either completely miscible in monomer or capable of being made miscible by addition of less amount of a water immiscible solvent
- It should be inert to monomers
- It should be stable in contact with polymerization catalyst and conditions of polymerization.
- 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 the vehicle. Otherwise the vehicle will deplete the microsponges before the application.
- The spherical structure of microsponges should not collapse.
- Polymer design and payload of the microsponges for the active must be optimized for required release rate for given time period.

Drugs explored in Microsponge delivery system[17-21]**:**

- Benzyl peroxide
- Fluconazole
- Ibuprofen
- Kotoprofen
- Retinol
- Tretinoin
- Trolamine

Formulation Aids

Various polymers can form a microspongecage. These include Eudragit RS100, Ethyl Cellulose, PHEMA and Polystyrene. In addition to actives; some microsponges contain plasticizers that help stabilize their structure.

Advantages over conventional formulation[12, 13]

Topical drug conventional formulations are planned to apply on the outer most layer of the skin, and that products release their active ingredients upon application, producing a highly concentrated layer of active ingredient that is quickly absorbed. When compared to the microsponge delivery system can prevent extreme accumulation of ingredients within the epidermis and the dermis. Potentially, the microsponge delivery system can decrease extensively the effective drug irritation without decreasing their efficacy. For example, Microsponge delivery system Benzoyl peroxide formulations have good efficacy with minimum irritation by delivering the active ingredient slowly to the skin.

Advantages over Ointments[15, 22]

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

Advantages over microencapsulation and liposomes[10, 15]

The Microsponge delivery system has benefits more than other technologies like liposomes and microencapsulation. Microcapsules regularly cannot control the actives release rate. Once the wall is burst the microcapsules which contains actives will be released. The liposomes suffer from difficult formulation, lower payload, limited microbial instability and chemical stability. While microsponge system in contrast to the above systems are stable over range of temperature up to 130˚C, pH 1-11 compatible with most ingredients and vehicles, higher payload (50-60%), self sterilizing as average pore size is 0.25 µm where bacteria cannot penetrate, still free flowing and can be cost effective.

MECHANISM OF DRUG RELEASE[24, 25]

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

pH triggered systems

Triggering the pH based release of the active can be achieved by modifying the coating on the microsponge. This has a lot of applications in drug delivery.

Temperature change[23]

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

Pressure

Microsponge system releases the entrapped material pressure/rubbing applied can release active ingredient from microsponges onto skin. The amount released depends upon different characteristics of the sponge. By varying the type of material and different process variables, the microsponge best suited for a given application may be optimized. When compared with mineral oil containing microcapsules, mineral oil containing microsponge showed much more softening effect. The emollient property duration was also much more for the microsponge systems.

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

Preparation of Microsponges:

Loading of drug in microsponges can get place in 2 ways, one step process or by two step processes as discussed in liquid-liquid suspension polymerization and Quasi emulsion solvent diffusion methods which are based on physicochemical properties of drug to be loaded.

Liquid-liquid suspension polymerization:

By suspension polymerization technique in liquid-liquid systems the porous microspheres are prepared. In preparation of porous microspheres, first dissolved the monomers along with active ingredients in a suitable solvent solution of monomer and are then dispersed in the aqueous phase, which consists of additives (suspending agents, surfactant, etc.). The polymerization is then initiated by adding catalyst or by increasing irradiation or temperature[26-28].

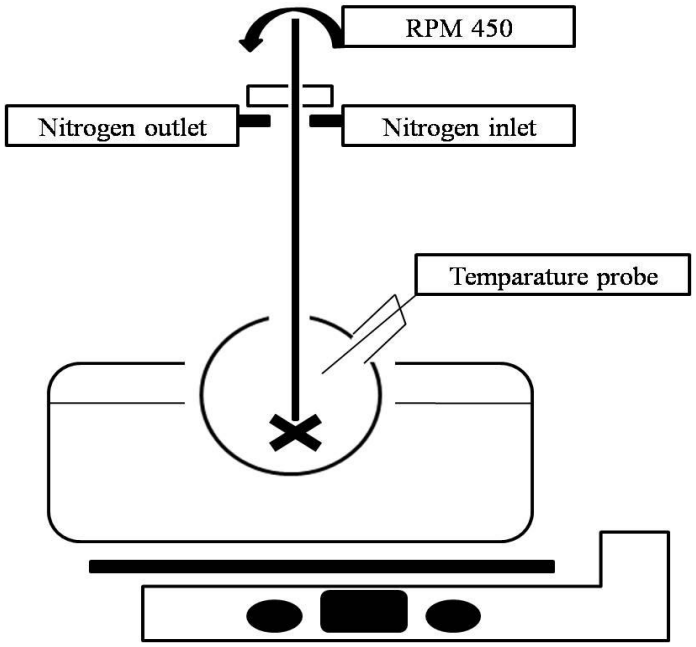

Figure 2: Reaction vessel for Microsponge.

The different steps in the preparation of microsponges are summarized as:

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

Quasi-emulsion solvent diffusion

Microsponges can be prepared by quasi emulsion solvent diffusion method by using the different polymer amounts. For preparation of internal phase, the polymer was dissolved in suitable solvent. Then the drug can be added to the solution and dissolved under ultrasonication at 35^{0}C. The internal phase was poured into the ploly vinyl alcohol (PVA) in water (External phase). The microsponges were dried in an air heated oven at 40^{0}C for 12 hr and weighed the microsponges to determine product yield[29,30].

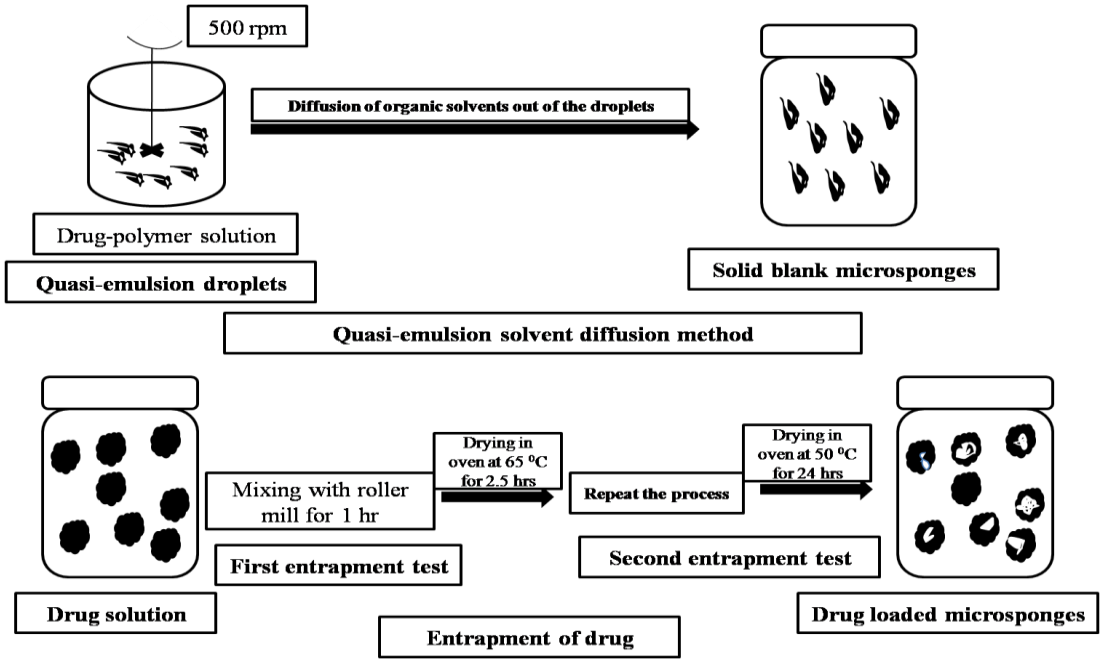

Figure 3: Preparation of Microsponges by Quasi-Emulsion solvent diffusion method.

Physical characterization of Microsponges:

Particle size determination:

Analysis of unloaded and loaded microsponge particle size can be performed by laser light diffractometry or any other suitable techniques. The values can be expressed for all formulations as mean size range. To study the effect of particle size on drug release, the drug release cumulative percentage from microsponges of different particle size will be plotted against to time. Particles which are bigger than 30 µm can impart gritty feeling and hence sizes of particles between 10 and 25µm are preferred to use in final topical formulation[31].

Morphology and surface topography of microsponges:

The microsponges surface morphology can be studied by scanning electron microscopy (SEM) and for the surface topography and morphology, the prepared microsponges can be coated with gold palladium under an argon atmosphere at room temperature[31].

Determination of true density:

The microparticles true density can measure by using an ultra pycnometer under helium gas and it is calculated from a mean of repeated determinations[32].

Compatibility studies:

Compatibility of drug with reaction adjuncts can be studied by Fourier transform infra red spectroscopy (FT-IR) and thin layer chromatography (TLC). The effect of polymerization on crystallinity of the drug can be studied by Differential scanning colorimetry and Powder X-ray diffraction (XRD)[33, 34]. For DSC approximately 5mg samples can be accurately weighed into aluminium pans and sealed and can be run at a heating rate of 15℃/min over a temperature range 25 -430℃ in atmosphere of nitrogen.

Polymer/monomer composition[35]:

Factors such as drug loading, microsphere size and polymer composition govern the drug release from microspheres. Microsponges polymer composition can affects partition coefficient of the entrapped drug between the microsponge and vehicle and hence have direct influence on the entrapped drug release rate. Drug releases from microsponges systems of different polymer compositions can be studied by plotting time against cumulative % drug release.

Resiliency (viscoelastic properties)[36, 37]:

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

Dissolution studies[38]:

By using of dissolution apparatus USP XXIII with a modified basket consisted of 5 µm stainless steel mesh the microsponges dissolution profile can be studied. The rotation speed is 150 rpm. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. From dissolution medium the samples can be analyzed by proper analytical method at different intervals.

Loading efficiency and production yield:

The Microsponges loading efficiency (%) can be calculated by the following equation:

$$\textbf{Loading efficiency} = \frac{\text{Actual drug content in microsponge}}{\text{theoretical drug content}}$$

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

$$\textbf{Production yield (PY)} = \frac{\text{practical mass of microsponges} \times 100}{\text{theoritical mass}}$$

Characterization of pore structure[31,39]:

Pore volume and diameter both are very important 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, interstitial void volume, percent porosity, percent porosity filled, shape and morphology of the pores, bulk and apparent density can be determined by using mercury intrusion porosimetry.

The microsponges pore diametercan 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 the contact angle (130^0)
P is the pressure (psia).
Total pore area (A_{tot}) was calculated by using following equation,

$$A_{tot} = \frac{1}{\gamma\cos\theta}\int_0^{Vtot} p.\,dV$$

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

$$D_m = \frac{4\,Vtot}{Atot}$$

Envelope (bulk) density (ρ_{se}) of the microsponges was calculated by using equation,

$$\rho se = \frac{Ws}{Vp - VHg}$$

Where; Ws is the weight of the microsponge sample (g)
Vp the empty penetrometer (mL)
V_{Hg} is the volume of mercury (mL).
Absolute (skeletal) density (ρsa) of microsponges was calculated by using equation,

$$\rho sa\,\frac{Ws}{Vse - Vtot}$$

Where; V_{se} is the volume of the penetrometer minus the volume of the mercury (mL).
Finally, the percent porosity of the sample was found from equation,

$$\text{Porosity (\%)} = \left(1 - \frac{Pse}{Psa}\right) \times 100$$

***In-vitro* diffusion studies[40]:**

The prepared microsponge gel *in-vitro* diffusion studies were carried out in Keshary – Chein diffusion cell using through a cellophane membrane. 100 ml of phosphate buffer was used as receptor compartment, and then 500 mg of gel it contains 10 mg of drug was spread equally on the membrane. The donor compartment was kept in contact receptor compartment and the temperature maintained at 37±0.5˚C.

By using the externally driven Teflon coated magnetic bar the solution on the receptor side were stirred at predetermined time intervals, from the receptor compartment 5 ml of solution was pipette out and immediately replaced with the 5 ml of phosphate buffer. The concentration of the drug on the receptor fluid was determined spectrophotometrically against to appropriate blank. The experiment was carried out in triplicate.

Stability studies:

In pharmaceutical sense, stability is exactly defined as the capacity of particular formulation in a specific closure or container system, to remain within its chemical, physical, therapeutic, toxicological and microbiological 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±1˚C, 25±2˚C and 37±5˚C & 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.

Applications of microsponges[41]:

Microsponge delivery system is used to improve the effectiveness, safety and aesthetic quality of topical prescription, over the counter and personal care products.

Microsponges can be used in variety of applications. It is used generally for topical and newly for oral administration. Due to its sustained release ability and high loading capacity several patents have reported that it can be used as an excipient. 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 improve stability, decrease side effects and modify drug release. Over the counter products that incorporate microsponge drug delivery system include numerous moisturizers, sunscreens and specialized rejuvenated products.

Applications of microsponges with respect to their advantages:

Table 1: Applications of microsponges with respect to their advantages.

S.No.	Active agents	Application
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 fungal	Sustained release of actives
3	Anti-inflammatory Eg: Hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatomes.
4	Anti-acne Eg: Benzoyl peroxide	Maintained efficacy with decreased skin irritation and sensitization.
5	Antidandruffs Eg: zinc pyrithione, selenium sulfide	Reduced unpleasant odor with lowered irritation with extended safety and Efficacy.
6	Antipruritics	Extended and improved activity.
7	Rubefacients	Prolonged activity with reduced irritancy greasiness and odor.
8	Skin depigmenting agents Eg: Hydroquinone	Improved stabilization against oxidation with improved efficacy and aesthetic Appeal.

List of Marketed Products based on Microsponges[42-44]:

Table 2: List of Marketed Products based on Microsponges.

S No	Product Name	Pharmaceutical Uses	Manufacturer
1	Line Eliminator Dual Retinol Facial Treatment	Anti-wrinkle	Avon
2	Glycolic Acid Moisturizer w/SPF 15	Anti-Wrinkles, soothing	AMCOL Health & Beauty Solution
3	Retinol cream	Helps maintain healthy skin	Biomedic
4	Salicylic Peel 20	Excellent exfoliation	Biophora
5	Oil free matte block SPF 20	Sunscreen	Dermalogica
6	Sports cream RS and XS	Anti inflammatory	EmbilPharmaceutical Co. Ltd.
7	Dermalogica Oil Control Lotion	Skin protectant	John and Ginger Dermalogica Skin Care Products
8	Retin A Micro	Acne vulgaris	Ortho-McNeil Pharmaceutical, Inc.
9	Lactrex™12% Moisturizing Cream	Moisturizer	SDR Pharmaceuticals, Inc
10	Ultra Guard	Protects baby's skin	Scott Paper Company
11	EpiQuin Micro	Hyper pigmentation	SkinMedica Inc
12	Retinol 15 Night cream	Anti-wrinkles	Sothys

Examples of microsponge drug delivery with their formulations[45-47]:

Table 3: Examples of microsponge drug delivery with their formulations.

S. No.	Microsponge Delivery Systems	Drug	Disease
1	Tablets	Chlorpheniramine maleate	Hay Fever
		Fenofibrate	Gout
		Indomethacin	Inflammation
		Ketoprofen	Musculoskeletal pain
		Meloxicam	Arthritis
		Paracetamol	Anti-pyretic
2	Creams	Hydroquinone and Retinol	Melanoma
3	Injection	Basic fibroblast growth facto	Growth factor
4	Gels	Acyclovir	Viral infections
		Benzoyl peroxide	Anti-Acne Treatment
		Diclofenac sodium	Inflammation
		Fluconazole	Inflammation
		Hydroxyzine HCl	Urticaria and atopic dermatitis
		Mupirocin	Antibacterial activity
		Terbinafine HCl	Anti-fungal
5	Lotions	Benzoyl peroxide	Anti-Acne Treatment
6	Grafts	Poly (lactic-co glycolic acid)	Cardiovascular surgery
7	Implants	Poly(DL-lactic-co-glycolic acid)	Skin tissue engineering

Patents Filed Related to Microsponges:

Table 4: Patents Filed Related to Microsponges[48-56]

S No	Patent No	Date of Publication
1	KR20160131487	2016
2	US9072667B2	2015
3	US9737557B2	2015
4	US20140102991 A1	2012
5	US9096755B2	2012
6	US7426776B2	2008
7	CA2644219C	2007
8	US20080069779A1	2007
9	US8956617B2	2006

Recent advances in microsponge drug delivery system:

Various advances were made by modifying the methods to form Nanosponges, nanoferrosponges and porous micro beads. β - CD nanosponges were also developed that can be used forhydrophilic as well as hydrophobic drugs, in contrast to polymeric microsponges or nanosponges.

These advanced systems werestudied for oral administration of Flurbiprofen, dexamethasone, itraconazole, doxorubicin hydrochloride and serum albumins model drug. These nanosponges were developed by cross- linking the β CD molecule by reacting the β CD with biphenylcarbonate.

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[57].

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[58].

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[59].

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[60].

CONCLUSION

Microsponge drug delivery system has become extremely competitive and rapidly developing technology and most research are carrying out to optimize the effectiveness of cost and therapy efficacy. Microsponge delivery system holds a promising future in different pharmaceutical applications in the upcoming years as they have excellent properties like elegancy and superior performance of product. In the topical delivery system the microsponges can be successfully incorporated for dosage form retention on the skin and it is also benefit for oral drug delivery using polymers which are biodegradable. Microsponge releases its actives on a time mode and also in response to other stimuli. The microsponge delivery system has a high potential and is very emerging field which is needed to be explored in the coming years with more research study.

Conflict of Interests

No interest.

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