A NEW CORNUCOPIA IN TOPICAL DRUG DELIVERY: MICROSPONGE TECHNOLOGY


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ABSTRACT

The expanding arena of emerging drugs, increased sensitivity to clinical outcomes and healthcare costs are driving the need for alternative drug delivery methods and devices. The drug delivery technology landscape has become highly competitive and rapidly evolving. More and more developments in delivery systems are being integrated to optimize the efficacy and cost effectiveness of the therapy. New classes of pharmaceuticals, biopharmaceuticals are fueling the rapid evolution of drug delivery technology. These new drugs typically cannot be effectively delivered by conventional means. Hence, benefits from targeted, localized delivery of therapeutic agents are other driving forces for the current market. Microsponge technology has been introduced in topical drug products to facilitate the controlled release of active drug into the skin in order to reduce systemic exposure and minimize local cutaneous reactions to active drugs. Microsponge consists of microporous beads loaded with active agent. When applied to the skin, the microsponge releases its active ingredient on a time mode and also in response to other stimuli (rubbing, temperature, pH etc.) that are used mostly for topical and recently for oral administration. Microsponge technology has many favourable characteristics which make it a versatile drug delivery vehicle. Microsponge Systems can suspend or entrap a wide variety of substances, and then be incorporated into a formulated product such as a gel, cream, liquid or powder. The outer surface is typically porous, allowing the sustained flow of substances out of the sphere. Microsponge delivery system (MDS) can provide increased efficacy for topically active agents with enhanced safety, extended product stability, enhanced formulation flexibility, reduced side effects and improved aesthetic properties in an efficient and novel manner. In addition these are non-irritating, non-mutagenic, non-allergenic, and nontoxic. The present review introduces microsponge technology in great detail.

KEY WORDS: Controlled Drug Delivery System, Microsponge Technology, Programmable Release, Microsponges.

INTRODUCTION

Drug delivery systems (DDS) that can precisely control the release rate or target drugs to a specific body site have had an enormous impact on the healthcare system. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle (such as microspheres, nanoparticles, liposomes etc.) which modulates the release and absorption characteristics of the drug [1]. To control the delivery rate of active agents to a predetermined site in human body has been one of the biggest challenges faced by drug industry. Several predictable and reliable systems were developed for systemic drugs under the heading of transdermal delivery system (TDS) using skin as portal of entry [2]. It has improved efficacy and safety of many drugs that may be better administered through skin, but TDS is not practical for delivery of drugs 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 that has only recently been addressed with success. No efficient vehicles have been developed for controlled and localized delivery of drugs into the stratum corneum and underlying skin layers, and not beyond the epidermis [3].

The major problem associated with TDS is most of the drugs are poorly water soluble which pose many problems while formulating them in conventional dosage forms [4]. One of the critical problems associated with poorly water soluble drugs is too low bioavailability and erratic absorption [5]. The problem is even more complex

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for drugs such as drugs belonging to BCS class II as they are poorly soluble in both aqueous and organic media. Dissolution rates of the sparingly soluble drugs are related to the shape as well as the particle size. Therefore decrease in particle size of such drugs result in an increase in dissolution rate [6-10]. There are number of formulation approaches to resolve the problems of low solubility and low bioavailability. These approaches include micronization, solubilization using co-solvents, use of permeation enhancer, oily solutions, surfactant dispersions, salt formation and precipitation techniques etc. [10]. Other techniques like liposomes [11], emulsions, microemulsions, solid-dispersion [12] and inclusion complexes using cyclodextrin show reasonable success but they lack in universal applicability to all drugs. Hence there is need of some different and simple approach which can resolve these problems [13-14].

Furthermore, the significance of topical drugs differs from various problems such as ointments, which are frequently unappealing, greasiness, stickiness etc. which in turn leads to lack of patient compliance. These vehicles necessitate high concentrations of active agents for successful therapy because of their less efficiency of delivery system resulting into irritation and allergic reactions in significant users. Additional potential limitations of topical formulations are unpleasant odor, uncontrolled evaporation of active ingredient and incompatibility of drugs with the vehicles. 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 [15-16].

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 [17-20].

### 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 [21]. 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 [22-24].

### Microsponge Drug Delivery System

The microsponge technology was developed by Won in 1987, and the original patents were assigned to Advanced Polymer Systems, Inc [18]. Microsponges are porous microspheres having myriad of interconnected voids of particle size ranging between 5-300 µm (Figure 1). 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 [19].

Microsponges consist of non-collapsible structures with porous surface through which active ingredients are released in controlled manner (Nacht and Katz, 1990). 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.) [25].

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 [25].

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 [26].

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 [27]. 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 [28].

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 (Figure 2).

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 [29].

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 thermal, 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 [30]

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 [31].
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 [32,33].

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 (Figure 3). 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.

Programmable Release
1) Pressure Triggered Systems
Microsponge system releases the entrapped material when pressurized; the amount released depends upon various characteristics of the sponge. By varying the type of material and different process variables, the microspone best suited for a given application may be optimized. When compared with mineral oil containing microcapsules, mineral oil containing microspone showed much more softening effect. The duration of emolliency was also much more for the microspone systems [34].

2) Temperature Triggered Systems
It is possible to modulate the release of substances from the microspone by modulation of temperature. For example, viscous sunscreens were found to show higher release from microsponges when exposed to higher temperatures; thus a sunscreen would be released from a microspone only upon exposure to the heat from the sun [34-35].

3) pH Triggered Systems
Triggering the pH-based release of the active can be achieved by modifying the coating on the microspone. Although this has many applications in drug delivery, only a few applications are possible for cosmetic delivery [34,35].

4) Solubility Triggered Systems
Presence of an aqueous medium such as perspiration can trigger the release rate of active ingredients. Ingredients such as antiseptics, deodorants and antiperspirants may be formulated in such types of systems. Release may be achieved based on the ability of the external medium to dissolve the active, the concentration gradient or the ability to swell the microspone network [34,35].

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, microspone system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Potentially, the microspone 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 microspone 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 [25].

**Preparation of Microsponges**

Drug loading in microsponges can take place in two ways, by one-step or two-step process; based on physico-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. The general assembly of reaction vessel is presented in **Figure 4**.

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 [6, 19, 36].

The various steps involved in the preparation of microsponges as presented in **Figure 5** are summarized as follows:

**Step 1**: Selection of monomer as well as combination of monomers.

**Step 2**: Formation of chain monomers as polymerization starts.

**Step 3**: Formations of ladders as a result of cross-linking between chain monomers.

**Step 4**: Folding of monomer ladder to form spherical particles.

**Step 5**: Agglomeration of microspheres leads to the production of bunches of microspheres.

**Step 6**: Binding of bunches to produce microsponges.

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.

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 [14].

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 24 h. The processing flow chart is presented in Fig 6.

**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 [38]. 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 [39].

Release Mechanisms from Microsponges

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 [39].

a) Pressure: Rubbing or pressure applied can release active ingredient from microsponges onto skin [40].

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 microsphere 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 microsphere only upon exposure to the heat from the sun [40].

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

d) Solubility: Microsponges loaded with water-soluble ingredients like antiperspirants and antisepsics 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 microsphere 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 [40].

Evaluation Parameters of Microsponges

Various factors are affecting the drug release from microsponges. So it can be evaluated by following factors.

Particle Size Determination

Particle size analysis of loaded and unloaded microsponges can be performed by laser light diffractometry or any other suitable method. The values (d90) can be expressed 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. Particles larger than 30 μm can impart gritty feeling and hence particles of size between 10-25 μm are preferred to use in final topical formulation [41].

Morphology and Surface Topography of Microsponges

For morphology and surface topography, prepared microsponges can be coated with gold–palladium under an argon atmosphere at room temperature and then the surface morphology of the microsponges can be studied by scanning electron microscopy (SEM). SEM of a fractured microsphere particle can also be taken to illustrate its ultrastructure.

Determination of Loading Efficiency and Production Yield

The loading efficiency (%) of the microsponges can be calculated according to the following equation

\[ \text{Loading efficiency} = \frac{\text{Actual Drug Content in Microsponge}}{\text{Theoretical Drug Content}} \times 100 \]  

...Equ. (1)

The production yield of the microsponges can be determined by calculating accurately the initial weight of the raw materials and the last weight of the microspore obtained.

\[ \text{Production Yield (PY)} = \frac{\text{Practical Mass of Microsponge}}{\text{Theoretical Mass (polymer + drug)}} \times 100 \]  

...Equ. (2)

Determination of True Density

The true density of microsponges can be measured using an ultra-pycnometer under helium gas and can be calculated from a mean of repeated determinations.

Characterization of Pore Structure

Pore volume and diameter are vital in controlling the intensity as well as duration of effectiveness of an active ingredient. Pore diameter also affects the migration of active ingredients from microsponges into the vehicle in which the material is dispersed. Mercury intrusion porosimetry can be employed to study effect of pore diameter and volume on rate of drug release from microsponges. Porosity parameters
of microsponges such as intrusion-extrusion isotherms pore size distribution, total pore surface area, average pore diameters, shape and morphology of the pores, bulk and apparent density can be determined by using mercury intrusion porosimetry. The pore diameter of microsponges can be calculated by using Washburn equation,

$$D = \frac{4\gamma\cos\theta}{P} \quad \text{...Equ. (3)}$$

Where, $D$ is the pore diameter (μm); $\gamma$ the surface tension of mercury (485 dyn cm$^{-1}$); $\theta$ the contact angle (130°); and $P$ is the pressure (psi). Total pore area (Atot) is calculated by using equation,

$$A_{\text{tot}} = \frac{1}{\gamma \cos \theta} \int_{0}^{V_{\text{tot}}} \frac{P}{dV} \quad \text{...Equ. (4)}$$

Where $P$ is the pressure (psi); $V$ the intrusion volume (mL g$^{-1}$); $V_{\text{tot}}$ is the total specific intrusion volume (mL g$^{-1}$). The average pore diameter ($D_m$) is calculated by using equation,

$$D_m = \frac{4V_{\text{tot}}}{A_{\text{tot}}} \quad \text{...Equ. (5)}$$

Envelope (bulk) density ($\rho_{\text{se}}$) of the microsponges is calculated by using equation,

$$\rho_{\text{se}} = \frac{W_s}{V_p - V_{\text{Hg}}} \quad \text{...Equ. (6)}$$

Where $W_s$ is the weight of the microspponge sample (g); $V_p$ the empty penetrometer (mL); $V_{\text{Hg}}$ is the volume of mercury (mL). Absolute (skeletal) density ($\rho_{\text{sa}}$) of microsponges is calculated by using equation,

$$\rho_{\text{sa}} = \frac{W_s}{V_{\text{se}} - V_{\text{tot}}} \quad \text{...Equ. (7)}$$

Where $V_{\text{se}}$ = the volume of the penetrometer minus the volume of the mercury (mL). Finally, the percent porosity of the sample is obtained from equation,

$$\text{Porosity (})% = \left(1 - \frac{\rho_{\text{se}}}{\rho_{\text{sa}}} \right) \times 100 \quad \text{...Equ. (8)}$$

Pore morphology can be characterized from the intrusion-extrusion profiles of mercury in the microsponges.

**Compatibility Studies**

Compatibility of drug with reaction adjuncts can be studied by thin layer chromatography (TLC) and Fourier Transform Infra-red spectroscopy (FT-IR). Effect of polymerization on crystallinity of the drug can be studied by powder X-ray diffraction (XRD) and Differential Scanning Calorimetry (DSC) [6].

**Polymer / Monomer Composition**

Polymer composition of the MDS can affect partition coefficient of the entrapped drug between the vehicle and the microsponge system and have direct influence on the release rate of entrapped drug. Release of drug from microsponge systems of different polymer compositions can be studied by plotting cumulative % drug release against time. The choice of monomer is dictated both by the vehicle into which it will be dispersed and characteristics of active ingredient to be entrapped. Various monomer combinations will be screened for their suitability with the drugs by studying their drug release profile [42].

**Resiliency**

Resiliency (visco-elastic properties) of microsponges can be modified to produce beadlets that are softer or firmer according to the need of the final formulation. Increased cross-linking tends to slow down the rate of release. Hence resiliency of microsponges will be studied and optimized as per the requirement by considering release as a function of cross-linking with time.

**Dissolution Tests**

Dissolution profile of microsponges can be studied by use of dissolution apparatus with a modified basket consisting of 5μm stainless steel mesh at 37°C under 150 rpm. The dissolution medium is selected while considering solubility of drug to ensure sink conditions. Samples from the dissolution medium can be analyzed by suitable analytical method at various intervals.

**Patent Information of Microsponge Technology/Products**

On September 1, 1987, Won R. (Palo Alto, CA) of ‘Advanced Polymer Systems, Inc. (Redwood City, CA)’ received US patent for developing method for delivering an active ingredient by controlled time release utilizing a novel delivery vehicle which can be prepared by a process utilizing the active ingredient as a porogen (United States Patent 4,690,825, 1987).

On September 8, 1992, Won R. (Palo Alto, CA) of ‘Advanced Polymer Systems, Inc. (Redwood City, CA)’ received US patent for developing two-step method for preparation of controlled release formulations. Here active substances intended for topical application were incorporated in novel formulations in which they are retained as impregnants inside the pores of porous solid particles. The pores form a continuous network open to the exterior of the particles, permitting outward diffusion of impregnants at a controlled rate depending on the pore size. (United States Patent 5,145,675, 1992).

On March 31, 1992, Dean Jr. et al., from ‘Verox Corporation, Hanover’, received a patent for the development of weighted collagen microsponges having a highly cross-linked collagen matrix suitable for use in culturing organisms in motive reactor systems. The
Microsponges have an open to the surface pore structure, pore sizes and volumes suitable for immobilizing a variety of bioactive materials [43].

On December 22, 1998, Froix et al., of ‘Advanced Polymer Systems, Inc. (Redwood City, CA)’ received US patent for developing retinoid formulations in porous microspheres for reduced irritation and enhanced stability by formulating the retinoids as particles or particle suspensions in which the particles are porous matrices with the retinoid retained inside the pore [44].

Advanced Polymer Systems, Inc. and subsidiaries (“APS” or the “Company”) is using its patented Microsponge(R) delivery systems and related proprietary technologies to enhance the safety, effectiveness and aesthetic quality of topical prescription, over-the-counter (“OTC”) and personal care products like tretinoin, 5-fluorouracil and Vitamin-A etc. As on July 23, 2006, the Company has a total of 10 issued U.S. patents and an additional 92 issued foreign patents, 21 patent applications are pending worldwide.

On November 21, 2000 Biedermann et al., of ‘Procter and Gamble Company, Ohio’, got a patent for topical compositions for regulating the oily/shiny appearance of skin by inhibiting sebaceous gland activity in mammalian skin comprising administration of a topical composition comprising dehydroacetic acid or salts thereof, and a dermatologically acceptable carrier utilizing porous microspheres [45].

In 2000 Embil V. P, got a patent for OTC external analgesic cream/topical analgesic anti-inflammatory, counter irritant compositions utilizing the microsponge delivery system for controlled release of actives [46].

On May 24, 2005 Singh et al., of ‘R. P. Scherer Technologies Inc., Las Vegas’, received patent for novel composition which comprises an oil-in-water emulsion containing free hydroquinone, hydroquinone entrapped in absorbent micro-agglomerates and/or impregnated in porous micro-particles; and retinol impregnated micro-particles. EpiQuin® Micro is a hydroquinone USP 4% formulation, under license from ‘Amcol Intl. Corp.’ utilizes the same technology with some variability and got an independent patent [47].

On October 26, 2010 Orsoni et al., of ‘Galderma Research and Development (FR)’, received patent of gel composition for once-daily treatment of common acne comprising a combination of benzoyl peroxide and adapalene and/or adapalene salts impregnated micro-particles [48].

On October 18, 2011 Lapidot et al., of ‘Sol-Gel Technologies Ltd., Ness Ziona’, received a patent for composition exhibiting enhanced formulation stability and delivery of topical active ingredients. The therapeutic, cosmetic or cosmeceutical compositions for topical application, capable of stabilizing active ingredients, and delivering active ingredients, comprising a plurality of microcapsules having a core shell structure, having at least one active agent and with a shell diameter of 0.1-100μ for actives like benzoyl peroxide that are unstable in other formulation or are irritating were claimed to be delivered efficiently [49].

Applications of Microsponge Systems; A Great Plethora

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. The system can have following applications as depicted in Table No. 1.

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 (Carac™)
- 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 [50].

Table 1. Applications of Microsponge Systems

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Active Agents</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Sunscreens</td>
<td>Long lasting product efficacy, with improved protection against sunburns and sun related injuries even at elevated concentration and with reduced irritancy and sensitization.</td>
</tr>
<tr>
<td>2.</td>
<td>Anti-acne</td>
<td>Maintain efficacy with decreased skin irritation and sensitization.</td>
</tr>
<tr>
<td></td>
<td>e.g. Benzoyl peroxide</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Anti-inflammatory</td>
<td>Long lasting activity with reduction of skin allergic response and dermatoses.</td>
</tr>
<tr>
<td></td>
<td>e.g. Hydrocortisone</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Anti-fungal</td>
<td>Sustained release of actives.</td>
</tr>
<tr>
<td></td>
<td>e.g. Itraconazole, Econazole</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Anti-dandruff</td>
<td>Reduced unpleasant odour with lowered irritation with extended safety and efficacy.</td>
</tr>
<tr>
<td></td>
<td>e.g. Zinc pyrithione, Selenium sulfide</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Antipruritics</td>
<td>Extended and improved activity.</td>
</tr>
<tr>
<td>7.</td>
<td>Skin depigmenting agents</td>
<td>Improved stabilization against oxidation with improved efficacy and aesthetic appeal.</td>
</tr>
<tr>
<td></td>
<td>e.g. Hydroquinone</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Rubefacients</td>
<td>Prolonged activity with reduced irritancy greasiness and odour.</td>
</tr>
</tbody>
</table>

Table 2. List of Marketed Products Using Microsponge Drug Delivery System

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Advantages</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retin-A Micro</td>
<td>0.1% and 0.04% tretinoin entrapped in MDS for topical treatment of acne vulgaris. This formulation uses patented methyl methacrylate cross-polymer MICROSPONGE® System to enable inclusion of the active ingredient, tretinoin, in an aqueous gel.</td>
<td>Ortho-McNeil Pharmaceutical, Inc.</td>
</tr>
<tr>
<td>Carac Cream, 0.5%</td>
<td>Carac Cream contains 0.5% fluorouracil, with 0.35% being incorporated into a patented Microsponge composed of methyl methacrylate / glycol dimethacrylate cross-polymer and dimethicone. Carac is a once-a-day topical prescription product for the treatment of actinic keratoses (AK), common pre-cancerous skin condition caused by over-exposure to the sun. The product has a number of advantages over existing topical therapies, including less irritation with shorter duration of therapy and reduced dosage frequency.</td>
<td>Dermik Laboratories, Inc.</td>
</tr>
<tr>
<td>Oil free matte block spf20</td>
<td>This invisible oil-free sunscreen shields the skin from damaging UV sun rays while controlling oil production, giving you a healthy matte finish. Formulated with microsponge technology, Oil free matte block absorbs oil and preventing shine without any powdery residue.</td>
<td>Dermalogica</td>
</tr>
<tr>
<td>Retinol Cream</td>
<td>The retinol molecule is kept in the microsponge system to protect the potency of the vitamin A. This helps to maximize retinol dosage while reducing the possibility of irritation. Retinol is a topical vitamin A derivative which helps maintain healthy skin, hair and mucous membranes.</td>
<td>Biomedic</td>
</tr>
<tr>
<td>Line Eliminator Dual Retinol Facial Cream</td>
<td>Lightweight cream with a retinol (Vitamin A) in MDS, dual-system delivers both immediate and time released wrinkle-fighting action. Clearly diminishes appearance of fine lines, wrinkles and skin discolorations associated with aging.</td>
<td>Avon</td>
</tr>
<tr>
<td>EpiQuin Micro</td>
<td>The Microsponge® system uses microscopic reservoirs that entrap</td>
<td>Skin Medica Inc.</td>
</tr>
<tr>
<td>Product Name</td>
<td>Description</td>
<td>Manufacturer</td>
</tr>
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</tr>
<tr>
<td>EpiQuin Micro</td>
<td>A prescription moisturizing fading cream that reduces the impact of conditions like melasma, post-inflammatory hyperpigmentation, or solar lentigines. Also helps in age spots, sun spots, and facial discoloration.</td>
<td>Embil Pharmaceutical Co. Ltd.</td>
</tr>
<tr>
<td>Sports cream RS and XS</td>
<td>Topical analgesic-anti-inflammatory and counterirritant actives in a Microsponge® Delivery System (MDS) for the management of musculoskeletal conditions.</td>
<td>Biomedic, Sothys</td>
</tr>
<tr>
<td>Retinol 15 Night Cream</td>
<td>A nighttime treatment cream with Microsponge technology using a stabilized formula of pure retinol, Vitamin A. Continued use will result in the visible diminishment of fine lines and wrinkles, a noticeable improvement in skin discolorations due to aging, and enhanced skin smoothness.</td>
<td>Biomedic</td>
</tr>
<tr>
<td>Micro Peel Plus/Acne Peel</td>
<td>The MicroPeel ® Plus procedure stimulates cell turnover through the application of salicylic acid in the form of microcrystals using Microsponge ® technology. These microsponges target the exact areas on the skin that need improvement. The MicroPeel ® Plus aggressively outperforms other superficial chemical peels by freeing the skin of all dead cells while doing no damage to the skin.</td>
<td>Biophora</td>
</tr>
<tr>
<td>Salicylic Peel 20 and 30</td>
<td>Salicylic acid 20%, microsponge technology has excellent exfoliation and used for stimulation of the skin for more resistant skin types or for faster results. It will considerably improve pigmentation, fine lines and acne concerns. Salicylic acid moves easily through the pores, clearing them out while reducing inflammation. This treatment effectively combats acne leaving an amazingly smooth and clear complexion.</td>
<td>Biophora</td>
</tr>
<tr>
<td>Oil Control Lotion</td>
<td>A feature-light lotion with technically advanced microsponges that absorb oil on the skin’s surface during the day, for a matte finish. Eliminate shine for hours with this feature-weight lotion, formulated with oil-absorbing Microsponge technology and hydrating botanicals. The naturally-antibiotic Skin Response Complex soothes inflammation and tightness to promote healing. Acne-Prone, oily skin conditions.</td>
<td>Fountain Cosmetics</td>
</tr>
<tr>
<td>Lactrex™ 12% Moisturizing Cream</td>
<td>Lactrex™ 12% Moisturizing Cream contains 12% lactic acid as the neutral ammonium salt, ammonium lactate. Microsponge® technology has been included for comfortable application and long lasting moisturization. Lactrex™ also contains water and glycerin, a natural humectant, to soften and help moisturize dry, flaky, cracked skin.</td>
<td>SDR Pharmaceuticals, Inc., Andover, NJ, U.S.A.</td>
</tr>
<tr>
<td>Dermalogical Oil Control Lotion</td>
<td>Exclusive skin response complex soothes and purifies, provides effective skin hydration, without adding excess oil; eliminate shine for hours with dermalogical Oil Control Lotion. Oil Control Lotion is a feather-light lotion, formulated with oil absorbing Microsponge technology and hydrating botanicals. The naturally antiseptic Skin Response Complex helps soothe and purify the skin.</td>
<td>John and Ginger Dermalogica Skin Care Products</td>
</tr>
<tr>
<td>Ultra Guard</td>
<td>Microsponge system that contains dimethicone to help protect a baby’s skin from diaper rash. The new wipe contains a skin protectant that helps keep wetness and irritants from the baby’s skin. The solution is alcohol-free, hypoallergenic and contains dimethicone, an ingredient found in baby creams, lotions and skin protectants.</td>
<td>Scott Paper Company</td>
</tr>
</tbody>
</table>
Aramis Fragrances

24 hour high performance antiperspirant spray sustained release of fragrance in the microsponge. The microsponge comes in the form of an ultra light powder, and because it is micro in size, it can absorb fragrance oil easily while maintaining a free-flowing powder characteristic where release is controlled due to moisture and temperature.

Aramis Inc.

Fig 1. Microsponge Technology

Fig 2. Mode of Action of Microsponge Delivery System

Fig 3. Picture Showing the Highly Porous Nature of Microsponge

Fig 4. Reaction Vessel for Microsponges Preparation by Liquid-Liquid Suspension Polymerization

Fig 5. Microsponges Synthesis by Suspension Polymerization

Fig 6. Quasi Emulsion Solvent Diffusion Technique
CONCLUSIONS

Drug delivery via polymer systems has been proposed to be prevailing in the controlled drug delivery devices both in present and in future. For scientific as well as economic reasons, such delivery systems have potential advantages which include enhanced therapeutic response, predictable rate of release and extent of absorption, topical and improved acceptance. MDS has become highly competitive and rapidly evolving technology and more researches are carrying out for cost-effective therapy. MDS which is originally developed for topical delivery of drugs like anti-acne, anti-inflammatory, anti-fungal, anti-dandruffs, antipruritics, rubefacients etc.; nowadays it is also used for tissue engineering and controlled oral delivery using bio-erodible polymers, especially for colon specific drug delivery. It provides a wide range of formulating advantages. Liquids can be transformed into free flowing powders; incompatible ingredients with prolonged stability without use of preservatives can be developed. Safety of the irritating and sensitizing drugs can be increased and programmed release can control the amount of drug release to the targeted site. Hence, MDS holds a promising future in various pharmaceutical applications in the coming years as they have unique properties like enhanced product performance and elegancy, extended release, reduced irritation, improved thermal, physical, and chemical stability and flexible to develop variety of novel product forms.

REFERENCES