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MICROSPONGE AS A NOVEL DRUG CARRIER SYSTEM: A REVIEW

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ABSTRACT

Day by day there are new developments in the field of drug delivery system. Microparticles and nanoparticles have been increasingly investigated to achieve targeted and sustained release of drugs. Microsponges are one of the novel drug delivery system which is gaining popularity now days because of their perceived application in controlled and site-specific drug delivery. The fundamental appeal of the microsponge technology arises from the difficulty experienced with conventional formulations in releasing active ingredients over an extended period of time, unpleasant odour, greasiness and skin irritation. Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge-like spherical particles with a large porous surface and are believed to contribute towards reduced side effects, improved stability, increased elegance and enhanced formulation flexibility. Microsponge delivery technology is being used mostly for topical and recently for oral administration. The present review describes microsponge technology including its preparation, characterization, evaluation methods along with recent research and future potential.

KEYWORDS: Microsponges, Programmable release, cosmetics, topical formulation.

INTRODUCTION

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.[1] 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. Another potential problem in topical delivery of drugs relates to the use of unaesthetic

vehicles which may be greasy, sticky and may cause discolorations, since this can result in the lack of patient compliance.[2] The vehicles of topical formulations need to contain high concentrations of active agents for effective therapy because of the low efficiency of delivery system, consequential into irritation and allergic reactions in significant users. Other disadvantages of topical formulations are uncontrolled evaporation of active ingredient, obnoxious odour and potential in-compatibility of drugs with the vehicles. Thus there is a requirement to maximize amount of time that an active ingredient is present either on skin surface or within the epidermis, while minimizing its transdermal penetration into the body.[3] 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. 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.[1]

The microsponge technology was developed by Won in 1987 and the original patents were assigned to advanced polymer system, Inc. At current, this technology has been licensed to Cardinal Health, Inc., for use in topical products.[3] A Microsponge Delivery System (MDS) is "Patented, highly cross-linked, porous, polymeric microspheres polymeric systems 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".[4] Microsponges 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 ingredients are released in a controlled manner. These microsponges have capacity to entrap a wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens and anti-infectives and used as a carrier for topical drug delivery.[5,6] The porous sphere polymers vary in diameter from 5 to 300µm. A 25µm sphere can have pore length up to 3000 mm, providing a total pore volume of about 1 ml/g. When applied to the skin, the MDS releases its active ingredient on a time mode and also in response to other stimuli such as rubbing, temperature, pH, etc. Depending upon their particle size, these porous systems can be divided into microporous microbeads (particle below 50µm) and microporous macrobeads (particle range of 100-200 µm).[7] The structure of microsponge is shown in the (Fig. 1).

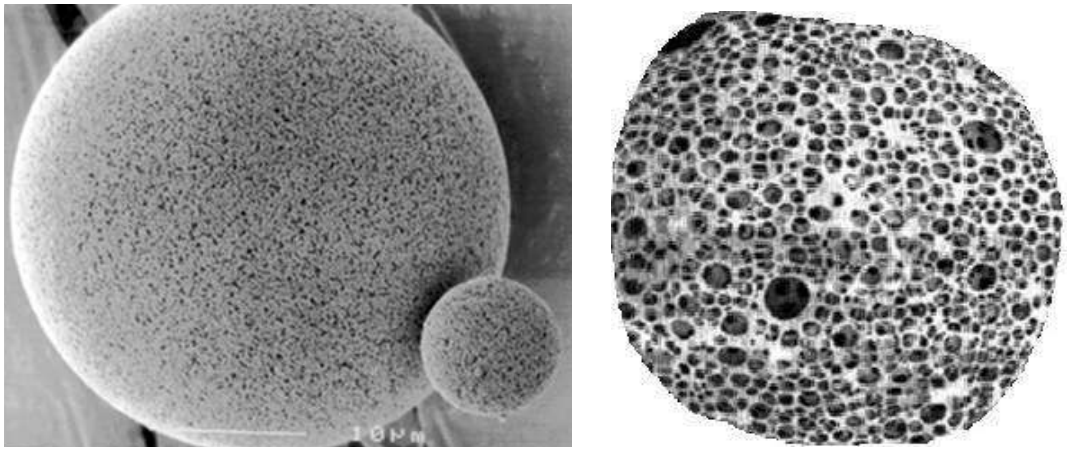

Fig. 1: Structure of microsponge.

Characterstics of Microsponges[1, 8]

- Microsponges show acceptable stability over pH ranging from 1 to 11 and at high temperatures (up to 130°C).
- These are compatible with most vehicles and ingredients.
- Self sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.
- It have higher payload (50 to 60%), still free flowing and can be cost effective.
- Microsponges can absorb oil up to 6 times their weight without drying.

Properties of the actives for the entrapment into the microsponge[9]

- It should exhibit complete miscibility in monomer or capable of being made miscible by addition of small amount of a water immiscible solvent.
- It should be inert to monomers and do not increase the viscosity of the preparation during formulation.
- It should be water immiscible or nearly only slightly soluble.
- The solubility of active ingredients in the vehicle should be minimum, otherwise the microsponge will be diminished by the vehicle before application.
- It should maintain (preserve) the spherical structure of microsponge.
- It should be stable in polymerization conditions.
- Not more than 10 to 12% w/w microsponge can be incorporated into the vehicle to eliminate cosmetic delinquent.
- Payload and polymer design of the microsponges for the active must be adjusted to obtain the desired release rate of a given period of time.

ADVANTAGES OF MICROSPONGES[1,9]

- **Advantages over Conventional Formulations**

Conventional formulations of topical drugs are intended to work on the outer layers of the skin. Such products release their active ingredient upon application, producing a highly concentrated layer of active ingredient that is rapidly absorbed. When compared to the conventional system, 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**

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 has a number of advantages like stable over a pH range of 1 to 11 and upto temperature of 130ºC, stable thermally, physicaly and chemically, have higher payload up to 50 to 60 %, have average pore size is 0.25µm where bacteria cannot penetrate.

- **Advantages over Ointments**

Ointments are often aesthetically unappealing, greasy and sticky those often result into lack of patient compliance. These vehicles require high concentrations of active agents for effective therapy because of their low efficiency of delivery system, resulting into irritation and allergic reactions in significant users. Other drawbacks of topical formulations are uncontrolled evaporation of active ingredient, unpleasant odour and potential incompatibility of drugs with the vehicles, whereas microsponge system maximizes 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.

PREPARATION OF MICROSPONGE[10-12]

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 drug to be loaded.

Liquid-liquid suspension polymerization

The porous microspheres are prepared by liquid-liquid suspension polymerization method. In their preparation, the monomers are first dissolved along with non-polar active ingredients in a suitable solvent solution of monomer and are then dispersed in the aqueous phase, which consist of additives (surfactant, suspending agents, etc.) in order to facilitate the formation of suspension. Once suspension with the discrete droplets of the desired size is established then, polymerization is initiated by adding catalyst or by increasing temperature or irradiation. The polymerization process leads to the formation of a reservoir type of system, which opens at the surface through pores. During the polymerization, an inert liquid immiscible with water but completely miscible with monomer is used to form the pore network. Once the polymerization process is complete, the liquid is removed leaving the microsponges which is permeate within preformed microsponges then, incorporates the variety of active substances like anti fungal, rubefacients, anti acne, anti inflammatory etc and act as a topical carriers. In some cases, solvent can be used for efficient and faster inclusion of the functional substances. If the drug is susceptible to the condition of polymerization then, two-step process is used and the polymerization is performed by means of alternate porogen and it is replaced by the functional substance under mild conditions. Reaction vessel for Microsponge preparation by liquid-liquid suspension Polymerization is shown in (Fig. 2).

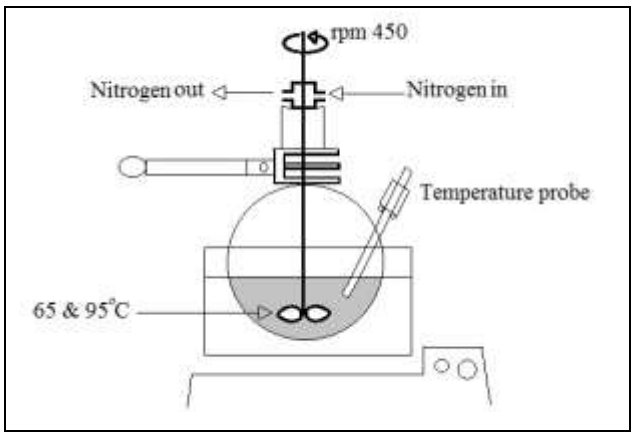

Fig. 2: Reaction vessel for Microsponge preparation by liquid-liquid suspension polymerization.

The various steps in the preparation of microsponges are summarized as

- Selection of monomer or combination of monomers.
- 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, leads to formation of bunches of microspheres.
- Binding of bunches to form microsponges.

Quasi-emulsion solvent diffusion

When the drug is sensitive to the polymerization conditions, two-step process is used. This is a two-step process where the microsponges can be prepared by quasi emulsion solvent diffusion method using the different polymer amounts (Fig. 3). In that an external phase of containing 200 ml distilled water and 40 mg polyvinyl alcohol (PVA) and an internal phase containing polymer such as Eudragit RS 100 was dissolved in ethyl alcohol. Then, the drug is slowly added to the polymer solution and dissolved under ultrasonication at 35°C and plasticizer such as triethylcitrate (TEC) was added in order to aid the plasticity. At first, the internal phase was prepared at 60°C and added to the external phase at room temperature. After emulsification, the mixture was continuously stirred for 2 hours and then the mixture is filtered to separate the microsponges. The microsponges are dried in an air heated oven at 40°C for 12 hours and weighed to determine production yield.

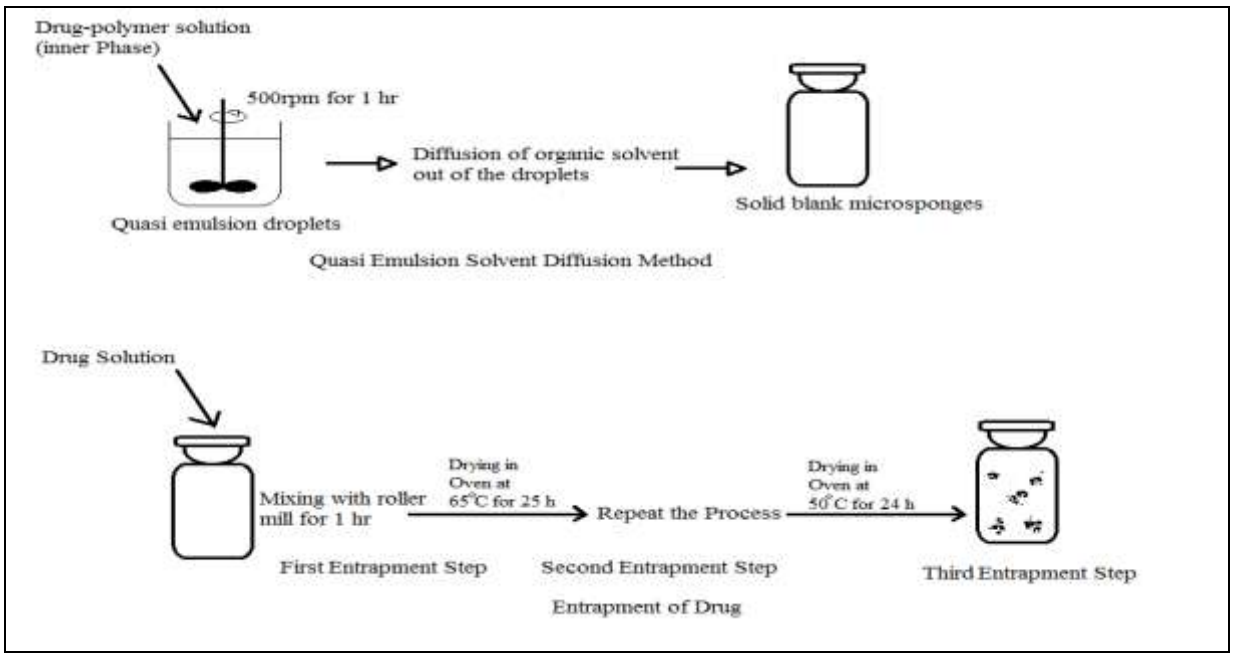

Fig. 3: Preparation of Microsponges by Quasi-emulsion solvent diffusion method.

Limitations

Both the methods generally uses organic solvents as porogens, that present an environmental hazard, as some may be highly inflammable, posing a safety hazard. Moreover, in case of the Liquid-Liquid Suspension Polymerization traces of residuary monomers have been observed, that may be toxic and hazardous to health. Even if the limitations seem to be serious, they can easily be overcome, by using proper quality control measures and proper washing post manufacture coupled with good standardization of the various processes.[13]

HYPOTHETICAL MECHANISM OF MICROSPONGE

The active ingredient is added to the vehicle in an entrapped form. As the microsponge particles have an open structure (i.e., 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.[10]

PROGRAMMABLE DRUG RELEASE[13,14]

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

- **Pressure triggered systems**

Microsponge system releases the entrapped material onto the skin when pressurized/rubbed; the amount released depends upon various characteristics of the sponge. By varying the form of material and different process variables, the microsponge best suitable for a given application may be optimized. When compared with mineral oil containing microcapsules, mineral oil containing microsponge showed much more softening effect. The duration of emolliency was also much more for the microsponge systems.

- **Temperature triggered Systems**

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. So it is possible to modulate the release of substances from the microsponge by modulation of temperature. For example, viscous sunscreens were found to show a higher release from microsponges when exposed to higher temperatures; thus a sunscreen would be released from a microsponge only upon exposure to the heat from the sun.

- **pH Triggered Systems**

Triggering the pH-based release of the active can be achieved by modifying the coating on the microsponge. Although this has many applications in drug delivery, only a few applications are possible for cosmetic delivery.

- **Solubility Triggered Systems**

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. Ingredients such as antiseptics, deodorants and antiperspirants may be formulated in such types of systems.

EVALUATION PARAMETERS OF MICROSPONGES

Various methods are used for the evaluation of the MDS.

Measurement of particle size[15,16]

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. Various formulation and process variables can greatly affect the particle size of microsponge formulations. Measurement of particle size of loaded and unloaded microsponges can be performed using laser light diffractometry or any other suitable method. Results can be expressed in terms of mean size range. It can be studied by plotting Cumulative (%) drug release from microsponges of different particle sizes against time to study the effect of particle size on drug release. Particles larger than 30 μm can impart grittiness and hence particles of sizes between 10 and 25 μm are preferred to be used in topical formulations.

Morphology and Surface Topography of Microsponges[15,16]

For morphology and surface topography, various techniques have been used like photon correlation spectroscopy (PCS), Scanning electron microscopy (SEM), transmission electron microscopy (TEM) etc. For morphology and surface topography, prepared microsponges are coated with gold palladium under an argon atmosphere at room temperature and then the surface morphology of the microsponges can be studied by scanning electron microscopy (SEM). SEM images may also be recorded for a fractured microsponge to study its ultrastructure.

Determination of true density[16]

True density of Microsponges can be measured using an ultra-pycnometer under helium gas and calculated as a mean of repeated determinations.

Compatibility Studies[15,17]

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

Polymer/ Monomer composition[15]

Factors such as microsphere size, drug loading, and polymer composition govern the drug release from microspheres. Polymer composition of the MDS can affect partition coefficient of the entrapped drug between the vehicle and the microsponge system and thus 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.

Loading efficiency and production yield[17]

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 microsponge obtained.

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

Resiliency[16]

Microsponges with varying Resiliency (viscoelastic) properties can be produced according to the needs of the final formulation. The degree of cross-linking affects the drug release from the prepared microsponges, where increased crosslinking tends to decrease the release rate. Hence, viscosity measurements should be done so that the viscoelastic properties of microsponges can be modified and adjusted to obtain the desired release properties.

Characterization of Pore Structure[15]

Pore volume and diameter are vital in controlling the intensity and duration of effectiveness of the active ingredient. Pore diameter also affects the migration of active ingredients from microsponges into the vehicle in which the material is dispersed. Mercury intrusion porosimetry can be employed to study effect of pore diameter and volume with rate of drug release from microsponges. Porosity parameters of microsponges such as intrusion–extrusion isotherms, pore size distribution, total pore surface area, average pore diameters, 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. Incremental intrusion volumes can be plotted against pore diameters that represented pore size distributions. The pore diameter of microsponges can be calculated by using Washburn equation.

$D = -4\gamma\cos\theta/P$

Where, D is the pore diameter (m); the surface tension of mercury (485 dyn cm−1); the contact angle (130^{o}); and P is the pressure (psia). Total pore area (Atot) was calculated by using 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); Vtot is the total specific intrusion volume (ml g−1). The average pore diameter (Dm) was calculated by using equation,

$Dm = 4V_{tot}/A_{tot}$

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

$\rho = Ws/V_{p}-V_{Hg}$

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 (ρse) of Microsponges was calculated by using equation,

ρse=Ws/Vse−Vtot

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,

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

Pore morphology can be characterized from the intrusion–extrusion profiles of mercury in the Microsponges.

In-vitro release studies[18]

In-vitro release studies have been carried out using dissolution apparatus USP XXIII equipped with a modified basket consisted of 5 µm 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.

Stability studies[19]

Technically stability and durability may be defined as the capacity of particular formulation in a specific container, to stay between its physical, chemical, microbiological, therapeutic and toxicological specification in pharmaceutical sense. 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.

Kinetics of release[20]

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.

$$Q = k_1 t^n \quad \text{or} \quad \log Q = \log k_1 + n \log t \ldots. (1)$$

Where Q is the amount of the released at time (h), n is a diffusion exponent which indicates the release mechanism, and k_1 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 k_1 were calculated.

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

$$Q = k_2 t^{0.5} + C \ldots\ldots. (2)$$

Eq. (2), for release data dependent on the square root of time, would give a straight line release profile, with k_2 presented as a root time dissolution rate constant and C as a constant.

SAFETY CONSIDERATIONS[3]

- Skin irritation studies in rabbits
- Anti-inflammatory activity by ear edema measurement
- Primary eye irritation study (Unwashed Eyes)
- Other evaluation studies

Oral toxicity examines in rats, mutagenicity in bacteria, allergenicity in guinea pigs, Compatibility studies by (TLC) thin layer chromatography.

PHARMACEUTICAL UTILIZATION OF MICROSPONGES

Microsponges are designed to deliver the pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects and modify drug release. Microsponge drug delivery systems offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, reduces systemic exposure and minimize local cutaneous reactions, increased elegance, and enhanced formulation flexibility.[3]

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.[21]

Products under development or in the market place utilize the Topical Microsponge systems in three primary ways.[22]

1. As reservoirs releasing active ingredients over an extended period of time,
2. As receptacles for absorbing undesirable substances, such as excess skin oils, or
3. As closed containers holding ingredients away from the skin for superficial action.

Topical drug delivery employing microsponge technology

Microsponge systems are made of biologically inert polymers. Extensive safety studies have demonstrated that the polymers are non-irritating, non-mutagenic, non-allergenic, non-toxic and non-biodegradable. As a result, the human body cannot convert them into other substances or break them down. Although they are microscopic in size, these systems are too large to pass through the stratum corneum when incorporated into topical products. Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne, with skin irritation as a common side effect. It has been shown that controlled release of BPO from a delivery system to the skin could reduce the side effect while reducing percutaneous absorption. Therefore, microsponge delivery of Benzoyl peroxide was developed using an emulsion solvent diffusion method by adding an organic internal phase containing benzoyl peroxide, ethyl cellulose and dichloromethane into a stirred aqueous phase containing polyvinyl alcohol and by suspension polymerization of styrene and divinyl benzene. The prepared microsponges were dispersed in gel base and microsponge gels are evaluated for

anti-bacterial and skin irritancy. The entrapped system released the drug at slower rate than the system containing free BPO. Topical delivery system with reduced irritancy was successfully developed.[22]

Amrutiya et al., developed microsponge based topical delivery system of mupirocin by using emulsion solvent diffusion method for sustained release and enhanced drug deposition in the skin.[23] Another, formulation of Hydroquinone (HQ) 4% with retinol 0.15% entrapped in microsponge reservoirs was developed for the treatment of melasmaand postinflammatory hyperpigmentation.[24]

Oral drug delivery employing microsponge technology

A Microsponge system offers the potential for active ingredients to remain within a protected environment and provide controlled delivery of oral medication to the lower gastrointestinal (GI) tract, where it will be released upon exposure to specific enzymes in the colon. If this approach is successful then it should open up entirely new opportunities for MDS. It has been shown that microsponge system enhances the rate of solubilisation of poorly water soluble drugs by entrapping such drugs in their pores. As these pores are very small, the drug is in effect reduced to microscopic particles and the significant increase in the surface area thus greatly increases the rate of solubilisation. Additionally, the time it takes the microsponge system to pass through the small and large intestine is considerably increased as a result maximizing the amount of drug that is absorbed.[25]

A) The formulation containing ketoprofen microsponges yielded good modified release tablets. An in vivo study was designed to evaluate the pharmacokinetic parameters and to compare them with the commercially available ketoprofen retard tablets containing the same amount of the active drug. Commercial ketoprofen retard tablets showed a more rapid absorption rate than modified release tablets and pea levels were reached within almost 3.6 h after administration.

B) The new modified release tablets showed a slower absorption rate and peak levels were reached 8 h after administration. Controlled oral delivery of ibuprofen microsponges is achieved with an acrylic polymer, eudragit RS, by changing their intraparticle density.

C) Paracetamol loaded eudragit based microsponges were prepared using quasi emulsion solvent diffusion method, then the colon specific tablets were prepared by compressing the

microsponges followed by coating with pectin: hydroxypropylmethylcellulose (HPMC) mixture. In vitro release studies exhibited that compression coated colon specific tablet formulations started releasing the drug at 6th hour corresponding to the arrival time at proximal colon.[26]

Bone and Tissue Engineering employing microsponge technology

Bone-substitute compounds were obtained by mixing pre-polymerised powders of polymethyl methacrylate and liquid methyl methacrylate monomer with two aqueous dispersions of α-tricalcium phosphate (α-TCP) grains and calcium-deficient hydroxyapatite (CDHA) powders. The final composites appeared to be porous and acted as microsponges. The Basic fibroblast growth factor (bFGF) incorporated in a collagen sponge sheet was sustained released in the mouse sub-cutis according to the biodegradation of the sponge matrix, and exhibited local angiogenic activity in a dose-dependent manner. The injection of collagen microsponges incorporating bFGF induced a significant increase in the blood flow, in the murine ischemic hind limb, which could never have been attained by the bolus injection of bFGF. These results suggest the significance and therapeutic utility of the type I collagen as a reservoir of bFGF.[22]

Cardiovascular engineering employing microsponge technology

A biodegradable material with autologous cell seeding requires a complicated and invasive procedure that carries the risk of transmission. To overcome these problems, a biodegradable graft material containing collagen microsponge that would permit the regeneration of autologous vessel tissue has developed. The power of this material to induce in situ cellularization with autologous endothelial and smooth muscle cells was tested with and without pre cellularization. Poly (lactic-co-glycolic acid) as a biodegradable scaffold was compounded with collagen microsponge to form a vascular patch material. Histologic results reveal the formation of an endothelial cell monolayer, a parallel alliance of smooth muscle cells, and reconstructed vessel wall with elastic and collagen fibers. The cellular and extracellular elements in the patch had increased to levels similar to those in native tissues at 6 months. This patch shows promise as a bioengineered material for promoting in situ cellularization and the regeneration of autologous tissue in cardiovascular surgery.[3]

Reconstruction of vascular wall using microsponge technology

The tissue-engineered patch was fabricated by compounding a collagen-microsponge with a biodegradable polymeric scaffold composed of polyglycolic acid knitted mesh, reinforced on

the outside with woven polylactic acid. Tissue-engineered patches without precellularization were grafted into the porcine descending aorta (n = 5), the porcine pulmonary arterial trunk (n = 8), or the canine right ventricular outflow tract (as the large graft model; n = 4). Histological and biochemical assessments were performed 1, 2 and 6 months after the implantation. There was no thrombus formation in any animal. Two months after grafting, all the grafts showed good in situ cellularization by hematoxylin/eosin and immunostaining. The limitation of the cell population by polymerase chain reaction showed a large number of endothelial and smooth muscle cells 2 months after implantation. In the large transplant model, i.e. 6 months after implantation the architecture of the patch was similar to that of native tissue and can be used as a novel surgical material for the repair of the cardiovascular system.[27]

Marketed Products based on Microsponges

Microsponge delivery system is ideal for skin and personal care products. They can take up large amounts of excess of skin oil while retaining an elegant feel on the surface of skin. This technology is currently employed in almost number of products (Table1) sold by leading cosmetic and toiletry companies worldwide.[14]

Table 1: Summarizes the various marketed products based on Microsponges[15, 28]

Product Name	Pharmaceutical Uses	Manufacturer
Ratin A Micro	Acne vulgaris	Ortho- McNeil Pharmaceutical,
Inc. Carac Cream, 0.5%	Actinic Keratoses	Dermik Laboratories, Inc.
Glycolic Acid Moisturizer	Anti-wrinkles, soothing	AMCOL Health & Beauty
Solution (w/SPF 15)		
Line eliminator dual	Anti-wrinkles	AVON
retinol facial treatment		
Retinol 15 night cream	Anti-wrinkles	Biomedic, Sothys
Retinol cream	Maintain healthy skin,	Biomedic
	hair & mucous membranes	
EpiQuin micro	Hyper pigmentation	Skin Medica Inc
Sports cream RS and XS	Anti-inflammatory	Embil pharmaceutical Co. Ltd.
Oil free matte block SPF 20	Sunscreen	Dermalogica
Lactrex™ 12% Moisturizing	Moisturizer	SDR Pharmaceuticals, Inc.
Cream		

Dermalogica oil control lotion	Skin protectant	John and Ginger Dermalogica skin care products
Ultra Guard	Protects baby's skin from diaper rash	Scott Paper Company
Aramis fragrances	Antiperspirant	Aramis Inc

SPF: Sun protection factor.

RECENT RESEARCH ON MICROSPONGE DRUG DELIVERY SYSTEM

Several studies reported the formulation and evaluation of Microsponge loaded drugs for different purposes. Recent research on microsponge drug delivery system is summarized in (Table 2).

Table 2: Summary of Recent Research on Microsponge Drug Delivery System.

Drug	Method used	Excipients used	Result	Reference
Naproxen	Quasi emulsion	Eudragit RS-100, carbopol, PVA	Increase in the ratio of the drug: polymer Resulted control release rate	[29]
Oxybenzone	Quasi emulsion	Ethyl cellulose-N10, PVA, HPMC, dichloromethane, methanol	*In vitro* and *ex vivo* study revealed enhanced topical retention of drug and increased SPF	[30]
Lornoxicam	Quasi emulsion	Eudragit, PVA, carbopol 940, Ethyl cellulose, Triethyl citrate	Drug release in a controlled manner	[31]
Diclofenac diethylamine	Quasi-emulsion	Eudragit RS 100, sodium alginate, dibutyl phthalate,	Extended drug release (75.88% at 8 h)	[32]
Domperidone	Quasi-emulsion	Eudragit RS 100, dichloromethane, dibutyl phthalate, PVA	Extended drug release (76.38% at 8 h)	[33]

PVA: Polyvinyl alcohol, HPMC: Hydroxy propyl methyl cellulose, SPF: Sun protection factor.

DEVELOPMENTS 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 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 reacting the β-CD with biphenyl 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.[34] 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.[35] 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.[36] 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.[37]

FUTURE PERSPECTIVE[9,38,39]

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.

Nanosponges

Today, as it has been realize that the huge advantages have been offered by the nanosize, the micro sized products are likely to be outdated. The nano sized particles have a very high surface area to size ratio and a greater potential to modulate the release of actives compared to micro-sized particles. While inorganic nanosponges have many applications in electronics,

the first pharmaceutical nanosponges based on cross linked cyclodextrins have been reported. These are nano sized, highly porous materials composed of beta-cyclodextrins cross linked with carbonate bonds.

Oral care and long lasting coloured cosmetics

A promising application of the microsponge technology could be in oral cosmetics, so as to sustain the release of volatile ingredients, thereby increasing the duration of the 'fresh feel'. Microsponges of such volatile ingredients may be easily incorporated in tooth pastes or mouth washes. Microsponges can also be utilized for long lasting colored cosmetics**.** Colors entrapped in microsponges may be used in a variety of colored cosmetic products such as rouge or lipsticks to make them long lasting as they help in uniform spreading and improving covering power.

Natural active

Although natural actives are important consumer attractants, now the focus has shifted on using multifunctional natural ingredients. The possibility of using such substances for constructing a microsponge structure appears to be cost effective and innovative.

CONCLUSION

Based on the literature surveyed, it may be concluded that the MDS have the ability to release the drug in a controlled manner to the targeted site. It is a unique technology which was originally developed for topical delivery of drugs and now it can also be used for tissue engineering and controlled oral delivery of drugs using bioerodible polymers, especially for colon specific delivery. Microsponge technology offers entrapment of ingredients and thus reduced side effects, improved stability, increases elegance and enhanced formulation flexibility.

Therefore, the microsponge drug delivery system focus as an important tool for future inventions in controlled drug delivery system.

CONFLICT OF INTERESTS

Declared None.

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