Microsponges as Innovative Drug Delivery Systems


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ABSTRACT

Transdermal drug delivery system (TDDS) 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 a challenging area of research. Microsponges are highly porous micro-sized particles with a unique ability for entrapping active pharmaceutical ingredients. To control the delivery rate of active agents to a predetermined site in human body has been one of the biggest challenges faced by scientists.

Microsponges are safe biologically and offer unique advantage of programmable release. This technology offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, increased elegance and enhanced formulation flexibility. This technology is being used for topical formulations and also for oral administration. The present review describes microsponge technology including its preparation, characterization, programmable parameters and release mechanism of microsponge drug delivery system.

KEY WORDS: Microsponges; transdermal drug delivery; programmable release; topical formulation; oral administration.

Introduction

To control the delivery rate of active agents to a predetermined site in the human body has been one of the biggest challenges faced by pharmaceutical scientists. Several predictable and reliable systems have been 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 (Kydonieus and Berner, 1987). 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 a challenging area of research.

Topical application of drugs suffers many problems. Ointments, which are often aesthetically unappealing faces the problems like greasiness, stickiness and often result in 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 delivery system fulfills these requirements. Microsponges are porous microspheres having myriad of interconnected voids of particle size range of 5-300 µm. These microsponges have capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, and anti-infectives and are used as a topical carrier system. Further these porous microspheres with active ingredients can be incorporated into formulations such as creams, lotions and powders (Vyas and Khar, 2002).

Microsponges consist of non-collapsible structures with porous surface through which active ingredients are released in controlled manner (Fig.1). Depending upon the size, the total pore length may range up to 10 ft and pore volume up to 1 ml/g. 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 such as rubbing, temperature, and pH (Vyas and Khar, 2002).

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.

The fundamental appeal of the microsponge technology stems from the difficulty experienced with conventional topical formulations in releasing active ingredients over an extended period of time. Cosmetics and skin care preparations are intended to work only on the outer layers of the skin. Yet, the typical active delivery

ABBREVIATIONS: TDS: Transdermal delivery system; MDS: Microsponge drug delivery system; SEM: Scanning electron microscopy; OTC: Over-the-counter; BPO: Benzoyl peroxide.
ingredient in conventional products is present in a relatively high concentration and, when applied to the skin, may be rapidly absorbed. The common result is over-medication, followed by a period of under-medication until the next application. Rashes and more serious side effects can occur when the active ingredients rapidly penetrate below the skin's surface. Microsponge technology is designed to allow a prolonged rate of release of the active ingredients, thereby offering potential reduction in the side effects while maintaining the therapeutic efficacy.

**Benefits of Microsponge Technology**

Microsponge technology offers:
- Enhanced product performance.
- Extended release.
- Reduced irritation and hence improved patient compliance.
- Improved product elegance.
- 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.
- Microsponge systems are non-irritating, non-mutagenic, non-allergenic and non-toxic (D'souza and More, 2008).

**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 or capable of being made miscible by addition of small amount of a water immiscible solvent.
- It should be water immiscible or at most only slightly soluble.
- It should be inert to monomers.
- It should be stable in contact with polymerization catalyst and conditions of polymerization (Emanuele and Dinarvand, 1995; Aritomi et al., 1996).

Microsponge technologies are shown in Figure 2 (Jelvehgari et al., 2006).

![Fig. 1.](image1.png) **Fig. 1.** Microsponges system (porous microspheres).

![Fig. 2.](image2.png) **Fig. 2.** Microsponges technology.
Advantages of Microsponges

Microsponges have several advantages which are explained below:

High surface area

A 25 µ sphere can have a total pore length of about 10 ft with a pore volume of about 1 ml/g and can have up to 25,000 pores. This provides an extensive surface area for high entrapment (Eambil and Nacht, 1996) (Figure 3).

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

Pressure triggered systems (Christensen and Nacht, 1983)

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 microsponge best suited for a given application may be optimized. When compared with mineral oil containing microcapsules, mineral oil containing microsponge showed much more softening effect. The duration of emolliency was also much more for the microsponge systems.

Temperature triggered systems (Christensen and Nacht, 1983)

It is possible to modulate the release of substances from the microsponge 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 microsponge only upon exposure to the heat from the sun.

pH triggered systems (Christensen and Nacht, 1983)

Triggering the pH-based release of the active can be achieved by modifying the coating on the microsponge. Although this has many applications in drug delivery, only a few applications are possible for cosmetic delivery.

Solubility triggered systems (Christensen and Nacht, 1983)

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 microsponge network.

Safety of microsponges (Christensen and Nacht, 1983)

Most polymers used in the formulation are inert and the inability of microsponges to pass through the stratum corneum enhances their safety. Furthermore, it reduces the irritation of various actives, and thereby demonstrates its harmlessness.

Advantages of Microsponges Over Other Formulations

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 MDS can reduce significantly the irritation of effective drugs without reducing their efficacy.

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 has several advantages such as:
It has stability over the pH range of 1 to 11 and temperature up to 130°C.

- It is compatible with most vehicles and ingredients.
- It has the property of self-sterilizing as their average pore size is 0.25 µm where bacteria cannot penetrate.
- It has higher payload and is still free flowing.
- It has advantage of cost effectiveness over the other formulations.

Advantages over ointments

Ointments are often aesthetically unappealing, greasy and sticky that often results in 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 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.

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.

Liquid-Liquid Suspension Polymerization

Microsponges are conveniently prepared by liquid-liquid suspension polymerization method. Polymerization of styrene or methyl methacrylate is carried out in round bottom flask.

In their preparation, monomers are first dissolved along with non-polar active ingredients in a suitable solvent solution of monomer and then dispersed in the aqueous phase, which consists of additives such as surfactant, and suspending agents, which help in formation of suspension. Once suspension with discrete droplets of the desired size is established, polymerization is achieved by activating monomers either by catalysis or by increased temperature irradiation (Won and Richard, 1987a, 1992b; Anderson et.al, 1994).

The various steps in preparation of microsponges are summarized as:

- Selection of monomer or combination of monomers.
- Formation of chain monomers as polymerization begins.
- Formations of ladders as a result of cross linking between chain monomers.
- Folding of monomer ladder to form spherical particles.
- Agglomeration of microspheres, which gives rise to formation of bunches of microspheres.
- Binding of bunches to form microsponges.

The polymerization process leads to formation of a reservoir type system, which opens at the surface through pores. In some cases an inert liquid immiscible with water but completely miscible with monomer is used during polymerization to form the pore network. After polymerization is over the liquid is removed leaving the porous microspheres, i.e. microsponges (Anderson et.al, 1994; Vyas and Khar, 2002) (Figure 4).

![Reaction vessel for microsponge preparation by liquid-liquid suspension polymerization.](image)

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 (Tansel and Omoglu, 2002).

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 hours 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 hours as shown in Figure 5 (Mine et.al, 2006).
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 (Franz, 1975).

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 like 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.

Release Mechanisms from Microsponges

MDS consists of a multitude of porous microspheres that contain a complex network of interconnected voids with a non-collapsible structure (Khopade and Jain, 1996). 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 (Embil and Nacht, 1996; Chadawar and Shaji, 2007). Microsponges can be designed to release given amount of active ingredients over time in response to one or more external triggers (Shah, 1989).

Pressure

Rubbing or pressure applied can release active ingredient from microsponges onto skin (Khopade and Jain, 1996).

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 (Khopade and Jain, 1996).

Solubility

Microsponges loaded with water-soluble ingredients like antiperspirants and antiseptics will release the
ingredient in the presence of water. The release can also be activated by diffusion taking into consideration the partition coefficient of the ingredient between the microsponges and the outside system (Khopade and Jain, 1996).

**Effect of Formulation Variables on Physical Properties of Microsponges**

**Effect of composition of internal and external phases**

(Jelvehgari et al., 2006)

It is found that particle sizes of microsponges were directly proportional to the apparent viscosity of dispersed phase. Larger the difference between apparent viscosity of dispersed and continuous phase, larger the mean particle size of the microsponges. When the dispersed phase with higher viscosity is poured into the continuous phase (external phase), due to the higher viscosity of the internal phase, the globules of the formed emulsion can hardly be divided into smaller particles and bigger droplets are found resulting in an increase in mean particle size.

Good microsponges can be produced only when 3 to 5 ml of internal phase is used. When the amount of internal phase is increased from 5 to 15 ml, the production yield and drug content of microsponges is found to be decreased. This is due to the lower concentration of the drug in the higher volume of internal phase.

**Effect of drug to polymer ratio** (Tansel and Omoglu, 2003)

When the amount of polymer is kept constant but the ratio of drug to polymer is varied, the drug loading capacity is not much affected by drug to polymer ratio but production yield can be enormously changed from minimum ratio to a maximum one. Another parameter which is affected from drug: polymer ratio change is particle size. It has been observed that when drug amount is increased, particle size of the microsponges is also increased.

**Effect of Process Variables on Physical Properties of Microsponges**

**Effect of stirring rate** (Jelvehgari et al., 2006)

As the stirring rate is increased, microsponges of smaller size are obtained. Increase in the stirring rate decreases the production yield but the drug content gets increased which indicates that the drug loss is decreased as the stirring rate is increased. This is due to the turbulence created within the external phase due to which polymer gets adhered to the paddle and production yield gets decreased.

**Physical Characterization of Microsponges**

**Particle Size Determination**

Free-flowing powders with fine aesthetic attributes are possible to obtain by controlling the size of particles during polymerization. Particle size analysis of loaded and unloaded microsponges can be performed by laser light diffractometry or by any other suitable method. The values (um) can be expressed for all formulations as mean size range. Cumulative percentage drug release from microsponges of different particle size is 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 sizes between 10 and 25 μm are preferred to use in final topical formulation. (Martin et al., 1991; Kawashima et al., 1991; Jelvehgari et al., 2006).
Porosity parameters of microsponges such as intrusion-extrusion isotherm 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. Incremental intrusion volumes can be plotted against pore diameters that represent pore size distributions.

**Pore diameter**

It is calculated by using Washburn equation (Washburn, 1921).

\[ D = \frac{4\gamma \cos \theta}{P} \quad \ldots \ldots (3) \]

Where \( D \) is the pore diameter (\( \mu \)m); \( \gamma \) the surface tension of mercury (485 dyne cm\(^{-1}\)); \( \theta \) the contact angle (130\(^{\circ}\)); and \( P \) is the pressure (psi).

**Total pore area \( (A_{tot}) \)**

It is calculated by using equation,

\[ A_{tot} = \frac{1}{\gamma \cos \theta} \int_{0}^{V_{tot}} P \, dV \quad \ldots \ldots (4) \]

Where, \( P \) is the pressure (psia); \( V \) the intrusion volume (ml g\(^{-1}\)); \( V_{tot} \) is the total specific intrusion volume (ml g\(^{-1}\)).

**Average pore diameter \( (D_m) \)**

It is calculated by using equation,

\[ D_m = \frac{4V_{tot}}{A_{tot}} \quad \ldots \ldots (5) \]

Where, \( V_{tot} \) is the total specific intrusion volume (ml g\(^{-1}\)); \( A_{tot} \) is the total pore area.

**Envelope (bulk) density \( (\rho_{se}) \)**

It is calculated by using equation,

\[ \rho_{se} = \frac{W_s}{V_p - V_{Hg}} \quad \ldots \ldots (6) \]

Where, \( W_s \) is the weight of the microsponge sample (g); \( V_p \) the volume of empty penetrometer (ml); \( V_{Hg} \) is the volume of mercury (ml).

**Absolute (skeletal) density \( (\rho_{sa}) \)**

It is calculated by using equation,

\[ \rho_{sa} = \frac{W_s}{V_{se} - V_{tot}} \quad \ldots \ldots (7) \]

Where, \( V_{se} \) is the volume of the penetrometer minus the volume of the mercury (ml).

**Percent porosity**

It is calculated by equation

\[ \text{Porosity (\%) = } \left( 1 - \frac{\rho_{se}}{\rho_{sa}} \right) \times 100 \quad \ldots \ldots (8) \]

Where, \( \rho_{se} \) is the bulk density; \( \rho_{sa} \) is the absolute density (Orr, 1969).

**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 Colorimetry (DSC) (Anderson et al., 1994).

**Polymer/ Monomer Composition**

Factors such as microsponge size, drug loading, and polymer composition govern the drug release from microsponge. Polymer composition of the MDS can affect partition coefficient of the entrapped drug between the vehicle and the microsponge system and hence it has 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 percent (\%) drug release against time.

Selection of monomer is dictated both by characteristics of active ingredient ultimately to be entrapped and by the vehicle into which it will be dispersed. Polymers with varying electrical charges or degrees of hydrophobicity or lipophilicity may be prepared to provide flexibility in the release of active ingredients. Various monomer combinations will be screened for their suitability with the drugs by studying their drug release profile (Barkai et al., 1990; Chowdary and Rao, 2004).

**Resiliency**

Resiliency (viscoelastic properties) of microsponges can be modified to produce beadlets that are softer or firmer according to the needs 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 (D’souza, 2008).

**Release Evaluations**

**Dissolution tests**

Dissolution profile of microsponges can be studied by use of dissolution test apparatus with a modified basket consisting of 5\( \mu \)m stainless steel mesh. The speed of the rotation is kept at 150 rpm. The dissolution medium is selected considering solubility of actives to ensure sink conditions. Samples from the dissolution medium can be analysed by suitable analytical methods at various intervals (D’souza, 2001).

**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 (D’souza et al., 2004; Kawashima et al., 1991). Various applications of microsponge systems are summarized in Table 1.
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 e.g. Benzoyl peroxide</td>
<td>Maintained efficacy with decreased skin irritation and sensitization.</td>
</tr>
<tr>
<td>3</td>
<td>Anti-inflammatory e.g. hydrocortisone</td>
<td>Long lasting activity with reduction of skin allergic response and dermatoses.</td>
</tr>
<tr>
<td>4</td>
<td>Anti-fungal</td>
<td>Sustained release of actives.</td>
</tr>
<tr>
<td>5</td>
<td>Anti-dandruffs e.g. zinc pyrithione, selenium sulfide</td>
<td>Reduced unpleasant odour with lowered irritation with extended safety and efficacy.</td>
</tr>
<tr>
<td>6</td>
<td>Antipurities</td>
<td>Extended and improved activity.</td>
</tr>
<tr>
<td>7</td>
<td>Skin depigmenting agents e.g. hydroquinone</td>
<td>Improved stabilization against oxidation with improved efficacy and aesthetic appeal.</td>
</tr>
<tr>
<td>8</td>
<td>Rubefacients</td>
<td>Prolonged activity with reduced irritancy greasiness and odour.</td>
</tr>
</tbody>
</table>

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 prescriptive 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 as over the counter (OTC) and personal care products are sold in the United States. Results from various human clinical studies affirmed that the technology offers the potential to reduce the drug side effects, maintains the therapeutic efficacy and potentially increases the patient compliance with the treatment regimen.

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

**Tretinoin Acne Medication**

In February 1997, the FDA approved the first ethical pharmaceutical product based on patented microponge technology; Retin-A-Micro™, which has been licensed to Ortho-McNeil Pharmaceutical Corporation. This product was launched in March 1997. However, skin irritation among sensitive individuals can limit patient compliance with the prescribed therapy. The company believes its patented approach to reduce the potentially irritating side effects of tretinoin. Ortho Dermatological began marketing this product in March 1997.

**5-Fluorouracil (5-FU)**

5-FU is an effective chemotherapeutic agent for treating actinic keratosis, a pre-cancerous, hardened-skin condition caused by excessive exposure to sunlight. However, patient compliance with the treatment regimen is poor, due to significant adverse side effects. Microsponge-enhanced topical formulation, that potentially offers a less irritating solution for treating actinic keratosis, is sold under the brand of Carac.

**Tretinoin Photo-damage Treatment:**

Product containing microsponge system for the treatment of photo-damage, which contributes to the premature aging of skin and in skin cancer, is also developed.

**Cosmeceutical Product Retinol:**

Retinol is a highly pure form of vitamin A which has demonstrated a remarkable ability for maintaining the skin's youthful appearance. However, it has been available only on a limited basis because it becomes unstable when mixed with other ingredients. Stabilized retinol in a formulation which is cosmetically elegant and which has a low potential for skin irritation is successfully developed and marketed.

**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 and toiletry companies worldwide. Among these products are skin cleansers, conditioners, oil control lotions, moisturizers, deodorants, razors, lipstick, makeup, powders, and eye shadows; which offer 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.

Table 2 summarizes the various marketed products utilizing microsponge drug delivery system.
TABLE 2
Marketed products using microsponge drug delivery system.

<table>
<thead>
<tr>
<th>Product</th>
<th>Advantages</th>
<th>Manufacturer</th>
</tr>
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<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/glycol dimethacrylate cross-polymer porous microspheres (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 porous microsphere (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), a common pre-cancerous skin condition caused by over-exposure to the sun.</td>
<td>Dermik Laboratories, Inc.</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, Inc.</td>
</tr>
<tr>
<td>EpiQuin Micro</td>
<td>The Microsponge ® system uses microscopic reservoirs that entrap hydroquinone and retinol. This provides the skin with continuous exposure to hydroquinone and retinol over time, which may minimize skin irritation.</td>
<td>SkinMedica Inc</td>
</tr>
</tbody>
</table>

APS developed microsphere precursors to the microsponge for use as a testing standard for gauging the purity of municipal drinking water. Marketed nationwide, these microspheres are suspended in pure water to form an accurate, stable, reproducible turbidity standard for the calibration of turbidimeters used to test water purity. The technology can have much broader applications than testing the turbidity of water and can even be used for the calibration of spectrophotometers and colorimeters.

Microsponges for Topical Delivery

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.

Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne and athletes foot. Skin irritation is a common side effect, and it has been shown that controlled release of BPO from a delivery system to the skin could reduce the side effect while reducing percutaneous absorption (D'souza, 2001).

Microsponge for Oral Delivery

A microsponge system offers the potential to hold active ingredients in a protected environment and provide controlled delivery of oral medication to the lower gastrointestinal (GI) tract, where it will be released upon exposure to specific enzymes in the colon. This approach if successful should open up entirely new opportunities for MDS.

In oral applications, the microsponge system has been shown to increase the rate of solubilisation of poorly water-soluble drugs by entrapping such drugs in the microsponge system's pores. Because these pores are very small, the drug is in effect reduced to microscopic particles with resultant increase in surface area and thus greatly increases the rate of solubilisation. An added benefit is that the time it requires for microsponge system to traverse the small and large intestine is significantly increased thus maximizing the amount of drug that is absorbed.

Ketoprofen was used as a model drug for systemic drug delivery of microsponges in the study. Ketoprofen microsponges were prepared by quasi-emulsion solvent diffusion method with Eudragit RS 100 and afterwards tablets of microsponges were prepared by direct compression method. Different pressure values were applied to the tablet powder mass in order to determine the optimum pressure value for compression of the tablets. Results indicated that compressibility was much improved over the physical mixture of the drug and polymer; due to the plastic deformation of sponge-like structure, microsponges produce mechanically strong tablets (Tansel and Omoglu, 2003).

Summary and future perspectives

There are several advantage offered by the nano-size particles. The nanosized particles have a very high surface area to size ratio and a greater potential to modulate the release of actives compared to micro-sized particles. The first pharmaceutical microsponges based on cross-linked cyclodextrins have been reported by Roberta Cavalli et al., (2006) and Swaminathan et al., (2007). These are nanosized, highly porous materials composed of beta-cyclodextrin cross-linked with carbonate bonds.
Microsponge technology offers a unique platform for topical delivery being safe, simple to produce and offering the advantage of programmable release. MDS has become highly competitive and rapidly evolving technology and more and more research should be carried out for cost-effective therapy. MDS holds a promising future in various pharmaceutical applications in the coming years as it has unique properties like enhanced product performance and elegance, extended release, reduced irritation, improved thermal, physical, and chemical stability and thus flexibility to develop novel product forms. MDS was originally developed for topical delivery of drugs but nowadays it can also be used for controlled oral delivery of drugs using bioerodable polymers, especially for colon specific delivery. Microsponge delivery systems that can precisely control the release rates or target drugs to a specific body site have an enormous impact on the health care system, and will be explored in great detail in the years to come.

References
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