Review article

Herbal microsponge incorporated sunscreen gel: A novel strategy

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ABSTRACT

Different dermatological disorders have different effects on the lives of patients. Recently microsponge formulations have been used to treat several dermatological complications. Microsponges are basically tiny sponge-like spherical particles with a porous surface having a valuable and attractive effect on topical delivery. The side effect of the used drug can be reduced, bioavailability can be increased, and the drug release can be modified. Microsponges can be used in different bases like gel, lotion, ointment and even in powder form. Microsponges used in sunscreen gel are now very popular. Excessive UV exposure leads to different pathological conditions like skin burns, erythema, skin carcinogenesis, etc., The microsponge sunscreen gel protects our skin from all these skin problems and most importantly, with a very less amount of side effects compared to others. Moreover, microsponges are very much cost effective, easy to handle, can deliver a minimum dose of drug and enhance the stability.

Keywords: Microsponges; erythema; skin carcinogenesis; ointment; sunscreen.

INTRODUCTION

Microsponges, sponge-like polymeric delivery systems, are used to stabilize the drug and its delivery at a lower dose. They are capable of absorbing skin secretions; thus, the oiliness of the skin can be reduced. Being inert, very small in size, and indestructible spheres, microsponges are not able to penetrate through skin (1).

Microsponge delivery systems can overcome the problem of unnecessary accumulation of pharmaceutical ingredients within the epidermis and dermis layer of the skin. The irritation of effective drug can be reduced by using microsponges without reducing their efficacy. Different types of polymers are used in the preparation of microsponge like ethyl cellulose, Eudragit RS 100 etc., Depending on smoothness, microsponges are different in size i.e., 5-300 µm in diameter. A size of 25 µm diameter possesses about 250000 pores approximately (1).

Medicinal plants which are extremely rich in medicinal values are used for treating several disorders. Medicinal plants have some secondary products like alkaloids, steroids and tannins that are responsible for physicochemical action in humans. Additionally, the secondary metabolites have several uses such as anti-inflammatory, anti-ulcer, anticonvulsant, sedative, anti-psoriatic, anti-tumor, anti-microbial etc., (1). In the formulation of the microsponge, the herbal extract can be used by using different methods like quasi-emulsion solvent diffusion method (1). Almost all microsponges are prepared by loading the drug into it and the best one is the preparation of hydrogel of herbal extracts incorporated microsponges. These enhance the efficiency of any dermatological agent and reduce the local adverse effects. The microsponges allow drug to be present in the skin for a prolonged period. Controlled release of the entrapped drug can be permitted by microsponges that lead to less deposition of the API in the dermis and epidermis. Microsponges can be formulated in topical bases like gel, ointment, emulgel, etc. Surrounding bases can affect the extent of drug release from microsponges.

Sunscreen has different kinds of photoprotective agents which can prevent and minimize the damaging effects of UV rays. When microsponges are introduced into the sunscreen, it can increase its effectiveness and drug release properties also. Skin tolerability to UV rays can also be increased by sunscreen. UV radiations can cause inflammation, photoaging, and especially sunburn which is one of the most common causes of skin damage nowadays. Sunburn happens mostly to white-skinned people therefore, in the USA, 34.4% of adults are affected by sunburn (2). Skin cancer like squamous and basal cell carcinomas are also caused by UV radiation. Due to this reason, photoprotective agents like sunscreen are used worldwide therapeutically or prophylactically.

Composition of microsponges

Microsponge 'cage' can be formulated by various polymers used in fabrication of microsponges. Different types of polymers can be used in the preparation of microsponges. However, among of all these, Eudrajit RS100 is the most used because of its

versatile nature. Polymethacrylate category polymers are FDA approved and safe, non-toxic. Ethyl cellulose can be used as a foundation material of microsponges. They are used for engineering of microsponges for their non-toxic, non-irritating, & non-allergic nature. Sometimes biodegradable polymers are used to prepare microsponges. Additionally, instead of polymers, some other ingredients are also used to prepare the microsponges. Triethyl citrate can be used as a plasticizer. Sucrose, pregelatinized starch is sometimes used to increase the drug release rate and polyvinyl alcohol, cellulose ethers can be used as emulsifying agents for maintaining the viscosity of aqueous phase (3).

Advantages of microsponges

Following are some advantages of microsponges over other delivery systems (4)

a. Microsponges are stable up to temperature of 130°C.
b. Stable between the pH range of 1-11.
c. Cost effective.
d. Wide and vast range of chemical stability.
e. The microscopic spheres can absorb sebum secretions, reduce oil, and shine from the skin (5; Fig.1).

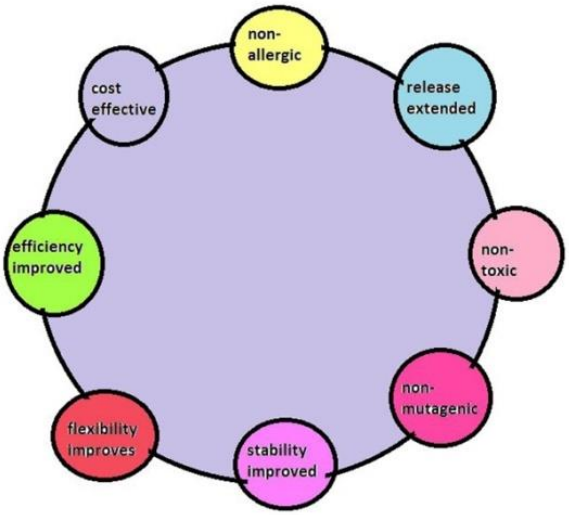

Fig. 1: Schematic diagram of several advantages of microsponges

Superiority of microsponges compared to other formulations

Microsponge provides extended release of drugs, decreases irritation of skin, and improves patient compliance. The microsponge formulations are thermally, chemically, and physically stable (6,7). They can absorb skin's oiliness and greasiness, protect the skin and are also affordable. The benefits of microsponges are discussed below.

Advantages of microsponges in comparison with conventional formulations

Conventional formulations such as ointment, creams, and gels are commonly used in cuts, wounds, and bleeding on the epidermis layer of the skin (7). The conventional formulations are mostly absorbed on the outer layer of the skin and cannot penetrate through the deeper layer. On the other hand, microsponge need a comparatively lesser amount of API to show their therapeutic effects thus the side effects can be reduced; it can penetrate and get absorbed through the dermis layer of the skin (Fig. 2).

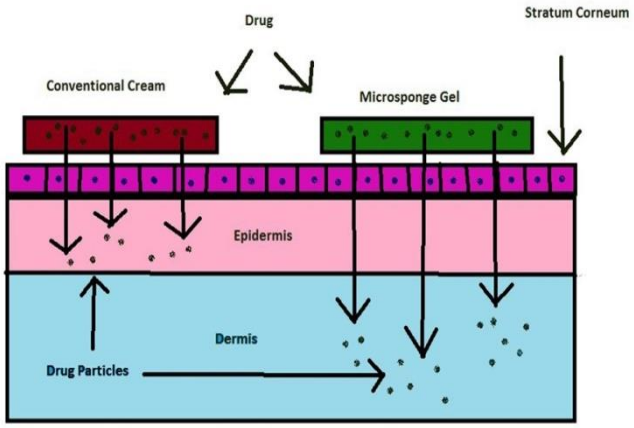

Fig. 2: Difference between the conventional cream and microsponge gel

Advantages over microcapsules and liposomes

Microcapsules can control the rate of drug release thus the dosing frequency can be minimized. However, when the wall of microcapsule ruptures, the whole drug present inside the capsules is released (8). On the other hand, the liposomes have solubility problems in the certain pH range however, the microsponge delivery system is totally stable in it. Liposomes need preservatives whereas microsponges are stable without it.

Advantages over ointment

The ointment has low permeation efficiency so high concentration of the drug is required. Though it gives proper therapeutic action however, it has several side effects such as irritation, sensitization, and allergic reactions on the skin surface for the high concentration (8,9). On the other hand, microsponge has no side effects, with better efficacy than ointments.

Different methods of preparation of microsponges

Liquid-liquid suspension polymerization

In this method, a suitable solvent is taken, and a monomer is dissolved in it along with active constituents. Then additives and other ingredients

present in the aqueous phase are added to the monomer solution (10,11). Polymerization is introduced by increasing the temperature and then a sphere is formed. Finally, the solvent is evaporated to get porous and spherical microspheres.

Quasi-emulsion solvent diffusion method

There are two phases in this method, one is the inner phase and the other one is the outer phase. The internal phase has volatile solvents such as ethanol, dichloromethane or acetone and the outer phase consists of PVA solution or water. In the internal phase the drug extract is introduced. Dichloromethane or triethyl citrate provides the plasticity for the formulation (12). Firstly, the internal phase is formulated with the solvents [ethanol and dichloromethane (1:1)] and ethyl cellulose and the drug extract at 60°C temperature and then added to the external phase with continuous stirring at room temperature (RT) to form microsponges. Then to separate the microsponges the obtained microsponge mixture is filtered and washing would be done. Separated and washed microsponges are then dried at 40°C in a vacuum oven for 24 hours (13; Fig. 3).

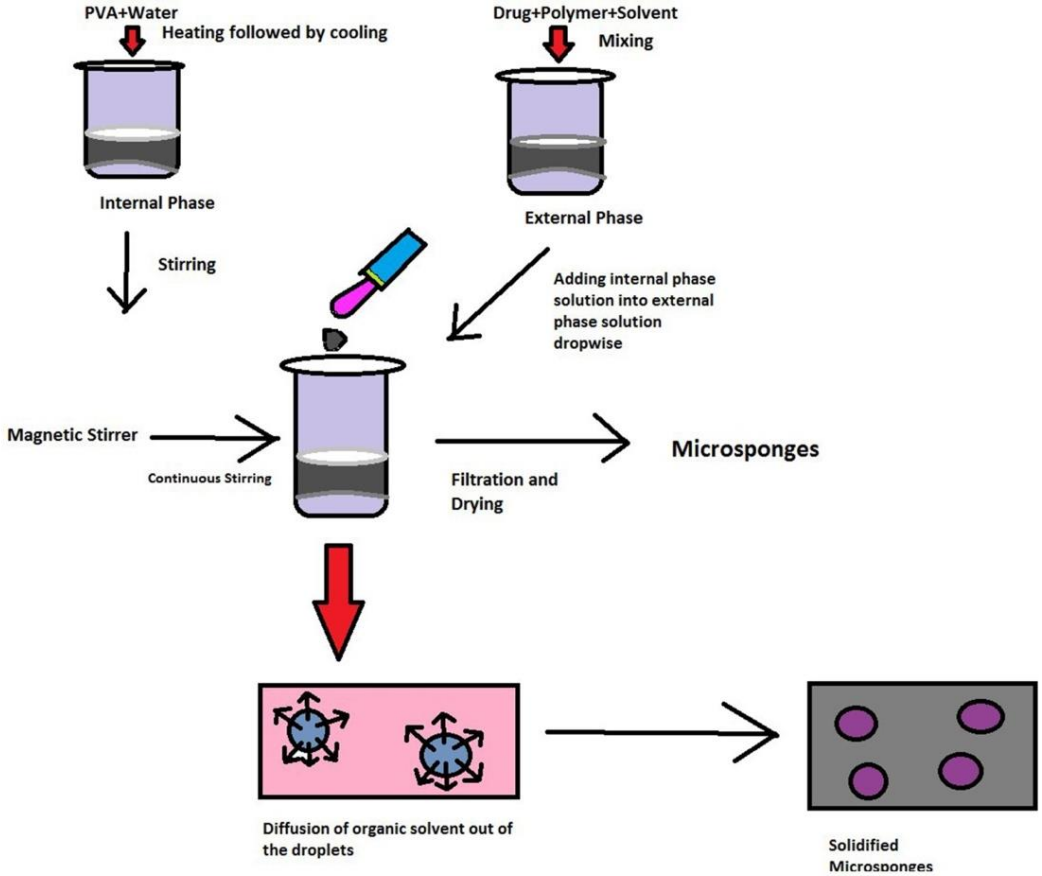

Fig. 3: Fabrication of microsponges using quasi-emulsion solvent diffusion method

Sun screening agent and its mechanism of action

There are different types of sun screening agents that can be used in sunscreen formulations, for example, talc, zinc oxide, titanium oxide etc. UV sun screening agents such as bemotrizinol, dometrizole trisilox etc. are very much popular. Sun screening agents have several mechanisms to protect the skin from direct sunlight either by blocking or reflecting or scattering the UV rays. Organic compounds are incorporated into the sun screening agent to protect the skin from different types of UV rays and inorganic compounds are added to increase the efficiency of the sunscreen formulation by enhancing the Sun Protection Factor (SPF).

An ideal sun screening agent should be safe, non-irritating, and chemically inert and protect the skin from both UVA and UVB rays (14). Sunscreen can protect the skin from UV rays as well as reduce the cumulative health risk caused over a period.

Method of application of sunscreen

Product labeling shows us that the sunscreen should be applied 15 minutes to 30 minutes before going outdoors. However, recently some sunscreens are available which protect our skin immediately against UV radiation. Recent studies showed that sunscreen can remain on our skin at its desired SPF for as long as 8 hours and reapplication is suggested, if the sunscreen is removed by sweating, friction and water immersion (15). Spray sunscreens are less popular than the cream-based sunscreen because the wind can disperse the sunscreen, resulting in inadequate application and aerosolized sunscreens are flammable.

Ideal characteristics of a microsponge sunscreen

The ideal characteristics of a sunscreen are as follows (16)

- Absorbs light over a range of 280 mμ-320 mμ.
- Resists water.
- Stable to heat, perspiration, and light.
- Odorless or might have acceptable odor.
- Non-staining, non-toxic and non-irritant.
- Neutral and soluble in suitable vehicles.

Preparation of microsponge sunscreen gel

Accurate quantities of carboxy polymer (gelling agent), preservatives are carefully weighed. Then the polymer is dispersed into distilled water and stirred to naturally form a gel base. Preservatives already dissolved in suitable solvent are then added and the mixture is stirred until it becomes homogeneous (17). Microsponge is properly introduced into the gel base and the optimum pH should be accurately adjusted using a suitable pH adjuster.

Parameters for microsponge characterization

Development of microcarriers relies on the characterization of microsponges. Basically, they are characterized by employing the methodologies discussed below (18).

Compatibility studies

It is important to check the compatibility between the drug and the excipient. Fourier Transform Infrared (FTIR) spectroscopy and Differential Scanning Calorimetry (DSC) are mainly used to determine the interaction between the drug and excipients (19-21). Thermal analysis and drug crystallinity can be analyzed by DSC and Powder X-ray Diffraction (pXRD).

FTIR

FTIR spectroscopy is performed to check stability, purity, and drug-excipient interaction of the developed microsponges. Drug-excipient interaction and purity of diclofenac diethylamine in microsponges was reported by Bhanu *et al.*, (19).

DSC

DSC is a much easier and cheaper process of analysis compared to other available analytical methods. DSC is used to determine the thermograms that elucidate the purity and interactions of API and other pharmaceutical ingredients (22,23). Due to melting, decomposition and weight loss of samples, different exothermic and endothermic peaks are obtained and analyzed.

pXRD

pXRD analysis is crucial to study the physicochemical properties of the developed microsponge. pXRD assesses changes in physical form (crystalline or amorphous) of drug and interactions between the ingredients in microsponges. Information on thermal stability of drug in microsponge formulation can also be acquired by pXRD analysis (23).

Size and porosity measurement of microsponge

Porosity studies are determined for checking nano activities formed in microsponges. Pore volume, diameter and structure are determined in these studies. Mercury Intrusion Porosimetry can be used for determining porosity. Drug encapsulation and release can be affected by pore size and volume. However, porosity studies receive much attention from the researchers (19,20). Formulation structure depends on the particle size. Microsponges, the free-flowing particles, have a diameter of 10μm-25μm. Greater particle size may cause grittiness and can change porous networks. The optical microscope is used for determining the mean size of the microsponges (20,21).

Surface topography and morphology

Morphology and surface topography are determined by Scanning Electron Microscopy (SEM), Field Emission Scanning Electron Microscopy (FESEM), Transmission Electron Microscopy (TEM) etc. SEM and TEM are used to determine the morphology and particle size of microsponges. The characterization of microsponges without SEM is incomplete as it reveals the size, shape, and nature of microsponge formulation (21).

Loading and entrapment efficiency

This study is used to determine the microsponge's efficiency to load and entrap the drug into it. To determine the loading and entrapment of microsponges, they are dispersed into a suitable solvent to release the drug. The drug dispersion is centrifuged to facilitate the solubilization (23). The percent of loading efficiency is calculated by the formula below:

Loading Efficiency = (Actual drug amount in microsponge /Initial drug amount) × 100

The percentage entrapment efficiency (EE) is calculated by the formula,

% EE = (Amount of drug entrapped in the microsponge/ Total amount of drug used) × 100

In vitro release study

Based on the microsponge drug:polymer ratio, drug release study is done. The rise in drug: polymer ratio specifies that the polymer amount is also increased in microsponges. The matrix network can be thickened by adding more polymer in microsponges which also minimizes the drug release. For performing the drug release, suitable dissolution apparatus is used (19). In dissolution study, samples are collected at various

time intervals and analyzed with different analytical approaches.

Rheological characterization

A controlled stress rheometer is employed to determine the rheological measurements of microsponge gels at a varying temperature (19).

Resiliency

By increasing or decreasing the required pharmaceutical ingredient, the viscoelasticity of the formulation can be modified to control the flow and deformational behaviour of the formulation. Drug release rate can be reduced by enhancing the concentration of cross-linking agents (19).

Stability studies

The ICH guidelines are followed to determine stability of the microsponge loaded system at specific storage conditions. Physical properties such as pH, physical appearance, drug content, drug release etc. are determined at varying intervals of time (20,21).

Characterization of microsponge sunscreen gel formulation

pH Measurement

The pH of the topical formulation should be similar with the pH of skin considering different therapeutic factors. Hence pH measurement is crucial for any microsponge gel formulation (24).

Spread ability test

Every topical preparation should have good spread ability. For the determination of spread ability, a simple apparatus is used. It consists of two glass slides of similar size and dimensions. The spread ability is determined based on "slip" and "drag" characteristics of the gel and can be represented as follows (24):
S=M. L/T, where S= Spread ability; M= Mass tied to upper slide (g); L=length of the glass slide (cm); T= Time taken by the slide to move the distance.

Drug content

Accurate quantities of microsponge gel can be dissolved in phosphate-buffered saline (pH 7.4). The solution is then shaken for 2 hours, filtered, and then measured spectrophotometrically (25).

Viscosity test

Viscosity denotes the resistance of gel to flow when applied on the surface of the skin (26). It can be determined by using a viscometer supplied with spindle 3 and 4.

Skin irritation test

This test can be applied to animals, especially rabbits. *In vitro* acute dermal irritation study is used for identifying and evaluating the toxic reactions when the test material comes in contact with skin. New Zealand white rabbit is commonly used for this purpose (26).

Therapeutic application of microsponges

Microsponges have a wide range of applications in the field of therapeutics. It can be used in various forms like topical formulations, in the treatment of different skin diseases and disorders. Most recently, it has also been used in the field of bone tissue engineering. Microsponges are self-sterilizing products, therefore, they can be used in cardiovascular engineering. Nanosponges, nanoferrosponges, and porous microbeads are advanced microsponges that are used for delivering hydrophilic and hydrophobic drugs orally and topically and have better drug releasing activity as compared to microsponges. These advanced microsponges are designed to enhance drug delivery and to reduce skin irritancy (27). Nanoferrosponges provide better penetration and delivery of drugs into the targeted site as it is driven by an external magnetic trigger.

Microsponges in arthritis

For delivering of diclofenac, topical application of microsponge has been demonstrated in arthritis. The diclofenac containing microsponges which is applied topically can overcome first pass metabolism and gastric irritation thus improving the patient's compliance. By using quasi emulsion solvent diffusion method microsponges gel of diclofenac diethylamine was formulated and showed prolonged and controlled release for arthritis therapy (24).

Microsponges in skin protection

Sunscreens prevent UV ray exposure thereby protecting our skin from sunburns and various types of cancers such as basal carcinoma and malignant melanoma. Oxybenzone microsponge sunscreen was developed with better UV protection ability and SPF value (28).

Microsponges in acne

Acne represents a major skin problem with associated skin irritation. Rizkalla *et al*., developed an anti-acne cream which consists of miconazole nitrate. They prepared microsponges with Eudragit RS-100 to obtain prolonged release and incorporated it into the cream. Studies showed that microsponges gave prolonged release of drug (78.28%) up to 8 hours, but the conventional formulation was exhausted within 4 hours and released 83.09% of drug (22).

Microsponges in psoriasis

Psoriasis is a skin inflammatory disease. Microsponges are also used in psoriasis treatment. A research study incorporated clobetasol propionate into microsponges for psoriasis treatment (27). They observed the release of the drug for up to 12 hours as compared to that of 2.5 hours in the conventional form.

Microsponges in skin infection

Microsponges have also been formulated as creams to treat various skin infections and skin diseases like atopic dermatitis and eczema. Amrutiya *et al*., incorporated mupirocin into microsponges and developed a stable formulation which was also non-irritant (29).

Microsponges in diabetic wound healing

Nebivolol loaded microsponges were developed and used to treat diabetic wound healing. The drug is basically a vasodilator and restores the function of endothelial cells in diabetic wounds. Particularly, the drug provides an optimal environment in diabetic wound healing process facilitating closure of the wound (30).

Microsponges in fungal infection

Microsponges anti-fungal gel formulations have shown to increase the drug release duration as compared to drug loaded plain gel. Oxiconazole nitrate microsponges formulations have been developed to treat fungal infection and a controlled release of the drug up to 12 hours was obtained (28).

Microsponges in melanoma

Hydroquinone microsponges (containing 4% hydroquinone and 0.15% retinol) were developed and used in the treatment of pro-inflammatory hyperpigmentation (PIH) and melanoma. Sustained release of the drug with minimum skin irritation was obtained and only one patient had an allergic reaction to the formulation (21).

Microsponges in colon cancer

Microsponges formulation of 5-fluorouracil (5-FU), a chemotherapeutic agent, has been developed and used in the treatment of colon cancer. The formulation improved the activity of drugs by increasing the relative accumulation in tumour regions and by reducing the toxicity (27). By comparing the drug release study, pure 5-FU released drugs up to 20 minutes, while the microsponges showed release up to 5 hours.

CONCLUSION

One of the most unique and important technologies for controlled release of drug is microsponge drug delivery system. This system reduces side effects, enhances formulation flexibility, and increases elegance. This delivery system currently can also be used in cosmetics, especially in sunscreen gel formulation. The herbal microsponge gel has various advantages over others. The gel can exhibit good physical and chemical characteristics such as appearance, consistency, pH, and skin irritancy test. Additionally, it can show anti-microbial activity. The herbal gel can easily be prepared and stored at room temperature. It is considered as a suitable candidate for new herbal antimicrobial pharmaceutical preparation and can be used as an alternative to the conventional antimicrobial topical gels. Sunscreen with microsponges is very much effective for controlling various skin diseases like skin cancer especially, for people with fair skin. It can also be used to prevent other photo damaging effects. Hence, this system of drug delivery proves to be a potential delivery system in the field of pharmaceutical applications.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

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