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MICROSPONGES: A COMPREHENSIVE REVIEW AND ITS RECENT INNOVATIONS

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ABSTRACT

In recent years many new pharmaceuticals sustain release formulation are developed like liposomes, niosomes, microspheres, nanaospheres etc. among them microsponges is one of the novel formulations. Physically microsponges are sponge like submicron structure with porous nature. As the formulation is porous nature with inter particular space, more amount of drug entrapment is possible and sustain release of drug can be achieved. Many microsponge preparations are limited to topical applications. Recent studies revels that this formulation can explore to other areas like gastro retentive systems, colon targeting, cosmetics, ophthalmic preparations etc. In the current review discuss about various aspects of microsponges like their preparation, characterization, safety aspects, recent developments and the future development aspects.

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INTRODUCTION

The development of new drug is not enough but the most important thing is to design a sustainable delivery system that delivers the drug to the site of action. The carrier system of the drug is also important to determine the *in vivo* fate of the drug which permits a controlled and localized release of the active drug according to the specific need of the therapy. However, the targeted drug delivery is not suitable if the final target is skin due to various reasons like skin is capable of metabolising many substances, the flux of the solutions will vary in accordance with skin even though they have similar flux properties as a saturated solution. Topical route of delivery has a wide range of advantages when compared to oral delivery like the bypass of the hepatic (first pass) metabolism and no gastric serum variability. The applications of topical route are like analgesics, anti-inflammatory, anti-fungal, anti-dandruff, antipruritic, skin depigmentation, rubefacient, sunscreen and the dosage forms available for topical effect are liquid, semisolid (gel, cream, emulsion), and solid (powders). As the topical formulations work on the outer layer of the skin, the main drawback associated with them are irritation and allergic reactions due to high concentration of active agents in these delivery systems and some may enter into the systemic circulation by transdermal penetration[1].

To minimize these side effects, carrier technology is the attainable solution to these challenges which maximize the period of time that an active moiety is present on the skin or within the epidermis and minimizing the transdermal penetration. Microparticles and nanoparticles have been progressively researched to gain targeted and sustained release of drugs and they include microspheres, liposomes, and nanoparticles etc. which alter the absorption and release characteristics of the drug. But these delivery systems have their own limitations like microspheres, which are unable to control the release rate of drug from formulation. If the outer wall is ruptured the drug contained within microspheres will be released. For liposomes preservatives are required as they have demerits like lower drug entrapment, difficulty in preparing formulation, limited chemical stability and microbial stability. The microsponge-based polymeric microspheres solitarily overcome problems associate with the formulation technologies that are mentioned above. They are extremely small, inert, indestructible spheres that do not pass through the skin and are designed to deliver a pharmaceutical active moiety intesify at the low dose and also to increase stability, decrease side effects and modify drug release. The spherical particles composed of clusters can capable of absorbing skin secretions therefore reducing oiliness and shine from the skin and even tinier spheres are capable of holding four times their weight in skin secretions. Recently their use is also being looked into for oral delivery. Microsponge Delivery System is a patented polymeric system comprising of porous microspheres. The tiny sponge like spherical particles of microsponges consist of a myriad of interconnecting voids within a non-destructible structure with a large porous surface through which active ingredient are released in a controlled way.

Microsponge technology was developed by Won in the year 1987; the original patents were assigned to Advanced Polymer Systems, Inc. This Company developed a large number of procedures with variations those are pertained to the cosmetic as well as over-the-counter and prescription pharmaceutical products. At present, this interesting technology has been licensed to Cardinal Health, Inc., for use in topical products. The size of the microsponges ranges from 5-300µm diameter. A typical 25µm sphere contain up to 250000 pores and an internal pore structure which is equivalent to 10 feet in length and providing a total pore volume of about 1ml/g of drug for extensive drug retention. The surface can varied from 20 to 500 m2/g and the pore volume range from 0.1 to 0.3cm3/g and this leads to a large reservoir within each microsponge, which can be stacked with up to its own weight of active agent. Microsponge does not pass through the skin and they can prevent excessive accumulation of ingredients within the epidermis and the dermis. The high degree of cross-linking leads to particles that are insoluble, inert and of sufficient strength to stand up to the greater shear commonly used in manufacturing of creams, lotions, and powders. The scanning electron microscopy of the microsponges will show its internal structure as the "bag of marbles" and the porosity is due to the interstitial spaces between the marbles. All the active ingredients such as emollients, fragrances, essential oils, sunscreens, anti-infective and anti-inflammatory agents gets entrapped into the interstitial pores during the formulation of products like creams, lotions, powders, soaps, capsules and tablets. These entrapped materials gets delivered to the skin in a controlled time release pattern or a pre-programmed manner by different triggers like rubbing or pressing the microsponge after it has been applied to the skin. Active ingredients entrapped in the porous polymeric structure display altered behaviour, with respect to their release, which is restricted and prolonged. It can provide extended action of drug release that is up to 12 hours. The sustained release of actives from the formulation to skin over time is an extremely valuable tool to prolong the efficacy and lessen the irritation commonly associated with powerful therapeutic agents like α- hydroxy acids which may produce burning, stinging or redness in individuals with sensitive skin[2].

CHARACTERSTIC FEATURES OF MICROSPONGES[2]

- As the microsponge particles are too large, so they are difficult to be absorbed into the skin and this add up a measure of safety to these microsponge materials by avoiding the side effects of the microsponge adjutants.
- As the average pore size of microsponges is small (0.25 micrometer), so they can avoid penetration of bacteria and they don't need sterilization or addition of preservatives.
- They have higher payload (50 to 60%) and are free flowing.
- They show continuous action up to 12 hours i.e. extended release and can absorb oil up to 6 times of its weight without drying.
- They show acceptable stability over pH ranging from 1-11 and at high temperatures up to 130^{o}C.
- They are non-irritating, non-mutagenic, non allergenic and non-toxic show good compatibility with various vehicles and other ingredients.

ADVANTAGES OF MICROSPONGE DRUG DELIVERY SYSTEM[3]

- Enhanced product performance.
- They have improved thermal, physical and chemical stability.
- They have superior flexibility to develop novel product forms.
- They can allows the incorporation of immiscible products in formulation
- Microsponges improve bio availability of the drugs.
- They improves control of condition and efficacy in treatment.
- They improves processing of materials Eg: liquid can be converted to powders.
- The aesthetics of the microsponges gives product an elegant feel.

ADVANTAGES OF MICROSPONGES OVER OTHER FORMULATIONS

Advantages over Conventional Formulations:

Topical drugs in the conventional dosage formulations used to work on the outer layers of the skin, which releases the active ingredients upon administration and producing a highly concentrated layer of active ingredient which is absorbed into systemic circulation. But in the case of microsponges, they can prevent the excessive accumulation of active ingredients within the dermis and potentially they can reduce the problems like irritation and itching without reducing their efficacy. For example, the active ingredient gradually to the skin like MDS Benzoyl peroxide formulations have excellent efficacy in delivery with minimal irritation[4].

Advantages over Microencapsulation and Liposomes:

There are several advantages of microsponges over the microencapsulation and liposomes. In the microcapsule they cannot control the release rate of the system once they get activated by rupturing the wall. In liposomes system the payload is very less and they are chemically and microbiologically instable. But in case of microsponges the drug release rate can be seen in controlled manner for prolonged period of time and the pay load of the system, stability over wide range of pH and temperature, compatibility with wide range of ingredients made them unique and preferable.

Advantages over ointments:

Ointments are generally unappealing, sticky, greasy etc which results in lack of patient compliance. They have the high concentration of active agents for effective therapy because of their low efficacy of delivery system which results in irritation and allergic reactions. The other disadvantages include unpleasant odor, uncontrolled evaporation of active ingredient and potential incompatibility of drugs with the vehicles, where microsponge system maximize the amount of time that an active ingredient is present either within the epidermis or on the surface of skin, and minimizing its transdermal penetration into the body[5].

HYPOTHETICAL MECHANISM OF ACTION[6]

The active ingredient in preparation microsponges is added to the vehicle in an entrapped form. Due to the open structure (they do not have a continuous membrane surrounding them), the active ingredient is unbound to move in and out of the particles and into the vehicle till equilibrium is attained, when the vehicle becomes saturated. The active ingredient that is already in the vehicle will be absorbed into the skin when the finished product is applied, depleting the vehicle, which will become unsaturated, therefore, disturbing the equilibrium. This is results in initiation of flow of active ingredient from the microsponge particle into the vehicle and there to skin, until the vehicle is either dried or absorbed. The vehicle will gradually release the active ingredient to the skin, providing prolonged release over time even after the microsponge particles retained on the surface of the stratum corneum. This proposed mechanism of action give prominence to formulating vehicles for use with microsponge entrapments. The products will behave as if the active was added to the vehicle in a free form and not provide the desired benefits of gradual release, if the active moiety is more soluble in the desired vehicle while compounding of the finished products. So, while formulating microsponge entrapments, it is important to design a vehicle that has minimal solubilising power for the active moieties. This principle is contrast to the conventional formulation principles usually applied to topical products as they basically recommended to maximize the solubility of the active ingredient in the vehicle. During microsponge entrapment, some solubility of the active moiety in the vehicle is allowable, because the vehicle can give the initial loading dose of the active moiety until release from the microsponge is activated by the transfer in equilibrium from the polymer into the carrier. Undesirable premature leaching of the active ingredient from the microsponge polymer during compounding can be avoided by formulating the product with some free and some entrapped active, so the vehicle is presaturated. Release of active ingredient can also be controlled through diffusion or other triggers such as moisture, pH, friction or temperature but the rate of active ingredient release will depend not only on the partition coefficient of the active moiety between the polymer and the vehicle, but also on some of the specifications that characterize the beads like area and preliminary pore diameter.

RELEASE MECHANISMS

The release mechanism of functional substances from the microsponge delivery systems over a period of time depends on one or more external stimuli.

The release mechanism of this system is mainly:-

A. Sustained or Time Release:

Different physical and chemical parameters of the entrapped active substance like volatility, viscosity and solubility are studied in the development of a sustained release microsponge, while in case of polymeric microsponge pore diameter, volume, and resiliency of the polymeric microsponge are evaluated to give necessary sustained release effects.

B. Release on Command:

Microsponges can be designed to release the active ingredients over time in response to one or more external triggers[6].

1. Pressure Release:

Fluid or active ingredient from the microsponge system can be release when it is pressed or squeezed, and thereby replenishing the level of entrapped active ingredient onto the skin. The released amount may also depend upon the release of the sponge and the resiliency of the microsponges.

2. Temperature Release:

Active ingredients from microsponges can be activated by temperature. Few entrapped active moieties can be too viscous to flow suddenly from microsponges onto the skin at room temperature. With the increase in skin temperature, flow rate is also increased and therefore release is also enhanced.

3. pH Triggering:

By modifying the coating on the microsponge, pH-based release of the active can be achieved and this has many applications in drug delivery.

4. Solubility:

In the presence of water, microsponges loaded with water miscible ingredients like antiseptics and antiperspirants will be released. The release of microsponges can also be activated by diffusion, by taking partition coefficient of the ingredient between the microsponge and the outside the system. Release rate of active ingredients can also trigger through perspiration[7].

CHARACTERSTICS OF ACTIVE MOIETIES THAT IS ENTRAPPED IN MICROSPONGES:

Active moieties that are entrapped in microsponge can be engulf into many products such as creams, gels, powders, lotions and soaps. While formulating in order to achieve desired product characteristics, certain considerations are taken into account:

1. The active moiety along with fully miscibility in monomer should be capable of being miscible by addition of water miscible solvent as well.
2. It should not increase the viscosity of the mixture during the formulation and should be inert to the monomer[5].
3. It should be immiscible in water or nearly, slightly soluble in water.
4. The spherical structure of the microsphere should not be collapsed
5. It should be steady in contact with polymerization catalyst and in conditions of polymerization.
6. In vehicle the solubility of active must be limited or else the vehicles will deplete the microsponges before the application.
7. To avoid cosmetic problems, there should not be more than 10 to 12% w/w microsponges must be incorporated into the vehicle.
8. Polymer design of the microsponges and payload for the active must be optimized for required release rate for given period of time.
9. Polymers like Eudragit RS100, Ethyl Cellulose, Polystyrene and PHEMA can form a microsponge cage. Other than actives, some microsponges also AQontain plasticizers like Triethylcitrate (TEC) that help to stabilize their structure[8].

METHODS OF PREPARATION

The entrapment of drug in microsponges can be done in two ways, depending on physicochemical properties of drug. One-step process and two-step process with respective to liquid-liquid suspension polymerization techniand quasi emulsion solvent diffusion techniques. If the drug is commonly an inert non-polar material, then it will create the porous structure and it is called porogen. Porogen drug, which not either hinders the polymerization or become activated by it and stable to free radicals is entangled with one step process.

1) Liquid-Liquid Suspension Polymerization Method:

In the vehicle of polymerization, the monomers are dissolved along with the active ingredients, i.e., surfactant in suitable solvent followed by addition of additives, suspending agent are added to the formation of suspension. By adding catalyst or by increasing temperature, the polymerization is initiated and the solvent is removed leaving the spherical structure porous. Various steps included in the preparation of microsponges are outlined as follows[6]

Step 1: Selection of monomer and combination of monomers.
Step 2: polymerization starts by formation of chains of monomers.
Step 3: Generation of ladders as a result of cross-linking between monomers chains.
Step 4: Spherical particles are formed by folding of monomer ladders.
Step5: Bunches of microspheres are formed by agglomerisation of microspheres
Step 6: Binding of bunches turn out to microsponges.

In polymerization process reservoir type of system if formed, which opens at surface through pores. An inert liquid immiscible with water however totally miscible with monomer is used during the polymerization to set up the pore network, in some cases. The liquid is removed leaving the porous microsphere after polymerization.

Advantages:

- Can be suitably altered to one step or two step methods for drug loading.
- Disadvantages
- Unreacted monomers and solvent traces are likely to be entrapped.
- May results in non-uniform structure and requires more time for the reaction of monomers.

Disadvantage:

A thermo sensitive drug that has low drug loading efficiency requires two-step method.

2) Quasi Emulsion Solvent Diffusion Method

Quasi emulsion solvent diffusion method is also called as top-down approach or two step process. This method mainly used when the drug is sensitive to the polymerization. In this method, the drug is dissolved in the suitable good solvent and then the solution is dispersed into the poor solvent to produces emulsion (quasi) droplets, even though the pure solvent is miscible. The poor solvent gradually diffuses into the droplets when the good solvent diffuses out of the emulsion and therefore, drug crystallizes inside the droplets. This top-down approach starts with preformed polymer along with the active ingredient, plasticizer and diffusible substance (porogen) and this process involved formation of quasi-emulsion of two different phases" i.e. internal phase and external phase similar to emulsions. The inner organic phase is prepared by polymer dissolved in suitable solvent followed by addition drug dissolved under ultrasonication at 35°C. The internal phase of drug--polymer solution was made in a volatile solvent like ethanol or acetone or dichloromethane and this was added to external phase comprising the aqueous polyvinyl alcohol (PVA) solution with vigorous stirring. Adequate amount of Triethyl citrate (TEC) was added in order to facilitate plasticity. The system is continuously stirred for 2 hours after emulsification and maintains higher temperature if required. Discrete emulsion globules called quasi-emulsion globules were formed by stirring. Then the solvent was extracted out from these globules to form insoluble, rigid micro particles. Porogen diffusion into the external phase or medium results the formation of a highly porous micro particles called "Microsponge". To separate the microsponges the mixture is filtered and then washed and dried in vacuum oven at 50^{o}C for 24 hours. In aqueous phase through counter diffusion of organic solvent and water in and out of the droplets the finely dispersed droplets of the polymeric solution of the drug (dispersed phase) get solidified. The drug and polymer solubility was decreased by aqueous phase within the droplets resulting in the co-precipitation of both the components and continued diffusion of the organic phase results in further solidification and producing matrix-type porous microspheres[9].

This method offered the advantage over liquid suspension polymerization method like, less exposure of the drug to the ambient conditions, low solvent residues in the product because the solvent get extracted out due to its solubility in aqueous media or due to its volatile nature. In this method, blank microsponges and drug solution in ethanol is added and bottles are arranged on roller mill and mixed for 1hr then mixture is dried in an oven at 65 °C for 2.5 hours. This process is rerunned for a second entrapment step and the drying process is held at 50 °C for 24h where in another method, drug loading is done after the formation of microsponges.

Advantages:

- Low solvent traces and no monomer entrapment.
- More drug loading and no exposure of drug to ambient condition.
- Size of microsponges can be in control of stirring rate.
- Spherical particles will be formed.

Disadvantages:

- Loading of water-soluble drugs may not be possible.
- Need long time for the reaction of monomers.
- Drug need to be soluble in a volatile water-soluble solvent[10].

EFFECT OF FORMULATION VARIABLES ON PHYSICAL PROPERTIES OF MICROSPONGES[11]

Effect of composition of internal and external phases:

It is well known that the particle size of microsponges were directly proportional to the apparent viscosity of the dispersed phase. Greater the difference between apparent viscosity of dispersed and continuous phase larger the mean particle size of the microsponges. When the dispersed phase with more viscosity is poured into the continuous phase (external phase), due to the higher viscosity of the internal phase, the globules of the formed emulsion can barely be divided into smaller particles and bigger droplets are formed resulting in an increase in mean particle size. Good microsponges can be produced with only 3 to 6 ml of internal phase. When the amount of dichloromethane is increased from 5 to 15 ml the production yield and drug content of microsponges were found to be reduced which is due to the lower concentration of the drug in the higher volume of internal phase (i.e., dichloromethane). A reduction in volume of external phase (water) results in decreased production yield, mean particle size and drug content.

Effect of concentration of emulsifier:

When the concentration of emulsifier was reduced the production yield and drug content will rise whereas the mean particle size of microsponges decreased. An increase in emulsifier concentration can attribute to an increase in apparent viscosity that results in larger emulsion droplets and finally in larger the size of microsponges.

Effect of drug to polymer ratio:

When the amount of polymer is kept unchanged but the ratio of drug to polymer is differed the drug loading capacity is not much affected yet production yield can be enormously changed from minimum ratio to a maximum. Particle size is another parameter which is affected from drug: polymer ratio change. When the amount of drug is increased, the particle size of microsponges is also increased.

EFFECT OF OPERATION VARIABLES ON PHYSICAL PROPERTIES OF MICROSPONGES[11]

Effect of stirring rate:

Increase in the stirring rate decreases the production yield yet the drug content gets increased which shows that the drug loss is decreased as the stirring rate is increased. This is due to the turbulence created within the external phase due to which polymer gets clanged to the paddle and production yield gets decreased. By increase in stirring rate will results in a reduction in mean particle size which results in increased tendency of globules to coalescence and aggregate. On the other hand, at increased stirring rates a vigorous uniform increased mechanical shear will impose and this results in a swift dispersion of the formed droplets which may have less chance of coalescing into bigger droplets which suggests that the size of droplets formed during the encapsulation process may therefore be closely related to the size of the final microsponges produced.

CHARACTERIZATION OF MICROSPONGES

Particle size determination:

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

Morphology and surface topography:

Surface morphology can be studied by scanning electron microscopy (SEM). In this study the prepared microsponge have to coat with gold-palladium under an argon atmosphere at room temperature. Scanning Electron Microscope of a fractured microsponge particle can also take to illustrate its ultra structure.

Determination of loading efficiency and production yield:

The loading efficiency (%) and production yield of the microsponges can be calculated by the following equations:

Loading efficiency = actual drug content in Microsponge / theoretical drug content X 100
Production yield = practical mass of microsponges/theoretical mass (polymer+ mass) X 100.

Determination of true density:

By using an ultra-pycnometer the true density of micro particles can be measured under helium gas and calculated with the mean of repeated determinations.

Resiliency:

Bead lets which is softer or firmer can be produced with resiliency (viscoelastic properties) of microsponges according to the requirements of the final formulation because increased cross linking tends to decline the release rate. Thus resiliency of microsponges will be studied and optimized as per the requirement by taking release into account as a function of cross-linking with time.

Polymer/monomer composition:

Factors like drug loading, size of microsphere and polymer composition will control the release of drug. Polymer composition of the microsponge delivery system can affect the partition coefficient of entrapped drug between the vehicle and microsponge, so they have direct influence on the release rate of entrapped drug. By different polymer composition drug release from microsponge can be studied by plotting cumulative % drug release against time. Various monomer combinations can screen to know the optimal compatibility with the drug by studying their release rate[4].

Determination of loading efficiency:

Loading efficiency (%) of the microsponges can be determined by the following equation:

$$\textbf{Loading efficiency} = \frac{actual\ drug\ content}{theoretical\ drug\ content} \textbf{X100}$$

Fourier transforms infrared (FTIR) analysis:

FTIR spectra of the drug, physical mixture of drug and polymers, formulations were recorded in potassium bromide disc to ascertain compatibility.

Differential scanning calorimetric (DSC) analysis:

Thermal analysis using DSC was carried out on drug, physical mixture of the drug and polymers by accurately weighed samples and loaded into aluminium pans and sealed. All samples were run at a heating rate of 20ºC/min at temperature range 40-430ºC to study the behaviour of materials as function of temperature.

Stability studies:

The stability of a product is defined as the capacity of any formulation remains unchanged physically, chemically and microbiologically in any container or closure system. By this the durability of the product with the specific container system and its stability can be known. The stability of a formulation is tested by storing it at 4 ± 1ºC, 25 ± 2ºC and 37 ± 5ºC & RH (Relative Humidity) 75 %. It was evaluated after one month and the three months for parameters like appearance, pH, Drug content analysis, Drug release profiles and rheological properties[12].

Production yield:

Production yield of micro particles can be calculated by the following formula:

$$\textbf{Production yield(Y)} = \frac{\text{Practical mass of Microsponges}}{\text{Theoretical Mass (polymer + drug)}} \times 100$$

Characterization of pore structure

Both pore diameter and volume are very important in rate and duration of effectiveness of active ingredient. Pore diameter of the microsponges also affects the migration of active ingredients, where they move from in and out of microsponges to vehicle where the materials are dispersed. To know effect of pore diameter and volume with rate of drug release from microsponges Mercury intrusion porosimetry can be used. Porosity parameters like intrusion extrusion isotherms pore size distribution, total pore surface area, average pore diameters, interstitial void volume, % porosity, % porosity filled, shape and morphology of the pores, bulk and apparent density can be known by using mercury intrusion porosimetry[5].

Pore diameter of microsponge can be calculated by using Washburn equation:

$$\mathbf{D} = \frac{-4\gamma cos\theta}{p}$$

Where; D - pore diameter (µm)

γ - surface tension of mercury (485 dyn cm−1)

θ - contact angle (1300)

P - pressure (psia).

The equation for calculating the total pore area a (A_{tot}) is

$$\mathbf{A_{tot}} = \frac{1}{\gamma cos\theta} \int_{o}^{Vtot} p.dv$$

Where; P - pressure (psia)

V - intrusion volume (mL g−1)

Vtot - total specific intrusion volume (mL g−1)

Average pore diameter (Dm) of microsponge was calculated by the equation

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

Bulk (envelope) density (ρse) of the microsponges was calculated by the equation

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

Where; Ws - weight of the microsponge sample (g)

Vp - empty penetrometer (ml)

VHg - volume of mercury (ml).

Absolute density (ρsa) of microsponges was calculated by the equation

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

Where; Vse - volume of the penetrometer minus the volume of the mercury (ml).

The equation for percent porosity of the sample was

$$\text{Porosity \%} = \left(1 - \frac{\rho se}{\rho sa}\right) \times 100$$

RELEASE EVALUATION

Release mechanism of microsponges: Release rate can be controlled through diffusion or through triggers like moisture, pH, friction and temperature. This release technology is convenient for absorbent materials to enhance the outcome aesthetics. Microsponge delivery system can be integrated into conventional dosage forms like creams, lotions, gels, ointments, and powder and share a vast package of benefits and these systems can and improve its formulation flexibility.

By using the Franz- type static diffusion cell drug release from the semi solid dosage forms are performed. In this diffusion cell, epidermal side of the skin was exposed to ambient condition and the dermal side was kept facing to the receptor compartment which contains 20 mL phosphate buffer of pH 5.8. It was thermo stated at 32±0.5°C and stirred at 600 rpm. Before the application of sample, skin was saturated with diffusion medium for 1 h. A 200 mg of sample was applied on the donor compartment. The diffusion cell was disassembled after a period of 4, 8, 16, and 24 hours for determination of drug deposited in the skin and after that the skin was carefully removed, and drug remained on the skin surface was cleaned with distilled water.

***In vitro* diffusion studies:**

In vitro diffusion studies of developed microsponge gel were performed by Keshary–Chien diffusion cell by using a cellophane membrane in the receptor compartment 100 ml of phosphate buffer was used and then 500 mg of gel consisting 10 mg of drug was spread uniformly on the membrane. The donor compartment and receptor compartment was kept in contact and the temperature was maintained at 37±0.5. By externally driven Teflon coated magnetic bars the solution on the receptor side were stirred and at fixed time intervals, pipette out 5ml of solution from the receptor compartment and straight away restored with 5ml of fresh phosphate buffer. The drug concentration on the receptor fl uid was determined by spectrophotometrically against appropriate blank. This experiment was carried out in triplicate.

Dissolution

By using USP XX1V apparatus, dissolution profile of microsponges can be studied with a modified basket consists of 5µm stainless steel mesh with 50 rpm and 0.1N HCL at temperature of 37±0.5 ºC. The dissolution medium is selected considering the solubility of active moiety to establish sink conditions. Samples from the dissolution medium could be analyzed by suitable analytical methods.

Kinetics of release:

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

$$\mathbf{Q = k1\ t\ n \text{ or } \log Q = \log k1 + n \log t}$$

Where Q - amount released at time (h)
n - diffusion exponent which indicates the release mechanism
k1 - constant characteristic of the drug – polymer interaction.
From the slope and intercept of plot, log t versus log Q, kinetic parameters k1 and n were calculated
For comparison purposes, the data was also subjected to the following equation, which may be considered a simple, Higuchi type equation.

$$\mathbf{Q = k2\ t\ 0.5 + C}$$

This equation for release data dependent on the square root of time, would give a straight line release profile, with k2 conferred as a root time dissolution rate constant and C as a constant[13].

SAFTEY CONSIDERATIONS

Skin irritation studies in rabbits:

In this test, to know the erythematic scores from 0 – 4 according to draize scale was done on intact and abraded skin 3 albino rabbits as patch test continued for 72 hours. The P.I.I (primary irritation index) was calculated by summation of scores at 1, 24, 48 and 72 hours and preparation was confirmed as negligible, slight, moderate or severe erythematic based on the readings[13].

Anti-inflammatory activity by ear edema measurement:

To know the anti inflammatory activity by ear edema can be done on male swiss mice (25–35 g). They are housed at 22±2 ºC under a 12- h light/12-h dark cycle with access to food and water, which were performed during the light phase of the cycle and let on to acclimate to the laboratory for at least 2 h before testing and were used only once. By topical application of 0.1mg/ear of croton oil dissolved in 20µL of acetone edema was induced in the right ear and In house gels of FA containing free, entrapped drug and marketed gel were applied topically simultaneously with the croton oil. The thickness of the ear was measured prior and 6 h after the induction of inflammation using a digital vernier callipers[15].

Rheological Characterization:

This test is mainly done in gel type formulation of microsponges. The prepared formulation was subjected to creep test of different forces of stress in increased manner and the formulation with higher elastic nature shows the better gelling nature.

Determination of Minimal Erythemal Dose (MED):

This study the MED wister rat models are used and they are convenient for the study due to the photochemical changes taking place in rat skin after UV exposure. This was performed out on total of nine rats and each divided into three different groups each comprising three rats and maintained separately to determine MED with respect to time of unprotected skin and protected skin of wister rat. A solar simulator of high pressure mercury vapour lamp is used as a UV light source and the first group of rats was kept directly under the solar simulator lamp and was sampled after every one minute. The second and third group rats should applied with marketed sunscreen lotion and prepared microsponge formulation respectively and the same sampling procedure was followed to rest. The presence of erythema on skin was noted after 3 hr of completion of study[16].

RECENT ADVANCEMENTS

β cyclodextrin based microsponges:

Recent advanced studies in microsponges used low soluble drugs in preparation of microsponges by using β cyclodextrin cross linking polymer called as nanosponges. These cyclodextrin based nanosponges can form complexes with different lipophilic or hydrophilic drug molecules and could used to improve aqueous solubility of poorly water soluble molecules, protect degradable substances and to achieve sustained delivery systems. By altering the degree of cross linking and the type of cross linker the polarity and dimension of polymer mesh can be easily tuned. The drugs can dispersed molecularly within the nanosponge and the drug releases as a molecule at target site by avoiding the dissolution step. Consequently the solubility of drug will be increased. Some studies also proven that these β-CD nanosponges are also able to hold the gases and acts as a reservoir for various types of gases[17].

Thakur et al[18] formulated nifedipine encapsulated with cyclodextrin due to its hydrophobic nature and short half life. They used both α- cyclodextrin and β – cyclodextrin and the β-cyclodextrin shows the better retention factor value. The PLGA used in this formulation shows high binding efficiency and results in better entrapment of drug. This study results shows that the retention time of PLGA increased with increase in the polymer ratio and by increasing the amount of cyclodextrin the hydration effect of the microsponge increases.

Swarupa Arvapalli et al[19] prepared nanosponges of gliplizide by using β-CD and HP- β-CD. The compatibility of the formulations was tested and established by FTIR and the surface morphology was examined by SEM. Increase in the drug polymer ratio increases the production yield. The drug content of formulations was resulted in the range of 94.4 to 98.6% and the entrapment effiency in the range 94.4 to 98.6%. The maximum release with HP- β-CD formulation was 99.71%.

Colon targeting:

Now-a-days people are suffering with colon diseases very common and these include irritable bowel disease, constipation, haemorrhoids, anal fissures, abscess, colitis, polyps. To treat these diseases colon targeting formulations are developed and these should prevent the release of drug in stomach and small intestine. To achieve the targeted delivery, the formulation should be coated with pH sensitive polymers[20].

Janaki devi et al[21] developed microsponge based colon specific delivery of mesalamine (5-amino salicylic acid) using three different acid resistant polymers Eudragit RS100, Eudragit S100 and Eudragit L100. Three different ratios were prepared by each polymer and the compatibility studies and surface morphology were studied. Initially microsponges were prepared and they compressed to tablets. The maximum drug release in the formulations was 81.27% in 24 hours and the release kinetics followed zero order kinetics.

Gastro retentive floating microsponges:

Gastro-retentive microsponge delivery system is a low-density system that has enough buoyancy to float over gastric contents and last in the stomach for a prolonged period. This type system is especially advantageous for the drugs which are absorbed from the stomach or the proximal part of the small intestine like furosemide and riboflavin and the drugs which have shorter half life. Complete absorption of the drug from the formulation is expected even at alkaline pH of intestine because the dissolved drug is available for absorption in the small intestine even after the gastric emptying occurs. The fluctuations in the plasma drug concentration will be minimized due to the sustain release effect, so the side effects associated with the concentration will also get minimized[22].

Imrankhan M Bhaishaikh et al[23] carried work on gastric floating microsponges by optimizing the targeted floating of lafutidine microsponge for site specific action on gastric ulcer. They used ethyl cellulose and Eudragit S100 polymers. The drug Entrapment efficiency of all formulations was in the range of 61.94 ± 1.7% to 86.74 ± 2.1%. As these are floating systems, the buoyancy effects of the formulation is most important and in this study the percent buoyancy of these microsponges formulations are in the range of 77.90% to 87.11%. The formulation with more amount of ethyl cellulose has more buoyancy effect. This study shows a new approach based on floating ability of microsponges for treatment of gastric ulcer.

Ocular microsponges:

Acetazolamide is an effective drug used from many years and to obtain the desired effect large amount of dose is used. Due to this many side effects like diuresis, gastrointestinal symptoms including cramping, epigastric burning, nausea, diarrhoea and metabolic acidosis. Acetazolamide is available in tablet form in market and topical administrative form is available. Several attempts were made but they are not successful. The main problem with topical application for eye is lachrymal drainage. To knockover these problems there is a need to increase in the contact time between drug and corneal surface by *in situ* gelling system which undergoes sol to gel transition.

M.M. Obiedallah et al.[15] done work on acetazolamide drug formulated as in situ gel, which mainly aimed to increase therapeutic efficiency and to overcome all the systemic side effects by its oral dosage form. In the preparation different ratios of ethyl cellulose polymer and drug are prepared. All satisfactory parameters for ophthalmics like eye irritation test, *In vivo* bioavailability on rabbits, gelation time, gelling capacity, rheological behaviour were evaluated and satisfactory results were obtained.

Microsponges in cosmetics:

Studies were conducted by Oxybenzone, a broad spectrum sunscreen agent widely used in the form of lotion and cream and formulated as a microsponge gel and the SPF results shows up to 25 when the marketed product is only SPF 20 and shows enhance topical retention on the site of application for extended period of time. Microponges due to their elegance, and uniform spreading with better colour entrapment this carrier system also found their use in cosmetics. Some studies show that these microsponges show usage in sunscreens to protect against UV-A and UV-B rays. Melanosponge-α which is a genetically engineered melanin designed to spread over the skin[7]. In some study a reduction in irritation by benzoyl peroxide was found when entrapped in microsponges and reported its commercial availability as cream for anti acne activity. Generally skin de-pigmentation products like hydroquinone are known for their high oxidation susceptibility. Studies found that when hydroquinone entrapped in microsponges shows improved stability[16].

Microsponges in bone and tissue engineering:

Bone-substitute compounds were acquired by mixing pre polymerized powders of polymethyl-methacrylate and liquid methyl methacrylate monomer with two aqueous dispersions of tricalcium phosphate grains and calcium deficient hydroxyl apatite powders. The final composites come into view as porous and acted as microsponges. Basic fibroblast growth factor engulfed in a collagen sponge sheet was sustainely released in the mouse sub-cutis endow to the biodegradation of the sponge matrix, and revealed local angiogenic activity in a dose-dependent manner. The injection of collagen microsponges engulfing basic fibroblast growth factor comprised a notable increase in the blood flow, murine ischemic hind limb which could never have been accomplished by the bolus injection of basic fibroblast growth factor. These results suggest that the importance and therapeutic usefulness of the type I collagen as a reservoir of basic fibroblast growth factor[24].

Nanoferrosponges:

Nanoferrosponge, a novel approach constituted the self-pore forming carriers having superior penetration to the targeted site due to the external magnetic trigger which impose the carriers to penetrate to the deeper tissue and then causing the removal of magnetic material from the particle leaving a porous system. These were developed by co-precipitating the polymer and magnetite. The ferrosponges showed high swelling ratios, together with excellent elasticity, hydrophilicity and swift response to an external magnetic stimulation for fast and repeatable swelling-de swelling (or expansion--contractile) operations[10].

TABLE 1: LIST OF SOME MARKETED PRODUCTS USING MICROSPONGES[12]

Product name	Content	Uses	Manufacturer
NeoBenz®Micro	Benzoyl peroxide, methyl methacrylate/glycol	Antibacterial properties and is classified as keratolytic	Intendis Inc. Morristown NJ07962 USA
Retin-A-Micro	0.1% and 0.04% Tretinoin, methyl methacrylate/ glycol dimethacrylate, Aqueous gel base.	Declination of fine lines and wrinkles, a noticeable improvement in the skin discolorations due to aging, and enhanced skin smoothness.	Biomedic, Sothys
Retinol cream, Retinol 15 Night cream	Retinol, Vitamin A	For the treatment of Actinic keratosis (AK), a typical precancerous skin condition caused by over-exposure to sun.	Dermik Laboratories, Inc. Berwyn , PA 19312 USA
Carac Cream	0.5% Fluorouracil, 0.35% methyl methacrylate / glycol dimethacrylate cross-polymer and dimethicone.	Visibly decline appearance of fine lines, wrinkles & skin discolorations associated with aging	Avon
Line Eliminator Dual Retinol Facial Treatment	Vitamin A	Improve fine lines, pigmentation, and acne concerns	Biophora
Salicylic Peel 20	Salicylic acid 20%	Improve fine lines, pigmentation and acne concerns.	Biophora
Salicylic peel 30	Salicylic acid 30%	Freeing the dead cells of skin while doing no damage to the skin	Biomedic
Dermalogica Oil Control Lotion	Niacinamide, Zinc Gluconate, Yeast Extract, Caffeine, Biotin,SalicylicAcid, EnantiaChlorantha Bark Extract.	To reduce oily shine on skin surface.	John and Ginger Dermalogica Skin Care Products
Ultra Guard	Dimethicone	To protect a baby's Skin from diaper rash, hypoallergenic and skin protectants	Scott Paper Company

FUTURE PROSPECTS OF MICROSPONGES

Microsponge drug delivery system holds a encouraging opportunity in various pharmaceutical applications in the forthcoming future as it has solitary properties like enhanced product performance and elegancy, prolonged release, enhanced drug release profile, reduced irritation, improved physical, chemical and thermal stability which makes it flexible to develop novel product forms. The real challenge in coming times is the development of the delivery system for the oral peptide delivery by varying ratio of polymers. The utilization of bio erodible and biodegradable polymers for the drug delivery is enabling it for the safe delivery of the active material. These carriers furthermore require to be developed for alternative drug administration routes like parenterals and pulmonary route. These particles can further be used as the cell culture media and thus can also be employed for stem cell culture and cellular regeneration in the body. Due to their elegance, these carrier systems have also found their application in cosmetics. These developments allowed researchers to utilize them variably. These novelties in formulation also open different ways for drug delivery.

CONCLUSION

With the increased urge for innovative and highly efficient pharmaceuticals, the market holds contemplate potential of microsponge technology and the adaptability they provide. As formulators consider advanced and creative ways to deliver active molecules, they can realize the full potential of these unique materials providing enhanced safety, improved stability, reduced side effects and improved ingredient compatibility. Complemented by novel development approaches and creative formulation techniques, Microsponge delivery system can be a winning strategy for upcoming generation of pharmaceuticals. Microsponges have a distinct advantage over the current conventional topical dosage forms for the treatment of tropical diseases as it is a unique technology for the controlled release of topical agents also useful for other targeting areas like Acetazolamide gel for ocular delivery, colon targeting, biopharmaceutical drug delivery and cosmetics as well. This reveals advantages over other products by non mutagenic, non toxic, non irritant. So microsponge drug delivery system has gain a lot of potential and is a very emerging field which is needed to be explored in the future with most research study.

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