INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

Review Article

MICROSPONGE DRUG DELIVERY STSTEM FOR TOPICAL DELIVERY-A REVIEW

Sruthi TP[1]*, Noby Thomas[1], Daisy PA[1] and Betty Carla[2]

[1]Department of Pharmaceutics, St.Joseph's College of Pharmacy, Dharmagiri College Campus, Cherthala, Alappuzha-688524, Kerala, India.

[2]St.Joseph's College of Pharmacy, Dharmagiri College Campus, Cherthala, Alappuzha-688524, Kerala, India.

ABSTRACT

Microsponge Delivery System (MDS) is a unique technology for the controlled release of topical agents and consist of macro porous beads, typically 10-25 microns in a diameter, loaded with active agent. Microsponges are porous, polymeric microspheres that are mostly used for prolonged topical administration. Microsponges are designed to deliver a pharmaceutically active ingredient efficiently at minimum dose and also to enhance stability, reduce side effects, and modify drug release profiles. When applied to the skin, the Microsponge releases its active ingredient on a time mode and also in response to other stimuli (rubbing, pH, etc.). MDS technology is being used currently in cosmetics, over -the – counter (OTC) skin care, sunscreens and prescription products. Conventional preparations have some disadvantages like unpleasant odour, greasiness and skin irritation. These problems are overcome by microsponge delivery system. Microsponge based drug delivery system produces controlled released action. It also produces site specific and target organ action produced. Microsponge (MDS) mainly developed in topical drug delivery as well as oral controlled delivery system. It also used in cosmetic formulations.

Keywords: Microsponge delivery system, Transdermal penetration, Polymeric delivery systems, Liquid-Liquid Suspension Polymerization, Quasi-Emulsion Solvent Diffusion.

INTRODUCTION

Conventional topical formulations are intended to work on the superficial layers of the skin. Normally, upon application such products release their active ingredients producing a highly concentrated layer of active ingredient that is quickly absorbed. Thus, need exists for a system to increase the amount of time that an active ingredient may remain present either on skin surface as well as within the epidermis, at the same time minimizing its transdermal penetration in the body. Microsponge delivery system (MDS) fulfills all these requirements and controls the release of drugs onto the epidermis with an assurance that the drug remains localized on the skin surface or within the epidermis and does not enter the systemic circulation in major amounts. They also offer an advantage of programmable release and are biologically safe. Additionally, this technology offers entrapment of active pharmaceutical ingredients which contribute towards reduced side effects, improved stability, increased elegance and enhanced formulation flexibility.[1, 2]

Topical Delivery Systems (TDS)

The purpose of topical dosage form is to conveniently deliver drugs across a localised area of the skin. To develop an ideal dosage form one must take into account the flux of drug across skin, retention of the dosage form and the patient acceptability of the formulation. The problem of formulating a drug is complex because of the wide diversity of drug solubility in vehicle components and the vast range in cutaneous fluxes. When it comes to the delivery of a drug to a specific site, topical formulations are probably among the most challenging products to develop. An effective topical formulation needs to provide a stable chemical

environment in order to accommodate multiple compounds that may have different, if not incompatible, physicochemical characteristics. Once applied, a topical formulation must interact with the skin environment, which can influence the rate of the release of the compound in order to achieve adequate skin absorption. The excipients themselves will exert additional physical effects on the skin, such as drying, occluding, or moisturizing. These insights have resulted in new delivery systems that are capable of enhancing the efficacy, tolerability, and cosmetic acceptability of topical formulations.[3]

Microsponge Drug Delivery System

The microsponge technology was developed by Won in 1987, and the original patents were assigned to Advanced Polymer Systems. Microsponges are porous microspheres having myriad of interconnected voids of particle size ranging between 5-300 µm. These microsponges have capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, and anti-infectives, anti-fungal and anti-inflammatory agents etc. and are used as a topical carrier system. Further these porous microspheres with active ingredients can be incorporated into formulations such as creams, gel, lotions and powders and share a broad package of benefits. Microsponges consist of non-collapsible structures with porous surface through which active ingredients are released in controlled manner. Depending upon the size, the total pore length may range up to 10 ft and pore volume up to 1 ml/gm. When applied to the skin, the microsponge drug delivery system (MDS) releases its active ingredient on a time mode and also in response to other stimuli (rubbing, temperature, pH, etc.). Microsponges have the capacity to adsorb or load a high degree of active materials into the particle or onto its surface. Its large capacity for entrapment of actives up to 3 times its weight differentiates microsponges from other types of dermatological delivery systems. Recently, microsponge delivery system has been successively addressed for the controlled release of drugs onto the epidermis with assurance that the drug remains chiefly localized and does not enter the systemic circulation in major amounts and resulted in a new creation of highly efficacious and well tolerated novel products.

The fundamental appeal of the microsponge technology stems from the difficulty experienced with conventional formulations in releasing active ingredients over an extended period of time. Conventional dermatological and personal care products typically provide active ingredients in relatively high concentrations but with a short duration of action. This may lead to a cycle of short-term overmedication followed by long-term under medication. Rashes or more serious side effects can occur when active ingredients penetrate the skin. In contrast, microsponge technology allows an even and sustained rate of release, reducing irritation while maintaining efficacy. Microsponges are capable to absorb skin secretions consequently, reducing oiliness and shine from the skin. Microsponge particles are extremely small, inert, indestructible spheres that do not pass through the skin. To a certain extent, they accumulate in the tiny nooks and crannies of skin and slowly release the entrapped drug, as the skin needs it. The microsponge system can also avoid unnecessary accumulation of ingredients within the epidermis and the dermis. Potentially, they can reduce considerably the irritation of effective drugs without reducing their efficacy. Resembling a true sponge, each microsphere consists of an innumerable of interconnecting voids within a non-collapsible structure with a large porous surface. When it is applied to the skin, the drug release can be controlled through diffusion. This controlled release of active ingredient onto skin over time is an enormously important tool for providing the benefits of enhanced product efficacy, tolerability, mildness and lessen the irritation usually associated with powerful therapeutic agents like retinoids or benzoyl peroxide etc. and extended wear to a wide range of skin therapies. This system has been utilized for the improvement of performance of topically applied drug. MDS technology is now being presently used in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products very popularly.

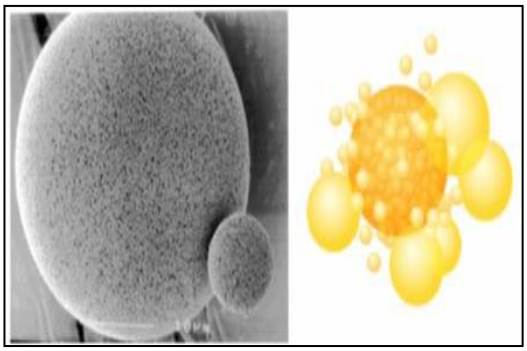

Fig. 1: Microsponge

Microsponges for Topical Delivery

The ability of a drug in a topical formulation to permeate the skin and to exert its effect is

dependent on two consecutive events. The drug must first diffuse out of the vehicle to the skin surface and then it must permeate through barrier to the site of action. Both steps are dependent upon the physicochemical properties of the drug; vehicle and barrier. The stratum corneum provides the principal barrier to the percutaneous permeation of topically applied substances. Several predictable and reliable systems were developed for systemic delivery of drugs under the heading of transdermal delivery system (TDS) using the skin as portal of entry. It has improved the efficacy and safety of many drugs that may be better administered through skin. But TDS is not practicable for delivery of materials whose final target is skin itself. Controlled release of drugs onto the epidermis with assurance that the drug remains primarily localized and does not enter the systemic circulation in significant amounts is an area of research. Topical application of drugs suffers from many problems. Ointments, which are often aesthetically unappealing faces the problems like greasiness, stickiness etc. and often results into lack of patient compliance. These vehicles require high concentrations of active agents for effective therapy because of the low efficiency of delivery system, resulting into irritation and allergic reactions in significant users. Other drawbacks of topical formulations are uncontrolled evaporation of active ingredient, unpleasant odour and potential incompatibility of drugs with the vehicles. Thus, there exists the need for system to maximize amount of time that an active ingredient is present either on skin surface or within the epidermis, while minimizing its transdermal penetration into the body.

The Microsponge systems are based on microscopic, polymer-based microspheres that can bind, suspend or entrap a wide variety of substances and then be incorporated into a formulated product, such as a gel, cream, liquid or powder. Like a true sponge, each microsphere consists of a myriad of interconnecting voids within a non-collapsible structure that can accept a wide variety of substances. The outer surface is typically porous, allowing the controlled flow of substances into and out of the sphere. Several primary characteristics, or parameters, of the microsponge system can be defined during the production phase to obtain spheres that are tailored to specific product applications and vehicle compatibility.

Benefits of Microsponge Technology

Microsponge technology offers:

- Enhanced product performance.
- Extended release.
- Reduced irritation and hence improved patient compliance.
- Improved product elegancy.
- Improved oil control as it can absorb oil up to 6 times its weight without drying.
- Improved formulation flexibility.
- Improved physical and chemical stability.
- Flexibility to develop novel product forms.
- In contrast to other technologies like microencapsulation and liposomes, MDS has wide range of chemical stability, higher payload and are easy to formulate.
- Microsponge systems are non-irritating, non-mutagenic, non-allergenic and non-toxic.

Salient Features of Microsponges

- MDS are stable over range of pH 1 to 11.
- These are stable at the temperature up to 130˚C.
- These are compatible with the majority of vehicles and ingredients.
- Self sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.
- These systems have higher payload up to 50 to 60%.
- These are free flowing and can be cost effective.

Characteristics of the Materials Entrapped in Microsponges

Most liquid or soluble ingredients can be entrapped in the particles. Actives that can be entrapped in microsponges must meet following requirements

- It should be either fully miscible in monomer as well as capable of being made miscible by addition of small amount of a water immiscible solvent.
- It should be inert to monomers and should not increase the viscosity of the mixture during formulation.
- It should be water immiscible or nearly only slightly soluble.
- It should not collapse spherical structure of the microsponges.
- It should be stable in contact with polymerization catalyst and also in conditions of polymerization.

Advantages of Microsponges

Microsponges have several advantages which are explained below:

- **High Surface Area**

A 25µ sphere can have a total pore length of about 10 ft with a pore volume of about 1 ml/gm and can have up to 25,000 pores. This provides an extensive surface area for high entrapment.

- **Controlled Release of Actives**

Because of the entrapment and adsorption of actives onto the polymeric cage, the release of actives is sustained. This facilitates the formulation of skin irritants or actives with short time of action, which otherwise may require re-application every few hours.

- **Simple Production Methodology**

The production of such microsponges is relatively simple in scaling up and hence there is a higher potential for commercialization.

- **Range**

Microsponges can be customized to modulate their properties and make them suitable for a specific purpose. The various parameters that can be changed include particle size, pore characteristics and hardness.

Advantages of Microsponges over Other Formulations

1) Advantages over Conventional Formulations

Conventional formulations of topical drugs are intended to work on the outer layers of the skin. Such products release their active ingredient upon application, producing a highly concentrated layer of active ingredient that is rapidly absorbed. When compared to the conventional system, microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Potentially, the microsponge system can reduce significantly the irritation of effective drugs without reducing their efficacy.

2) Advantages over Microencapsulation and Liposomes

The MDS has advantages over other technologies like microencapsulation and liposomes. Microcapsules cannot usually control the release rate of actives. Once the wall is ruptured the actives contained within microcapsules will be released. Liposomes suffer from lower payload, difficult formulation, limited chemical stability and microbial instability, while microsponge system in contrast to the above systems overcomes these limitations.

3) Advantages over Ointments

Ointments are often aesthetically unappealing, greasy and sticky those often result into lack of patient compliance. These vehicles require high concentrations of active agents for effective therapy because of their low efficiency of delivery system, resulting into irritation and allergic reactions in significant users. Other drawbacks of topical formulations are uncontrolled evaporation of active ingredient, unpleasant odour and potential incompatibility of drugs with the vehicles, whereas microsponge system maximizes amount of time that an active ingredient is present either on skin surface or within the epidermis, while minimizing its transdermal penetration into the body.

Preparation of Microsponge

Drug loading in microsponges can take place in two ways, by one-step or two-step process; based on physio-chemical properties of drug to be loaded. If the drug is typically an inert non-polar material, it will create the porous structure which is called as porogen. Porogen drug, which neither hinders the polymerization nor become activated by it and stable to free radicals is entrapped with one-step process.

1) Liquid-Liquid Suspension Polymerization

Microsponges are prepared by suspension polymerization process in liquid-liquid systems (one-step process). Firstly, the monomers are dissolved along with active ingredients (non-polar drug) in an appropriate solvent solution of monomer, which are then dispersed in the aqueous phase with agitation. Aqueous phase typically consists of additives such as surfactants and dispersants (suspending agents) etc. in order to facilitate the formation of suspension. Once the suspension is established with distinct droplets of the preferred size then, polymerization is initiated by the addition of catalyst or by increasing temperature as well as irradiation. The polymerization method leads to the development of a reservoir type of system that opens at the surface through pores.

During the polymerization, an inert liquid immiscible with water but completely miscible with monomer is used to form the pore network in some cases. Once the polymerization process is complete, the liquid is removed leaving the microsponges which permeate within preformed microsponges then, incorporates the variety of active substances (like anti fungal, rubefacients, anti-acne, anti-inflammatory etc.) and act as a topical carriers. In some cases, solvent can be used for efficient and faster inclusion of the functional substances.

When the drug is sensitive to the polymerization conditions, two-step process is used. The polymerization is performed using substitute porogen and is replaced by the functional substance under mild experimental conditions.

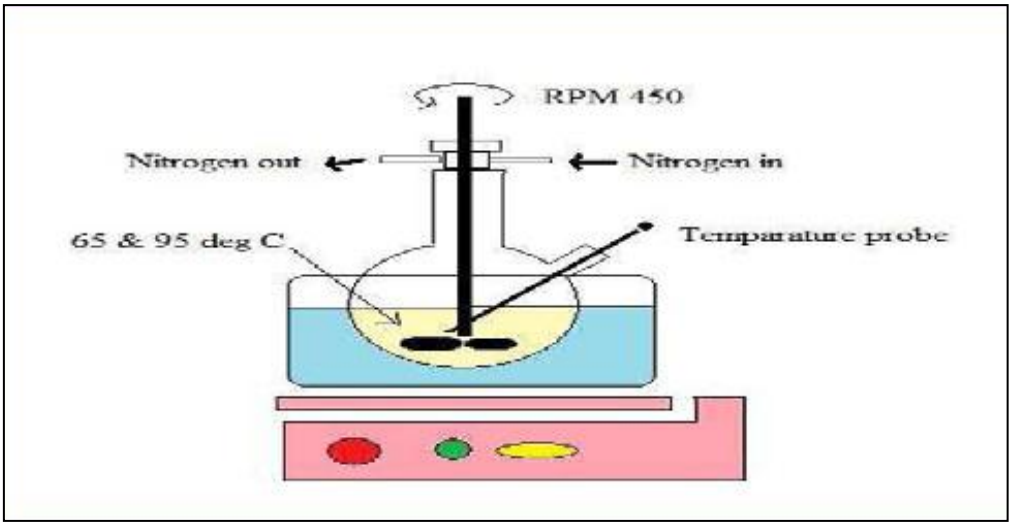

Fig. 2: Liquid-Liquid Suspension Polymerization

2) Quasi-Emulsion Solvent Diffusion

When the drug is sensitive to the polymerization conditions, two-step process is used. Microsponges are prepared by a quasi-emulsion solvent diffusion method using the different polymer quantities.

In the emulsion solvent diffusion the affinity between the drug and the good solvent is stronger than that of the good solvent and the poor solvent. The drug is dissolved in the good solvent, and the solution is dispersed into the poor solvent, producing emulsion (quasi) droplets, even though the pure solvents are miscible. The good solvent diffuses gradually out of the emulsion droplets into the surrounding poor solvent phase, and the poor solvent diffuses into the droplets by which the drug crystallizes inside the droplets.

This is a two-step process wherein the polymer along with the active, plasticizer and diffusible substance (porogen) is poured into an external aqueous phase, which typically consists of a stabilizer such as polyvinyl alcohol. After emulsification, the system is continuously stirred for 2 h and maintained at a high temperature if required. Diffusion of the porogen into the external medium results in a highly porous microparticle called 'Microsponge'. Then the mixture is filtered to separate the microsponges. The product is washed and dried in vacuum oven at 50°C for 24h.

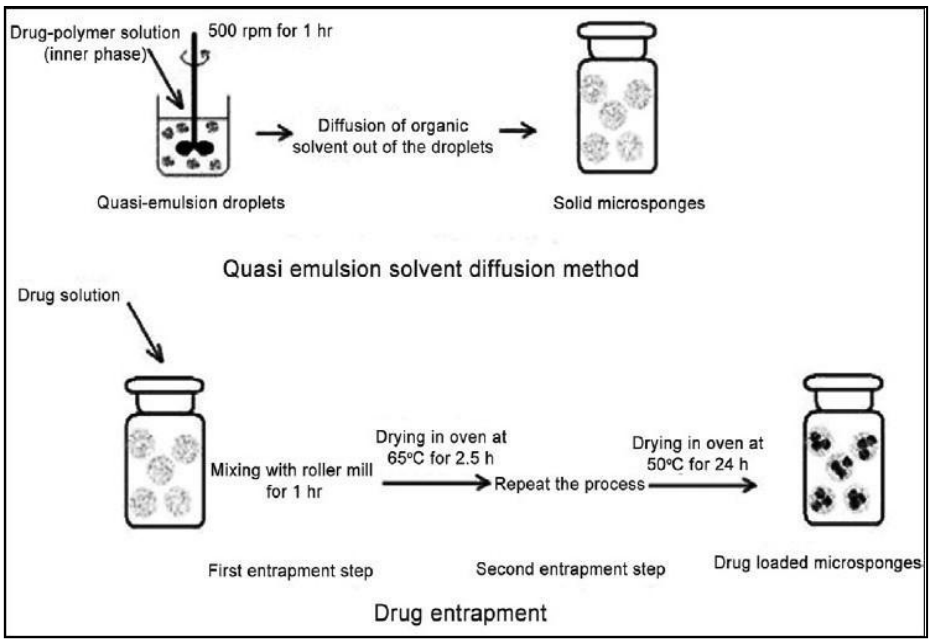

Fig. 3: Quasi emulsion solvent diffusion method

Formulation Considerations

Actives entrapped in microsponge delivery system can then be incorporated into many products such as creams, lotions, powders and soaps. While formulating the vehicle, certain considerations are taken into account in order to achieve desired product characteristics. These are as follows:

1. The solubility of actives in the vehicle must be limited. Otherwise the vehicle will deplete the microsponges before the application.
2. To avoid cosmetic problems; not more than 10 to 12% w/w microsponges must be incorporated into the vehicle.
3. Polymer design and payload of the microsponges for the active must be optimized for required release rate for a given time period.

There remains equilibrium between microsponge and vehicle, and microsponge releases drug in response to the depletion of drug concentration in the vehicle. Drug concentration in the vehicle is depleted by absorption of the drug into skin. Hence continuous and steady release of actives onto the skin is accomplished with this system.

Sustained release microsponges can also be developed. Various factors that are to be considered during development of such formulations include physical and chemical properties of entrapped actives. Physical properties of microsponge system include pore diameter, pore volume, resiliency etc. Particle size, pore characteristics, resiliency and monomer compositions can be considered as programmable parameters and microsponges can be designed to release given amount of actives in response to one or more external triggers like; pressure, temperature and solubility of actives.[4, 5]

Release Mechanisms from Microsponges[6]

MDS consists of a multitude of porous microspheres that contain a complex network of interconnecting voids with a non-collapsible structure. Depending on several modifiable factors, the rate of release of the active ingredients can be determined before they are entrapped in the microspheres. These modifiable factors include the pore diameter, the extent of cross-linking of the polymers, the difference in concentration of the active ingredient between the microspheres, and the vehicle in which these spheres reside. The topical agent formulation with the MDS can be prepared in many different forms, such as a gel, cream, or lotion. Once the formulation is topically applied to the desired area of the skin, the active ingredients diffuse out of the spheres into the vehicle and then onto the skin. Microsponges can be designed to release given amount of active ingredients over time in response to one or more external triggers.

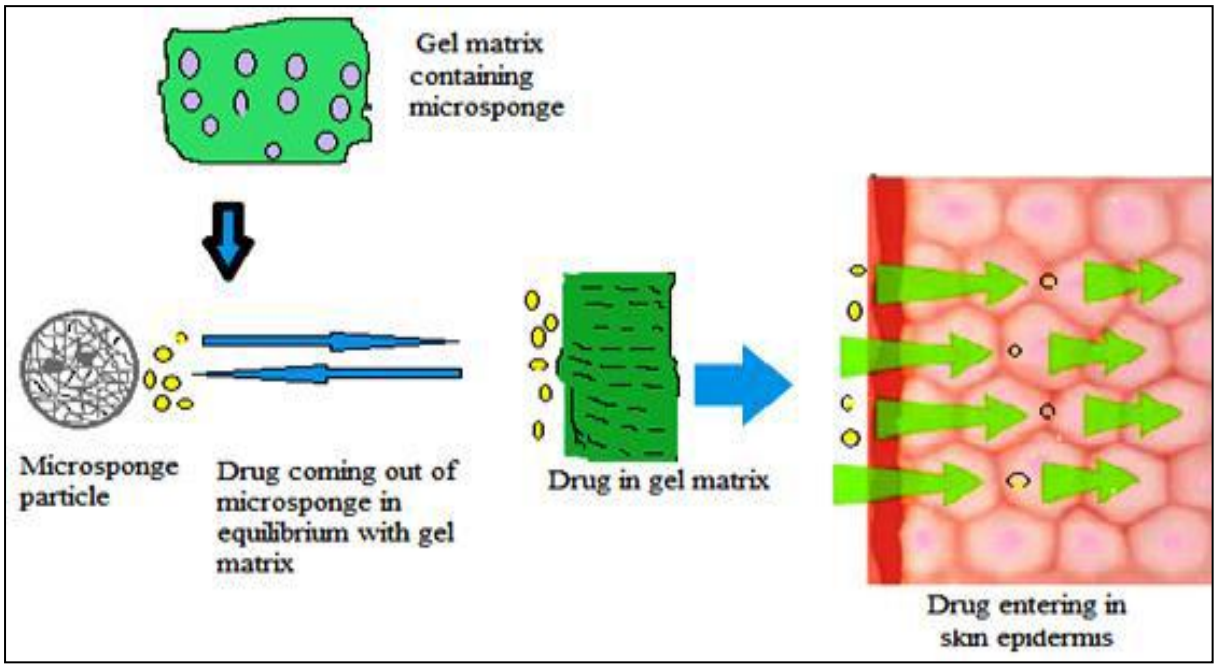

Fig. 3: Release mechanism of Microsponge

a) **Pressure**

Rubbing or pressure applied can release active ingredient from microsponges onto skin.

b) **Temperature Change**

Some entrapped actives can be too viscous at room temperature to flow spontaneously from microsponges onto the skin. Increase in skin temperature can result in an increased flow rate and hence an increase in release. So it is possible to modulate the release of substances from the microsponge by modulation of temperature. For example, viscous sunscreens were found to show a higher release from microsponges when exposed to higher temperatures; thus a sunscreen would be released from a microsponge only upon exposure to the heat from the sun.

c) **pH**

Triggering the pH-based release of the active can be achieved by modifying the coating on the microsponge. This has many applications in drug delivery.

d) **Solubility**

Microsponges loaded with water-soluble ingredients like antiperspirants and antiseptics will release the ingredient in the presence of water. Thus release may be achieved based on the ability of the external medium to dissolve the active ingredient, the concentration gradient varies or the ability to swell the microsponge network. The release can also be activated by diffusion, taking into consideration the partition coefficient of the ingredient between the microsponges and the outside system

Applications of Microsponge Systems

Microsponges are porous, polymeric microspheres that are used mostly for topical and recently for oral administration. It offers the formulator a range of alternatives to develop drug and cosmetic products. Microsponges are designed to deliver an active pharmaceutical ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects and modify drug release.

Microsponge delivery systems are used to enhance the safety, efficacy and aesthetic quality of topical, over-the-counter ("OTC") and personal care products. Products under development or in the marketplace utilize the topical microsponge systems in three primary ways:

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

The resulting benefits include extended efficacy, reduced skin irritation, cosmetic elegance, formulation flexibility and improved product stability.

Marketed Formulation Using the MDS

Marketed formulation using the MDS includes Ethical Dermatological Products **(**APS defined ethical dermatological products as prescriptional and non-prescriptional drugs that are promoted primarily through the medical profession for the prevention and treatment of skin problems or diseases). Several ethical dermatology products approved by US FDA, OTC and personal care products are sold in the United States. Results from various human clinical studies reaffirmed that the technology offers the potential to reduce the drug side effects, maintain the therapeutic efficacy and potentially increase patient compliance with the treatment regimen.

Ethical dermatological products that have been developed or are under development includes,

- Tretinoin Acne Medication (Retin-A Micro®)
- 5-Fluorouracil (5-FU) for actinic keratosis (CaracTM)
- Tretinoin Photo-damage Treatment
- Personal Care and OTC Products

MDS is ideal for skin and personal care products. They can retain several times their weight in liquids, respond to a variety of release stimuli, and absorb large amounts of excess skin oil, while retaining an elegant feel on the skin's surface.

The technology is currently employed in almost number of products sold by major cosmetic companies worldwide. Among these products are skin cleansers, conditioners, oil control lotions, moisturizers, deodorants, razors, lipstick, makeup, powders, and eye shadows; which offers several advantages, including improved physical and chemical stability, greater available concentrations, controlled release of the active ingredients reduced skin irritation and sensitization, and unique tactile qualities.

CONCLUSION

The microsponge drug delivery system is a controlled release system in which active pharmaceutical ingredient is loaded in the porous beads and initiates reduction in side effects with improved therapeutic efficacy. Microsponge can be effectively incorporated into topical drug delivery system for retention of dosage form on skin, and also use for oral delivery of drugs using bio erodible polymers. This technology is being used currently in

cosmetics, over the counter skin care, sunscreens, and prescription products. This kind of drug delivery technology may lead to a better understanding of the healing of several diseases. Hence, the microsponge- based drug delivery technology is likely to become a valuable drug delivery matrix substance for various therapeutic applications in the future.

REFERENCES

1. Riyaz Ali Osmani, Nagesh H. Aloorkar, Ajit S. Kulkarni, Bhargav R. Harkare, Rohit R. Bhosale. A New Cornucopia in Topical Drug Delivery: Microsponge Technology. Asian Journal of Pharmaceutical Sciences and Technology. 2014; 4(1): 48-60
2. Sandhyarani R. Sagavkar, Dr. Shrinivas K Mohite. Innovative and Novel Strategy: Microsponge Drug Delivery System. International Journal of Universal Pharmacy and Bio Sciences, 2014; 3(4): 79-92
3. Ajay Saraf , Amit Dasani, H. K.Pathan. Microsponge drug delivery system as an innovation in Cosmetic world: A Review. Asian Journal of Pharmaceutical Education and Research, 2012; 1(2): 67-87
4. Yerram Chandramouli, Shaik Firoz, B. Rubia Yasmeen, Amaravathi Vikram, B. Mahitha, U. Aruna. Microsponges: A Novel Drug Delivery System for Controlled Delivery of Topical Drugs. International Journal of Pharmaceutical Research and Analysis, 2012; 2(2): 79-86
5. Manisha K. Tile, A.Y. Pawar. Microsponges: A Novel Strategy for Drug Delivery. International Journal of Pure and Applied Bio sciences, 2015; 3(1): 224-235
6. Saroj Kumar Pradhan. Microsponges as The Versatile Tool For Drug Delivery System. International Journal Of Research In Pharmacy and Chemistry, 2011; 1(2): 243-258.