EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 7
144-152
Year: 2020

MICROSPONGE DRUG DELIVERY SYSTEM: AN INNOVATIVE STRATEGY

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Article Received on 24/04/2020 **Article Revised on 15/05/2020** **Article Accepted on 05/06/2020**

ABSTRACT
The drug delivery technology 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. To control the delivery rate of active agents to a predetermined site in the human body has been one of the biggest challenges faced by the drug industry. Microsponge releases its active ingredient in a time mode and also in response to other stimuli (rubbing, temperature, pH, etc.). Microsponge technology offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility. In addition, numerous studies have confirmed that microsponges systems are nonirritating, on-mutagenic, non-allergenic, and non-toxic. Microsponge technology is being used currently in a wide range of formulations.

KEYWORDS: Microsponge Delivery System, Controlled release, Quasi- emulsion solvent diffusion, Recent Advances.

INTRODUCTION
The control, effective, targeted drug delivery systems have been a dream for a long time, but it has been largely frustrated by the complexity that is involved in the formulation development of new systems.[1] Drug Delivery Systems that control the release rate and target to a specific site of the body has an immense impact on the health care system.[2] The invention of microsponges has become a significant step toward overcoming these problems. These tiny sponges give the action at a specific target site and stick on the surface and begin to release the drug in a controlled and predictable manner for drugs with poor solubility.[3] In recent years, there has been considerable emphasis given to the development of novelmicrosponges based drug delivery systems, to modify and control the release behaviour of the drugs. By incorporation into a carrier system, it is possible to alter the therapeutic index and duration of the activity of drugs.[4] The microsponge technology was developed by Won in 1987, and the original patents were assigned to Advanced Polymer Systems, Inc. This company developed a large number of variations of the technique and applied it to the cosmetic as well as over the counter products. At present, this technology has been licensed to Cardinal Health, Inc., for use in topical products.[5] Micro sponges are polymeric delivery systems composed 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.[6] Micro sponges release their active ingredients upon application, producing a highly concentrated layer of active ingredient that is rapidly absorbed. The significance of topical drugs suffers from various problems like greasiness, stickiness associated with the ointments and so on, which often result in a lack of patient compliance. To overcome these drawback of the ointment microsponge delivery system used.[7] Microsponges widely regarded as a leading technology for addressing skin conditions such as acne, hyperpigmentation, keratosis, aging, and photo damage.[8]

Engineering of Microsponges
Active ingredients can have entrapped in microsponge polymers either at the time of synthesis[9] or if the material is too labile to withstand polymerization condition, they can be post loaded after the sponge structure formed.[10] The post-loading is preferred mode since many cosmetic ingredients and most pharmaceutical ones would decompose at the temperatures of polymerization. Microsponge particles loaded by diffusion in a manner quite similar to a regular sponge and can then be gradually released when the polymer is placed in contact with the skin.[11]

Benefits/ Advantages of Microsponge Technology
1. Enhanced product performance with extends release.[12]
2. Reduced irritation and hence to improved product elegancy, patient compliance.[13]

3. Compare to other technologies like microencapsulation and liposome, microsponges has a wide range of chemical stability, higher payload, and ease in the formulation.[14]
4. Improves materials processing as liquid converted into solid forms and improves formulation flexibility.[15]

Characteristic of Microsponge Drug Delivery Systems
1. Micro sponges are stable over the extended pH range from 1 to 11 and constant up 130^0c.[16]
2. Microsponge formulations have a higher payload (50 to 60%) and can be cost-effective.[17]
3. It must be either fully miscible in a monomer or capable of being made miscible by the addition of a small amount of a water-immiscible solvent.[18]
4. They are non-irritating, non-mutagenic, no allergenic and non-toxic.
5. They can absorb oil up to 6 times its weight without drying.
6. They show good compatibility with various vehicles and ingredients.[19]
7. Microsponges formulations are self-sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.[20]

Advantages of microsponges
1. They offer entrapment of numerous ingredients and are thermal, physical and chemically stable.
2. They are self-sterilizing as the average pore size is 0.25 µm where bacteria cannot penetrate.[21]
3. Provides Modified release drug delivery and Site targeting delivery by using external stimuli like pH, temperature, pressure, and rubbing.
4. It provides gradual release up to 12 h. and improves product elegance, efficacy, and bioavailability.
5. They facilitate accurate delivery of small quantities of the potent drug and reduced concentration of drug at a site other than the target organ or tissue.[22],[23],[24]

Advantages over conventional formulation
The existing formulations in the market are having huge side effects and adverse effects in the treatment. Conventional formulations of topical drugs are intended to apply to the outer layers of the skin. Such products release their active ingredients upon application. 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, Jelvehgariet al. prepared the microsponges of Benzoyl peroxide formulations which have excellent efficacy with minimal irritation.[25][26]

Advantages over microencapsulation and liposomes
The Microsponges has advantages over other technologies like microencapsulation and liposomes. Microcapsules cannot control the release rate of actives as once the wall is ruptured the actives contained within microcapsules will be released disorderly. Liposomes suffer from the lesser payload, challenging formulation, partial chemical stability, and bacterial instability. While the microsponge system in contrast to the above systems is stable over a range of pH 1 to 11, temperature up to 130C, compatible with most vehicles and ingredients, higher payload (50 to 60%), free-flowing and can be cost-effective.[27][28]

Limitations
The prime limitation of microsponge technology is the use of various organic solvents in formulations. The use of organic solvents poses threats, such as toxicity and flammability. Traces of residual monomers in the bottom-up approach can be toxic and dangerous to health. But these limitations can be overcome by quality control measures, optimization and standardization of procedures e. g, post-manufacture washing.[29][30]

Drugs Explored In The Microsponge Delivery System
Examples of microsponge drug delivery with their formulations

APPLICATIONS OF MICROSPONGES
Oral drug delivery
The microsponge drug delivery providing the enhancement of solubility, efficacy to the poorly aqueous soluble drug. The Kawashima achieved the controlled and effective oral delivery of ibuprofen microsponges by changing their intraparticle density. The Microsponge system has been shown that the upturn in the rate of solubilisation of poorly water-soluble drugs by trapping such drugs in the micro sponge pores.[47] *In vitro* studies showed that compression-coated colon-specific tablet formulations started to release the drug at the eighth hour while the drug release from the colon-specific formulations prepared by pore plugging the microsponges showed an increase up to the eighth hour.[48]

Ophthalmic drug delivery
The ophthalmic drug delivery systems have rapid and extensive precorneal loss caused by the drainage and the high tear fluid turnover. To overcome these problems an increase in the contact time between drug and the corneal surface is required. In situ, gelling systems are viscous liquids, which undergo a sol to gel transition, when applied to the human body, due to change in a physicochemical parameter such as temperature, pH or ionic strength. In situ, gelling systems allow accurate and reproducible administration of drugs unlike the preformed gels and are capable of prolonging the residence time to the mucosal surfaces. Obiedallah and team formulate novel acetazolamide loaded microsponges and formulating them into in situ gel for ocular drug delivery, in order to decrease the systemic side effects of acetazolamide and increase patient compliance. The formulation showed higher therapeutic efficacy compared to a free drug in the gel. It was non-irritant as it passes the safety parameters. These results

indicated that micro sponges in situ gel have the potential ability for ophthalmic delivery.[49]

Topical drug delivery

The microsponge systems are based on microscopic, polymer-based microspheres that can bind, suspend or entrap a wide variety of substances and then be incorporated into a formulated product, such as a gel, cream, liquid or powder. Broad safety studies have demonstrated that the polymers are non-irritating, non-mutagenic, non-allergenic, non-toxic and non-biodegradable.[50] Bothiraja et al. prepared ethyl cellulose-based microsponges of eberconazole and incorporated it into a gel for topical delivery. The characterization of microsponges and skin irritation studies were conducted to demonstrate controlled release and non-irritancy. Further, antifungal activity was carried out on the microsponge gel. Results of the in vivo skin deposition study demonstrated four times higher drug retention in the stratum corneum when compared to commercial cream. Results signified that the prepared eberconazole microsponge gel may be a potential topical delivery system for antifungal therapy.[51]

Hypothetical Mechanism of Microsponges

The microsponge particles have an open structure as there is no continuous membrane surrounding them and active is free to move in and out from the particles and into the vehicle until equilibrium is grasped. When the vehicle becomes saturated. Let's take an example of topical delivery, once the complete product is applied to the skin, the activity that is already in the vehicle will be immersed into the skin, depleting the vehicle, which will become unsaturated, therefore, disconcerting the equilibrium. This will jerk a flow of the active from the microsponge particle into the vehicle, and from it, to the skin until the vehicle is either dehydrated or absorbed. The steady release of the active to the skin providing prolonged release over time. This suggested mechanism of action highlights the importance of formulating vehicles for use with microsponge entrapments. If the active is too soluble in the chosen vehicle during compounding of the finished products, the products will not provide the desired benefits of gradual release. Instead, they will work as if the active was added to the vehicle in a free form. When using microsponge's entrapments, some solubility of the active in the vehicle is suitable, because the vehicle can provide the preliminary loading dose of the active until release from the microsponge is triggered by the shift in equilibrium from the polymer into the carrier. Another way to sidestep unwanted 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. The rate of active release will eventually depend on the partition coefficient of the active ingredient between the polymer and the vehicle, surface area, mean pore diameter and some other triggers such as moisture, pH, friction or temperature.[52][53] This principle is contrary to the conventional formulation principles usually applied to the topical products. For this conventional system, it is normally recommended to maximize the solubility of the active into the vehicle.[54]

Formulation Consideration

When formulating the microsponge, certain consideration is taken into account in order to achieve the desired product characteristics. The aqueous solubility must be limited otherwise, the continuous phase will deplete the microsponge during formulation, and polymer design and payload of microsponges for the action must be optimized for required release after given time period the solubility of actives in vehicle is must be limited. Otherwise the vehicle will deplete the active ingredient before the application.[55]To avoid cosmetic problems; not more than 10 to 12% w/w microsponges must be incorporated into the vehicle.[56]

Method of preparation: Drug loading in microsponges can take place in two ways, one-step process or by two-step process as discussed in liquid-liquid suspension polymerization and quasi emulsion solvent diffusion techniques which are based on physicochemical properties of the drug to be loaded. If the drug is typically an inert non-polar material, it will create the porous structure it is called porogen.[57] A Porogen drug neither hinders the polymerization process nor become activated by it.[58]

Liquid-liquid suspension polymerization:

The porous microsponges are prepared by the suspension polymerization method in a liquid-liquid system. The liquid-liquid suspension polymerization method is carried out by using a round bottom flask which is prepared by adding monomer to the non-polar active ingredient and this is added to the aqueous phase. Usually containing surfactant and dispersant as the additives and suspension are formed. Polymerization is initiated by adding catalysts or by increasing the temperature.[59] The polymerization process lasts the formation of a reservoir type of system with a spherical structure. After the polymerization process, the solvent is removed leaving the circular structured porous sponge, i.e., microsponges. The various steps involved in the preparation of microsponges.[60][61]

The various steps to summarize

1. Selection of monomer or combination of monomers
2. Formation of chain monomers as polymerization begins
3. Formation of ladders as a result of crosses linking between chain monomers
4. Compact of monomer folding ladder to form spherical particles
5. Agglomeration of microspheres, which give rise to the formation, bunches of microspheres
6. Binding of bunches to form microsponges.[62][63]

Quasi-emulsion solvent diffusion

Porous microsponges were also formulated by a quasi-emulsion solvent diffusion method (two-step process) using an internal phase containing polymer such as eudragit which is dissolved in ethyl alcohol. Then, the drug is slowly added to the polymer solution and dissolved under ultra-sonication at 35°C and plasticizers such as triethyl citrate (TEC) were added to aid the plasticity. The inner phase is then poured into the external phase containing polyvinyl alcohol andmicrosponges. microsponges were washed and dried in an air- heated oven at 40°C for12 h.[64][65]

RELEASE MECHANISM

Microsponges can be designed to release a given amount of active ingredients over time in response to one or more external triggers. There appear to be lots of other factors affecting the release of the drug from the microsponges.[66]

Temperature-triggered systems: at room temperature, few entrapped active ingredients can be too viscous to flow suddenly from microsponges onto the skin. With an increase in skin temperature, the flow rate is also increased and therefore release is also enhanced.[67]

Solubility: 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 triggered by diffusion but taking into attention, the partition coefficient of the ingredient between the microsponges and the external system.[68]

pH: The pH-responsive microsponges involve the coating of Conventional Microsponge delivery systems with the enteric-coating type of material, which imparts pH responsiveness to this delivery system.[69] Triggering the pH-based discharge of the active can be achieved by adapting the coating on the microsponge.[70]

Pressure: Pressure/ Rubbing applied can release active ingredients from microsponge onto the skin in a controlled manner. The pressure triggered microsponges system releases the entrapped material when pressurized/rubbed; the amount released depends upon various characteristics of the sponge by varying the type of material and different process variables. When compared with mineral oil containing microcapsules, mineral oil containing microsponge showed a much more softening effect as the microcapsules show irritancy effect.[71]

Safety Parameters

As such Microsponge delivery systems are made up of biologically inert polymers, the substantiation of safety required insight of more than the 30 safety parameters. 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.[72][73]

Evaluation Parameter of Microsponges

Various factors are affecting the drug release from microsponges. So it can be evaluated by the following factors.

Particle Size and shape: Free-flowing powders with fine aesthetic attributes are likely to obtain by directing the size of particles during polymerization. Particle size analysis of loaded and unloaded Microsponges can be performed by laser light diffractometry or any other appropriate method. The values (d50) can be expressed for all formulations as a mean size range. Cumulative percentage drug release from microsponges of different particle sizes will be plotted against time to study the conclusion of particle size on drug release. A particle larger than 30 μm can impart grittily.[74]

Morphology and Surface Topography of Microsponges

The occurrence of pores is an essential feature of microsponges, its internal and external morphology, and surface topography can be obtained by using scanning electron microscopy and transmission electronmicroscopy.[75]

Determination of Production Yield and Loading Efficiency[76][77]

Production Yield The production yield of the microsponges can be determined by calculating accurately the initial weight of the raw materials and the last weight of the Microsponge obtained.

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

$$\text{Production Yield} = \frac{\text{Practical mass of Microsponge}}{\text{Theoretical mass (polymer + drug)}} \times 100$$

Loading efficiency The loading efficiency (%) of the microsponges can be calculated by putting the value of Actual drug content and Theoretical drug content in the following equation.

The loading efficiency (%) is calculated using the following equation:

$$\text{Loading Efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Determination of True Density: True density can be measured by an ultra-pycnometer using helium gas, and calculated as a mean of repeated determinations.[78]

Characterization of Pore Structure: Mercury intrusion porosimetry can be employed to study the effect of pore diameter and volume with the rate of drug release from microsponges. Porosity parameters of microsponges such as intrusion–extrusion isotherms pore size distribution, total pore surface area, average pore diameters, shape and morphology of the pores, bulk and apparent density can be determined by using mercury intrusion porosimetry.[79]

Recentadvances in Porous Drug Delivery Systems

Nano sized porous systems are being approached as a further advancement to their microsized counterparts. Nanosponges are hyper cross-linked polymer-based colloidal structures, consisting of countless interconnecting voids within a collapsible structure with a porous surface.[80] These offer passive targeting of dermal agents to the skin leading to dosage form retention on the skin, total dose reduction, and systemic absorption avoidance. Very few research groups have attempted to investigate these nanoporous carriers for encapsulating dermally relevant moieties. Swaminathan et al. formulated cyclodextrin nanosponges for solubility enhancement of itraconazole, a poorly water-soluble drug.[81] The babchi oil loaded cyclodextrin nanosponges were also fabricated by our research group for solubility and photostability enhancement of entrapped essential oil.[82] Sharma and Pathak fabricated ethyl cellulose nanosponges as an alternative system for targeting econazole nitrate to the skin through hydrogel formulation. Hence, nanosponges can be looked upon as an emerging alternative for dermatological disorders. Because of the safety concerns associated with nanoscale particles, exploration of these nanoporous systems as carriers for dermatological agents demands a great deal of attention and in-depth investigation. Veritably, this domain offers tremendous scope and scientists looking to enter this field should give due consideration to the issues stated above.[83]

Table No. 1: Examples of microsponge drug delivery with their formulations.

Microsponge Delivery Systems	Drug	Disease
Gels	Tazarotene, Tretinoin	Facial acne vulgaris[31]
	Oxiconazole nitrate	Antifungal[32]
	Miconazole	Diaper dermatitis[33]
	Benzoyl peroxide	Anti-Acne Treatment[34]
	Nebivolol	Diabetic wound[35]
	Mupirocin	Antibacterial activity[36]
	Silver sulfadiazine	Burn wounds[37]
Lotions	Benzoyl peroxide	Anti-Acne Treatment[38]
Oil	Babchi oil	Antimicrobial[39]
Cream	Hydroquinone and Retinol	Hyperpigmentation[40]
Capsule	5-fluorouracil	Colorectal cancer[41]
Powder	Calcium phosphate	Bone substitute[42]
	Nicorandil	Cardiovascular uses[43]
Implants	Polylactic-co-glycolic acid	Tissue engineering[44]
Grafts	Polylacticglycolic acid	Cardiovascular uses[45]
Injection	Fibroblast growth factor	Growth factor[46]

FIGURE

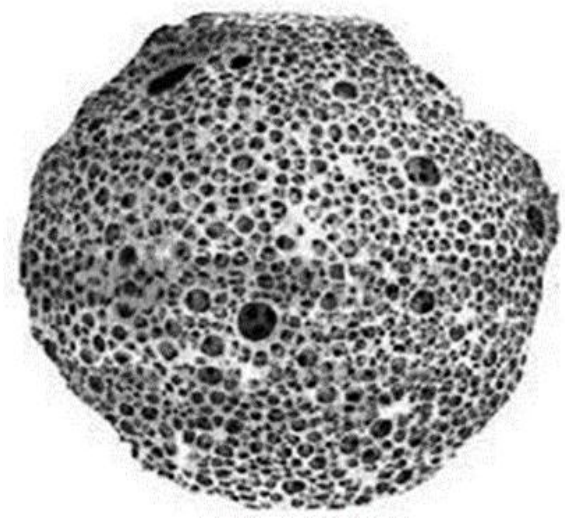

Figure 1: Porous structure of microsponge (Engineering of Microsponges).

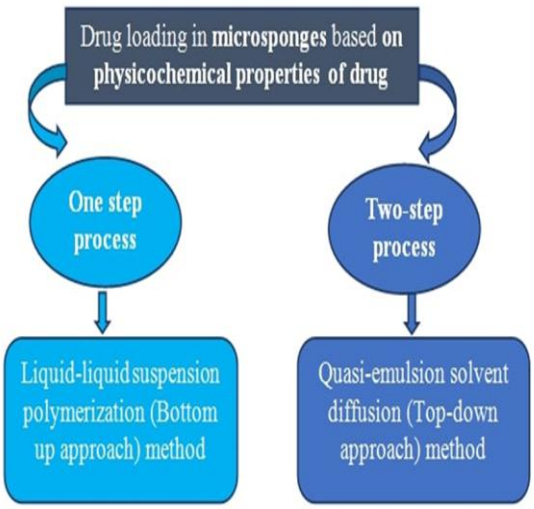

Figure 2: Methods of Preparation of Micro- Sponges.

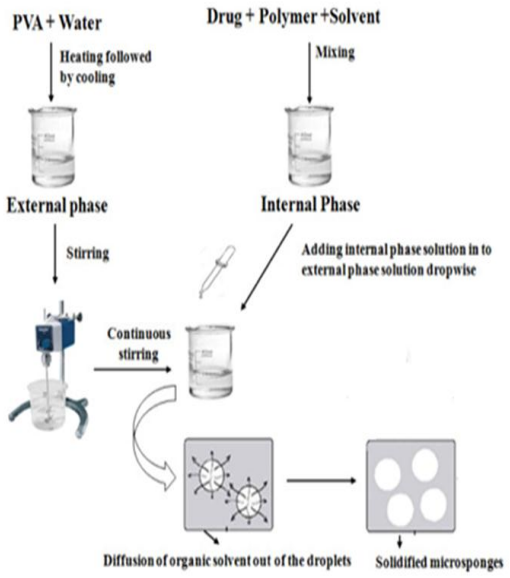

Figure 3: Quasi-emulsion solvent diffusion method.

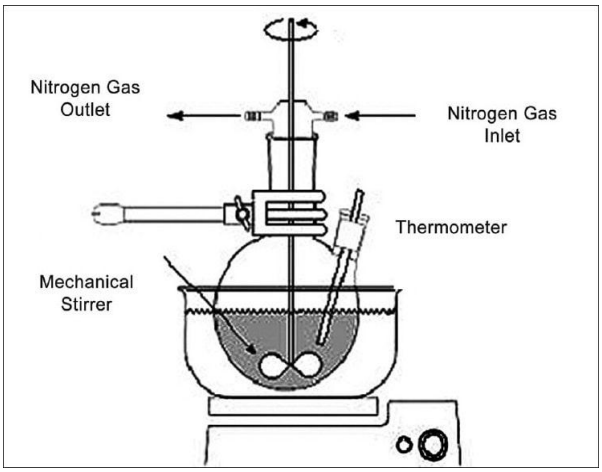

Figure 4: Preparation of microsponges by liquid-liquid suspension polymerization.

CONCLUSION AND DISCUSSION

The formulators consider microsponge's technology as a new and creative way to deliver actives with enhanced safety, improved stability, reduced side effect and enhanced multi-functionality and improved ingredient compatibility. Microsponge delivery systems can be an attractive strategy for a new generation of Pharmaceutical and Cosmeceuticals. Microsponges have a distinct advantage over all types of existing conventional formulation. It is an exclusive technology for the controlled, extended, and target release of topical agents, cardiovascular, ophthalmic, and oral as well as biopharmaceutical drug delivery. The microsponge drug delivery system has got a lot of forthcoming and is an emerging field which is needed to be explored in the future for the attractive characteristics of microsponges with the revolutionized nanotechnology trend to enhance their performance.

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