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K Balamurugan
Assistant Professor,
Department of Pharmacy,
FEAT, Annamalai University,
Annamalai Nagar,
Chidambaram, Tamil Nadu,
India

Naresh Kshirasagar
Annamalai University,
Annamalai Nagar,
Chidambaram, Tamil Nadu,
India

P Govardhan
Vaagdevi College of Pharmacy,
Ramnagar, Hanamkonda,
Telangana, India

Correspondence
K Balamurugan
Assistant Professor,
Department of Pharmacy,
FEAT, Annamalai University,
Annamalai Nagar,
Chidambaram, Tamil Nadu,
India

Microsponges: As a drug delivery system

K Balamurugan, Naresh Kshirasagar and P Govardhan

Abstract
Microsponges are particulate drug delivery system composed of porous nature. They are small tiny sponges like spherical particles with large porous surface moreover they may heighten the stability by modifying the drug release pattern with reduced side effects. Microsponges Delivery System (MDS) can suspend or entrapped a wide variety of substance which act as carrier and can then be incorporated into a formulated product such as a gel creams or powder. The main aim of the formulation is to achieve desired concentration of the drug in the blood. Microsponges of its porous nature that are mostly used for topical application but recently been used for oral administration. Microsponges are design to deliver a pharmaceutical active ingredient in efficiently without adverse effects in sustained manner, one of the best feature of Microsponges is it has self-sterilizing property, numerous study has confirmed that Microsponges are non-irritation, non-mutagenic, non-allergic and nontoxic.

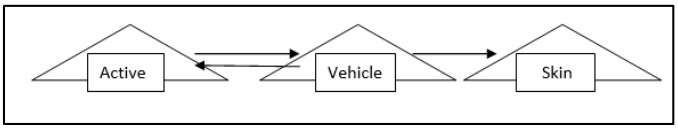
Keywords: Microsponges, sustained release, effective delivery, reduced side effects, local action

Introduction
Conventional formulations of transdermal applications of gels, ointments are available, such products release the drug called as Active Pharmaceutical Ingredient (API) upon application which lead to irritation, accumulation of large amount of drug due to high amount of release of drug from dosage form. The active ingredients can be applied directly to the skin, either in a considerably pure form or in combination with a liquid vehicle. Such direct application, however, is limited in a number of respects. First, direct application allows rapid evaporation of volatile active substance; second, application of the active substance in considerably pure form can often leads to sudden increase in blood plasma levels which leads to serious side effects such as toxicity and/or allergic reaction. Such adverse reaction can be minimized by dilution of the active ingredient in a suitable liquid carrier; the resultant dilution will also reduce the effectiveness of the final product. Care should be taken no to dilute the formulation more, which may leads to show sub therapeutic effect. For this reason, it would be desirable to provide delivery composition or system capable of providing controlled and prolonged delivery of active substances after they have been applied to the skin. Desirably, such delivery systems should also control toxicity which may be associated with the active substance. In topical dosage form API fail to reach the systemic circulation in sufficient amount and for certain period of time due to enzymatic degradation and dosage form design modules, which often results in poor patient compliance this problem can be overcome by design of novel drug delivery systems called as MDS.

The non-rigid polymeric beads are designed to release the active substance for prolonged time. The prolonged activity reduces the need to frequent reapply the active substance. Additionally, prolonged release reduces the possibility of toxicity and allergic reaction. The Microsponges approach was developed by Richard Won scientist; the delivery system is a patented polymeric sponge, porous spherical particles with entrapped drug in system. the actual morphological structure of Microsponges consists of interconnecting vacuum within a non- collapsible structure with a large porous surface through which the API are intended to release in the sustained manner.

The bead diameter is normally maintained in the range from about 5-100 µm. Average pore size of human skin is 5 microns, particle larger than 10µm remains on the skin surface, microsponges with 10 to 40 microns will provide best results and imparting a smooth fell to touch. Mechanism of action highlights the importance of formulation. Microsponges are proficient to absorb skin secretion subsequently reducing oiliness and shine from the skin. However, these particles are extremely minute, inert, imperishable spheres unable to pass through the skin, but they are arranged in the pores of the skin and slowly release the entrapped drug into the skin.

Furthermore, these formulations can prevent excessive accumulation of ingredient within the interior parts of the skin. The entrapped API 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, which will become unsaturated therefore, disturbing the equilibrium. This will start a flow of the active form the microspheres particles into the vehicle and from it to the skin. Moreover, most of the products is need are subjected to external application on the skin, which upon application release the drug slowly and act upon the external fungal/bacterial/viral infection, thereby local action is exerted. The active ingredient was depleted in the vehicle where again the different in concentration gradient appears help the active form to move from high concentration to low concentration called as diffusion by this mechanism the active entrapped in the microsponges more into the vehicle and form it to the skin until the vehicle is either dried or absorbed even after that the Microsponges particles retained on the surface release the active to the skin providing sustained release. Microsponges delivery system executes all those requirements by giving assurance of drug localization on the skin surface and within the epidermis without entering into systemic circulation to great extent. If the actives too soluble in the vehicle during the formulation that product will not provide the sustained release therefore while formulating microsphere, it is important to design the vehicle which as minimal soluble for the API. (Atmaram *et al*., 2015) [1].



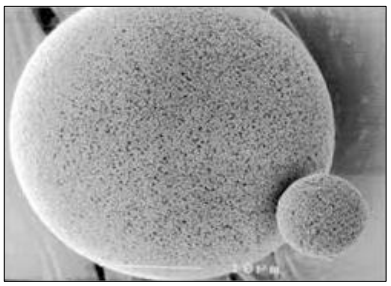


Fig 1: Ideal structure of Microsponge

Advantage of the Mds (Afrasim *et al*., 2016) [2].

1. MDS has stability over the wide range of pH from 1 to11.
2. MDS can withstand at high temperature up to 130 °C.
3. Loading efficiency of MDS is up to 60%.
4. MDS act as good adsorbent over the skin.
5. It will bypass first pass hepatic metabolism.
6. It will resist attack by moisture.
7. It will not undergo any unwanted reaction.
8. It can resist moderate oxidation & reduction.
9. MDS processes relatively longer half-life.

Suitability of Drug to Dosage Form (Marija *et al*., 2005) [3].

1. MDS are used to treating skin diseases like fungal infections include ringworm, athlete's Foot, Candidiasis (Yeast Infection), Sporotrichosis, and viral infection like herpes simplex virus infection, Varicella Zoster (chicken pox)Cytomegalovirus (Epstein bar virus).
2. MDS releases API for prolonged period *i.e*., sustained release, which are suitable for anti-inflammatory drug
3. API molecular weight should be very less *i.e.,* 600 g/mole which can penetrate easily.
4. Drug's $t_{1/2}$ should be less than less than 5hrs, which is suitable for sustained action of drug.

Ideal Properties of MDS (Marija *et al*., 2005) [3].

1. The structure of the Microsponges should not collapse i.e., it should maintain its structure integrity.
2. It should have slightly soluble property in water.
3. It should be stable when in contact with the polymerization catalyst and under condition of polymerization.
4. It should not react with monomer used in the formulation.
5. MDS should not increase the viscosity of the mixture during formulation.
6. Microsponges having particle size of 10-25 μm in diameter.

Formulation Consideration

The solubility of active in the vehicle must be limited otherwise the vehicle will deplete the Microsponges before the application to avoid cosmetic problems not more than 10 to 12 %w/w Microsponges must be incorporated into the vehicle.

Polymer design and payload of the Microsponges for the active must be optimized for required release rate for given period. (Namrata *et al*., 2013) [4].

Methods of Preparation of Microsponges

Liquid-Liquid Suspension Polymerization (Namrata *et al*., 2013) [4].

Microsponges are formulated by suspension polymerization technique in liquid-liquid system. Former the monomers are dissolved with active ingredients, which is them dispersed in the aqueous solution where API should have less soluble to solvent. Aqueous phase typically consists of additives such as surfactants and suspending agents in order to formulate into suspension. One the suspension is formed with droplets of the preferred size then; polymerization is started by the addition of catalyst or by increasing temperature these methods leads to development of reservoir type of system. During the process of polymerization an inert liquid immiscible with water which is completely miscible with monomer is used to form the pore network in some cases. Once the polymerization process is completed the liquid is removed leaving the Microsponges.

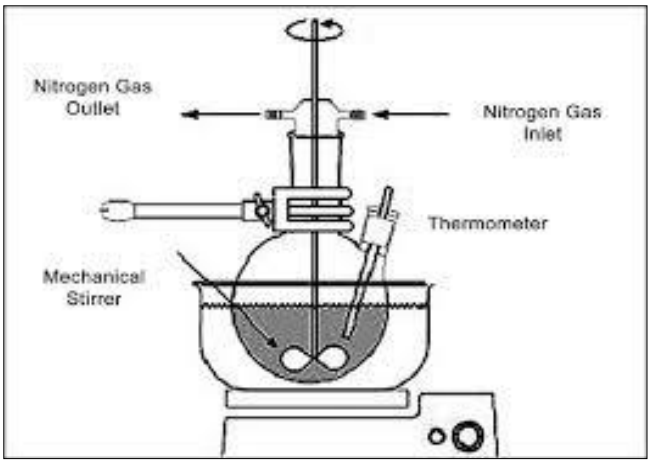


Fig 2: Liquid-Liquid Suspension Polymerization

Quasi-emulsion solvent diffusion (Namrata *et al*., 2013) [4].
Microsponges are formulated by a quasi-emulsion solvent diffusion method using an internal phase containing polymer which is dissolved in ethyl alcohol. Then the API is added to the polymer solution and dissolved under ultra-sonication at 35 °C and plasticizer is added in order to produce the plasticity. The inner phase is then poured into external phase containing polyvinyl alcohol and distilled water with continuous stirring for 2 hr. Then the mixer was filtered to separate the Microsponges. The obtained product was washed and dried in an air heated oven at 40 °C for 12 hr.

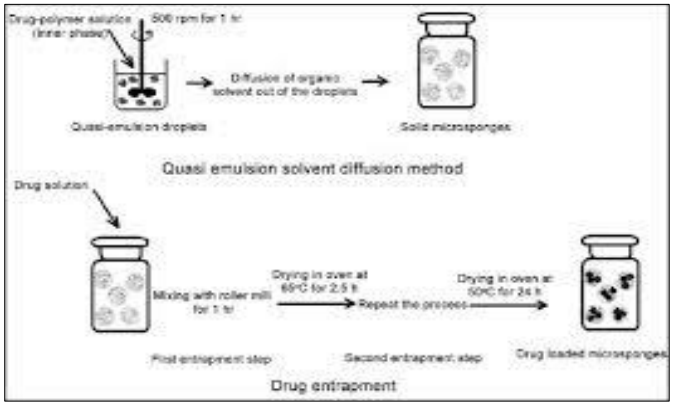


Fig 3: Quasi-emulsion solvent diffusion

Hypothetical Mechanism of Action (Neelam *et al*., 2011) [5].
The active ingredient is added to the vehicle as its solubility is merely soluble but not completely the microsponges have a porous nature (they do not have a continuous membrane) The active ingredient is free to move in and out from the particles and into the vehicle until equilibrium is attained when the vehicle become saturated. Due to this nature when the formulated Microsponges are applied to the skin, the active that is already in the vehicle will be absorbed into the skin. Because the vehicle can provide the initial dose and followed by sustained release. Initially vehicle should be treated with the drug when the microsponges are added to the vehicle it prevents from drug to leach out when added into the vehicle. The rate of active release will ultimately depend not only on the partition coefficient of active ingredient but also concentration gradient between polymers and the vehicle.

Drug Release Mechanism (Poornima *et al*., 2013) [6].
Release can also be enhanced by temperature pH, friction and moisture.

Temperature changes
The active ingredient is to viscous when it is entrapped in the microsphere on application to skin with increased temperature of skin, flow rate is also increased and therefore release also enhanced with less viscous, due to temperature viscous changes from gel to sol.

Pressure
Microsponges system releases active ingredient when it is pressed, thereby replacing the level of entrapped active ingredient onto the skin.

Solubility
Microsponges loaded with soluble/less soluble active pharmaceutical ingredient (API) will release the drug by diffusion mechanism but it depends upon the partition coefficient the ingredient between the microsponges and the external skin surface.

Characterization of Microsponges
Evaluation of Microsponges
Particle size analysis: (Sha-sha *et al*., 2013) [9].
Particle size and size distribution are evaluated using an optical microscope or electron microscope. This is a fundamental step; the size of the particles greatly affects the surface of the formulation and its stability. Particle size analysis of loaded and unloaded Microsponges can be performed by laser light diffractometric or any other suitable method. The values of (d50) can be stated for all formulations as mean size range. Cumulative percentage drug release from Microsponges of different particle size will be plotted against time to study effect of particle size on drug release from microsponges.

Determination of entrapment efficiency: (Sha-sha *et al*., 2013) [9].
The loading efficiency (%) is calculated using the following equation

$$\text{Loading efficiency} = \frac{\text{Actual drug content in microsponges}}{\text{Theoretical drug content}} \times 100$$

The production yield of the microsponges can analyzed by calculating accurately the initial weight of the raw materials and the final weight of the microsponges obtained.

$$\text{Production yield} = \frac{\text{Practical mass of micro sponges}}{\text{Theoretic mass Polymer drug}} \times 100$$

Morphology and surface topography of Microsponges: (Sha-sha *et al.*, 2013) [9].
For morphology and surface topography, various techniques have been used like photon correlation spectroscopy (PCS), Scanning electron microscopy (SEM), transmission electron microscopy (TEM) etc. SEM is used extensively for which prepared Microsponges are coated with gold–palladium under an argon atmosphere at room temperature and then the surface morphology of the Microsponges is studied.

Characterization of pore structure
Pore volume and diameter are dynamic in regulatory the concentration and duration of efficacy of the active ingredient. Pore diameter also affects the migration of active ingredients from microsponges into the vehicle. The rate of drug release from microsponges can affect by pore diameter of microsponges. Numerous porosity parameters of microsponges such as total pore surface area, intrusion-extrusion isotherms, pore size distribution, average pore size diameters, shape and morphology of the pores, bulk and apparent density are also being studied. (Sha-sha *et al*., 2013) [9].

Determination of pore diameter
The conventional method of measuring and expressing pore sizes, the pore diameter are calculated by B.E.T. nitrogen multipoint analysis and from the measurement of the pore volume by the mercury intrusion method. (Richard Won *et al*., US Patent 5145675).

Determination of true density
The true density of micro particles is measured using an ultra-pycnometer under helium gas and is calculated from a mean of repetitive identified obtained values. (Sha-sha *et al*., 2013) [9].

Polymer/Monomer composition
Polymer composition has great influence on the partition coefficient of the entrapped drug between the microsponges system and the vehicle and thus has effect on the rate of release of entrapped drug. Drug release from microsponges systems of different polymer compositions can be studied by plotting cumulative % drug release against time. As the concentration of polymer increases the rate of release becomes sustained manner. Thus, by altering the concentration of polymer one can achieve sustained release of drug. (Pushpa *et al.,* 2016) [7].

Drug-Polymer Compatibility studies
The drug-excipients compatibility studies are carried out in order to ensure that there is no reaction between the two ingredients, when formulated into a dosage form. These studies are commonly carried out by recording the differential scanning Calorimetry (DSC) of the chemicals *viz*., API and excipients individually and together and checking for any addition or deletion of peaks or troughs. For DSC approximately 5 mg samples can be accurately weighed into aluminum pans and sealed and can be run at a heating rate of 15°C/min over a temperature range 25–430°C in atmosphere of nitrogen. (FTIR) spectroscopy can also reveal the incompatibilities between the chemical moieties. (Pushpa *et al.,* 2016) [7].

Resiliency
Resiliency (viscoelastic properties) of Microsponges can be modified to produce bead lets that is easier or firmer according to the needs of the final formulation. Increased cross-linking incline to slow down the rate of release of drug. Hence resiliency of Microsponges is studied and optimized as per the requirements and amount of drug should reach to have optimum concentration of drug at site by considering release as a function of cross linking with time. (Pushpa *et al.,* 2016) [7].

***In-vitro* release studies**
In-vitro release studies must be being carried out using dissolution apparatus USP XXIII equipped with a modified basket consisted of 5µm stainless steel mesh. Dissolution rates were measured at 37 °C under 150 rpm 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 the content by suitable analytical method (UV-Visible spectrophotometer) at regular intervals of time. (Patil RS *et al.,* 2012) [10].

Evaluation of Microsponges Gels
Visual inspection
The organoleptic properties, are to be examined for color, texture, consistency, homogeneity, and physical appearance of gel containing microsponges were checked by visual observation. (Pushpa *et al.* 2016) [7].

pH measurement
The finalized gel formulation pH was recorded using digital pH meter. 5 g gel was dispersed in 45 ml distilled water at 27 °C and solution pH was measured. (Pushpa *et al.,* 2016) [7].

Spreadability studies
Spreadability was determined wooden block and glass slide apparatus. It consists of two slides upper movable slide and lower non-movable slide. Weights about 20 gm were added to the pan and time was noted for upper slide to separate completely from the fixed slides. Spreadability was then calculated by using the formula. (Yadav *et al*.)

$$S = M.L/T$$

Where, S= Spreadability; w= weight tide to upper slide; L= length of glass slide; T= time taken to separate the slide completely from each other.

Viscosity
The viscosity of the gel formulation was measured with a Brookfield viscometer using 1x model and cone number 01, with an angular velocity of 5 rpm at 25 ºC. An average of five readings was used to calculate viscosity. (Pushpa *et al*. 2016) [7].

Skin irritation studies
The score for erythema was calculated by the giving the, extend of irritation from one to ten, one represents least irritation and 10 represents serious irritation. (Rahul *et al*., 2012) [10].

In-Vitro release studies
The *in vitro* release of gel formulations should be carried out using Franz diffusion cells. The cellophane membrane (pore size 0.45 µm) or egg membrane was mounted onto the diffusion cell with 25 ml receptor compartment volume. PBS (pH7.4) was used as receptor medium, and the system was thermostatic to 37 ± 1 °C under stirring with magnetic bead inside. Aliquots of 1 ml volume were withdrawn at specific time intervals by maintaining sink condition simultaneously. Withdrawn aliquots were then diluted using receptor medium and analyzed by UV spectrophotometer. (Pushpa *et al*., 2016) [7].

Stability study
The optimized gel formulation was subjected to stability testing as per ICH norms. Gel was filled in clean, lacquered, collapsible aluminum tubes, and various replicates were kept at 40 ± 2 °C and 75 ± 5% relative humidity in a humidity chamber. Gel was assessed for change in appearance, pH and *in vitro* release profile at an interval of 30, 60 and 90 days. (Sha-sha *et al*., 2013) [9].

Table 1: Application of Microsponges delivery systems (Atmaram *et al.,* 2015) [1].

Category	Drug
Antifungal	Miconazole, Clotrimazole, Tioconazole, Terbinafine.
Antiviral	Acyclovir.
Anticholinergic	Dicyclomine.
Analgesic	Indomethacin.
Antiprotozoal	Tinidazole.
Musculoskeletal	Ketoprofen.
Antipyretic	Paracetamol.
Anti-wrinkle	Retinol.
Anti-acne	Benzoyl peroxide, Erythromycin.
Anti-inflammatory	Hydrocortisone, Lornoxicam, Naproxen.
Antidandruff	Zinc pyrithione, Selenium sulfide.
Skin depigmentation agent	Hydroquinone.

Table 2: Marketed dosage form available (Atmaram *et al.*, 2015) [1].

Delivery systems	Drugs
Gel's	Benzoyl peroxide, Fluconazole, Mupirocin, Diclofenac sodium, Acyclovir, Hydroxyzine, Terbinafine HCl
Lotion	Benzoyl peroxide.
Creams	Hydroquinone, Retinol.
Tablets	Indomethacin, Paracetamol, Chlorpheniramine, Ketoprofen, Fenofibrate, Flurbiprofen, Dicyclomine, Meloxicam,

Table 3: List of marketed products using microsponges drug delivery system

Product Name	Manufacturer
Carac Cream 0.5%	Dermik Laboratories, U.S.A.
Oil control lotion	Fountain Cosmetics
Oil free matte block spf20	Dermalogica
Retinol cream	Biomedic
Salicylic peel 20 & 30	Biophora
Sportcream RS & XS	Embil pharmaceutical Co. Ltd.
Micro peel plus	Biomedic
EpiQuin Micro	SkinMedicaInc
Lactrex 12 % Moisturizing Cream	SDR pharmaceuticals, U.S.A.
Retin-A micro	Ortho- Mc Neil Pharmaceutical, Inc
Retinol 15 night cream	Sothys

Conclusion

MDS holds significant potential in both pharmaceutical as well as cosmetic industries because of its release technique is novel and its ease of administration with fewer side effects, more research works are carried out to optimize its efficacy for the therapy. It is a unique technology for the sustained release of topical agents which act locally. It is originally developed for topical delivery of drug like anti-acne, anti-inflammatory, anti-fungal, anti-dandruffs, antipruritics, and rubefacients. Microsponges delivery system that can release its active ingredient on stimuli. Therefore, a microsponge has got a lot of potential in drug delivery technology today.

Prospects

A Microsponge consists of a myriad of interconnecting voids with in non-collapsible structure that can accept a wide variety of substance. The outer surface is typically porous allowing the flow of substance into and out of the sphere, scientist are more concentrating on delivery of sunscreen, antidandruff, anti-acne, agents which can also use in delivery of thermo labile substance such as vaccines, proteins, peptides, and DNA based therapeutics, now-a-days, it is also used in tissue engineering and in controlled drug delivery for therapeutic agents, which requires long duration of therapy Optimization techniques are carried out in these studies to get best out come from various formulation. Hence it requires lot of skills for developing novel formulation for the topical diseases. Some Microsponges based products are already approved; several others are currently under development and clinical assessment.

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