Microsponges: A novel strategy for drug delivery system

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ABSTRACT

Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge-like spherical particles with a large porous surface. Moreover, they may enhance stability, reduce side effects and modify drug release favorably. Microsponge technology has many favorable characteristics, which make it a versatile drug delivery vehicle. Microsponge Systems are based on microscopic, polymer-based microspheres that can suspend or entrap a wide variety of substances, and can then be incorporated into a formulated product such as a gel, cream, liquid or powder. The outer surface is typically porous, allowing a sustained flow of substances out of the sphere. Microsponges are porous, polymeric microspheres that are used mostly for topical use and have recently been used for oral administration. Microsponges are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects, and modify drug release.

Key words: Controlled release, drug delivery, healthcare systems, microsponges

INTRODUCTION

In recent years, there has been considerable emphasis given to the development of novel microsponge base drug delivery systems, in order to modify and control the release behavior of the drugs. By incorporation into a carrier system, it is possible to alter the therapeutic index and duration of the activity of drugs. The ever-increasing interest among consumers with regard to skin care and skin treatment products has been fostered by the widespread use of ingredients like α-hydroxy acids and vitamins in topical products, which can induce perceivable and demonstrable benefits — especially in aging or photo-damaged skin. Although quite useful, in many instances, these ingredients may produce irritancy; such irritancy can be perceived as burning, stinging or redness and particularly occurs in individuals with sensitive skin. Recognizing this problem, the formulators have attempted to deal with this problem in one of the two methods. They have reduced the concentration of such ingredients, but in the process, sacrificed efficacy. They have also modified the vehicle in order to make the product more emollient or skin-compatible.[1] However, this approach, in many cases, also reduces the beneficial effects of the final product. 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. Drug delivery systems that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the healthcare system. Several predictable and reliable systems been developed for systemic drugs under the heading of transdermal delivery systems (TDS) using the skin as a portal of entry.[2] It has improved the efficacy and safety of many drugs that may be better administered through skin. However, TDS is not practical for delivery of materials whose final target is the skin itself. Controlled release of drugs onto the epidermis with an 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. Moreover, the application of topical drugs has many problems, such as, ointments that are often aesthetically unappealing, greasiness, stickiness, and so on, that often results in lack of patient compliance. These vehicles require a high concentrations of active agents for effective therapy because of their low efficiency of delivery system, resulting in irritation and allergic reactions in significant users. Other drawbacks of topical formulations are uncontrolled evaporation of the active ingredient, unpleasant odor, and the potential incompatibility of the drugs with the vehicles. Conventional formulations of topical drugs are intended to work on the outer layers of the skin. Typically, such products release their active ingredients upon application, producing a highly concentrated layer of active ingredient

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that is rapidly absorbed. Thus the need exists for a system to maximize the amount of time that an active ingredient is present either on the skin surface or within the epidermis, while minimizing its transdermal penetration into the body. Microsponges are microscopic spheres capable of absorbing skin secretions, therefore reducing oiliness and shine from the skin. Spherical particles composed of clusters of even tinier spheres are capable of holding four times their weight in skin secretions. Microsponge particles are extremely small, inert, indestructible spheres that do not pass through the skin. Rather, they collect in the tiny nooks and crannies of the skin and slowly release the entrapped drug, as the skin needs it. The microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Potentially, the microsponge system can significantly reduce the irritation of effective drugs without reducing their efficacy. The empty spheres are then washed away with the next cleansing. The microsponge delivery system fulfills these requirements and has resulted in a new generation of very well-tolerated and highly efficacious, novel products. These products are typically presented to the consumer in conventional forms like creams, gels or lotions and they contain a relatively high concentration of active ingredients.

Microsponges are patented polymeric delivery systems consisting of porous microspheres that can entrap a wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, and anti-infective, anti-fungal, and anti-inflammatory agents.[3] Like a true sponge, each microsphere consists of a myriad of interconnecting voids within a non-collapsible structure, with a large porous surface. The microsponge technology was developed by Won in 1987, and the original patents were assigned to Advanced Polymer Systems, Inc.[4] This company developed a large number of variations of the technique and applied those to the cosmetic as well as over-the-counter (OTC) and prescription pharmaceutical products. At the present time, this interesting technology has been licensed to Cardinal Health, Inc., for use in topical products. The size of the microsponges can be varied, usually from 5 – 300 μm in diameter, depending upon the degree of smoothness or after-feel required for the end formula. Although the microsponge size may vary, a typical 25 μm sphere can have up to 250000 pores and an internal pore structure equivalent to 10 ft in length, providing a total pore volume of about 1 ml/g. This results in a large reservoir within each microsponge, which can be loaded with up to its own weight of active agent. The microsponge particles themselves are too large to be absorbed into the skin and this adds a measure of safety to these microsponge materials. Another safety concern is the potential bacterial contamination of the materials entrapped in the microsponge. As the size of the pore diameter is smaller, the bacteria ranging from 0.007 to 0.2 μm cannot penetrate into the tunnel structure of the microsponges [Figure 1].[3]

Potential Advantages of the Microsponge Drug Delivery System

- Microcapsules cannot usually control the release rate of the active pharmaceutical ingredients (API). Once the wall is ruptured the API contained within the microcapsules will be released. Can the MDS can do it, is the question.
- Liposomes suffer from a lower pay load, difficult formulation, limited chemical stability, and microbial instability. Do the MDS have a wide range of chemical stability and are they easy to formulate?
- MDS have stability over a pH range of 1 – 11.
- Stable up to temperature 130 °C.
- Pay load is up to 50 – 60%.
- Free flowing and cost effective.
- Microsponges are microscopic spheres capable of absorbing skin secretions, therefore, reducing oiliness and shine from the skin.

Properties of the Actives for the Entrapment into Microsponges

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

Methods of Preparation of Microsponges

Liquid–liquid suspension polymerization

In general, a solution is made comprising of monomers and the functional or active ingredients, which are immiscible with water. This phase is then suspended with agitation in an aqueous phase, usually containing additives, such as surfactants and dispersants, to promote suspension. Once the suspension is established with discrete droplets of the desired size, polymerization is effected by activating the monomers either by catalysis, increased temperature or irradiation. As the polymerization process continues, a spherical structure is produced containing thousands of microsponges bunched together like grapes, forming

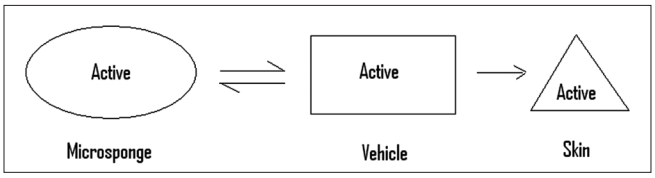

Figure 1: Schematic representation of the distribution of the loaded material (active) on skin

interconnecting reservoirs [Figure 2].

Once the polymerization is complete the solid particles that result from the process are recovered from the suspension. The particles are then washed and processed until they are substantially ready for use. The microsponge products can be made using styrene and divinylbenzene or methyl methacrylate and ethylene glycol dimethacrylate as starting materials.[5]

Quasi-emulsion solvent diffusion

To prepare the inner organic phase, Eudragit RS 100 is dissolved in ethyl alcohol. Next, the drug is added to the solution and dissolved under ultrasonication at 35° C. The inner phase is poured into the polyvinyl alcohol solution in water (outer phase). Following 60 minutes of stirring, the mixture is filtered, to separate the microsponges. The microsponges are dried in an air-heated oven at 40°C for 12 hours [Figure 3].[6]

Ingredients can be entrapped in microsponge polymers either at the time of synthesis, or if too labile to withstand polymerization conditions, they can be post-loaded after the microsphere structure has been pre-formed. In general, the latter process is the preferred mode, as many cosmetic ingredients, and most pharmaceutical ones, would decompose at the temperatures employed for polymerization.

Hypothetical mechanism of action

The active ingredient is added to the vehicle in an entrapped form. As the microsponge particles have an open structure (i.e., they do not have a continuous membrane surrounding them), the active is free to move in and out from the particles and into the vehicle until equilibrium is reached, when the vehicle becomes saturated. Once the finished product is applied to the skin, the active that is already in the vehicle will be absorbed into the skin, depleting the vehicle, which will become unsaturated, therefore, disturbing the equilibrium. This will start a flow of the active from the microsponge particle into the vehicle, and from it to the skin, until the vehicle is either dried or absorbed. Even after that the microsponge particles retained on the surface of the stratum corneum will continue to gradually release the active to the skin, providing prolonged release over time. This proposed mechanism of action highlights the importance of formulating vehicles for use with microsponge entrapments. If the active is too soluble in the desired vehicle during compounding of the finished products, the products will not provide the desired benefits of gradual release. Instead they will behave as if the active was added to the vehicle in a free form. Therefore, while formulating microsponge entrapments, it is important to design a vehicle that has minimal solubilizing power for the actives. This principle is contrary to the conventional formulation principles usually applied to topical products. For these conventional systems it is normally recommended to maximize the solubility of the active in the vehicle. When using microsponge entrapments, some solubility of the active in the vehicle is acceptable, because the vehicle can provide the initial loading dose of the active until release from the microsponge is activated by the shift in equilibrium from the polymer into the carrier. Another way to avoid undesirable premature leaching of the active from the microsponge polymer is to formulate the product with some free and some entrapped active, so the vehicle is pre-saturated. In this case there will not be any leaching of the active from the polymer during compounding. The rate of active release will ultimately depend not only on the partition coefficient of the active ingredient between the polymer and the vehicle (or the skin), but also on some of the parameters that characterize the beads. Examples of these include surface area and primarily, mean pore diameter.[7] Release can also be controlled through diffusion or other triggers such as

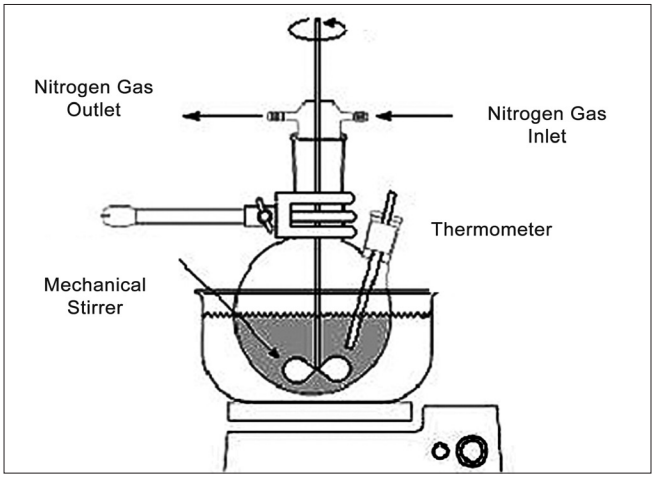

Figure 2: Reaction vessel for microsponge preparation by liquid–liquid suspension polymerization

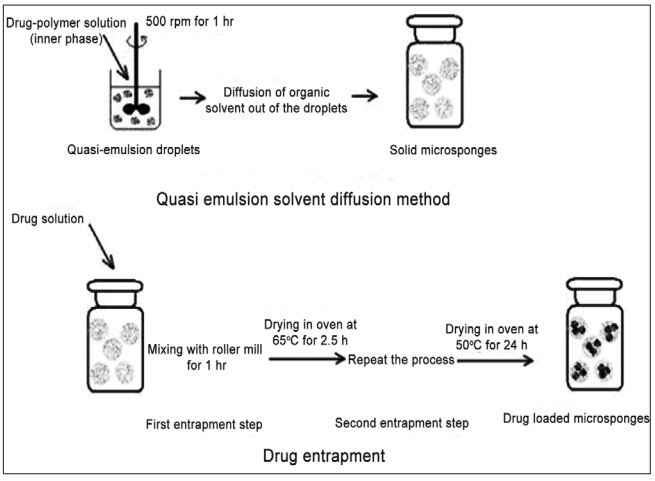

Figure 3: Preparation of microsponges by the quasi-emulsion solvent diffusion method

moisture, pH, friction or temperature.

Characterization of the microsponge

The microsponges are generally characterized for particle size, shape, pore volume, pore diameter. And so on. Different parameters and evaluation methods for microsponges is given in Table 1.

Microsponge-based Delivery Systems for Drug Triggering

Topical drug delivery using microsponge technology

Microspongic delivery of Benzoyl peroxide was developed using an emulsion solvent diffusion method, by adding an organic internal phase containing benzoyl peroxide, ethyl cellulose, and dichloromethane into a stirred aqueous phase containing polyvinyl alcohol,[23] and by suspension polymerization of styrene and divinyl benzene.[24,25] The prepared microsponges were dispersed in a gel base and the microspongic gels were evaluated for anti-bacterial and skin irritancy. The entrapped system released the drug at a slower rate than the system containing free BPO. The topical delivery system with reduced irritancy was successfully developed.[26] A new formulation of Hydroquinone (HQ) 4%, with retinol 0.15%, entrapped in microsponge reservoirs, was developed to release HQ gradually, to prolong exposure to treatment and to minimize skin irritation. The safety and efficacy of this product were evaluated in a 12-week, open-label study. In this open-label study, HQ 4% with retinol 0.15% was safe as well as effective.[27] The microspongic system for topical delivery of fluconazole gel was observed to have the potential to extend the release.[28] An MDS system for retinoic acid was developed and tested for drug release and anti-acne efficacy. Statistically significant, greater reductions in inflammatory and non-inflammatory lesions were obtained with tretinoin entrapped in the microsponge.[29] Topical analgesic, anti-inflammatory, and counter-irritant drugs in a microsponge® are used for the management of the musculoskeletal system.[30]

Oral drug delivery using microsponge technology

In oral applications, the microsponge system has been shown to increase the rate of solubilization of poorly water-soluble drugs by entrapping such drugs in the microsponge system's pores. As these pores are very small, the drug is in effect reduced to microscopic particles and the significant increase in the surface area thus greatly increases the rate

Table 1: Different parameters and characterization methods for microsponges

Parameters	Characterization methods	References
Measurement of particle size, size distribution, and polydispersity index	Laser light diffractometry	[8]
Morphology and surface topography	Scanning electron microscopy	[9]
Determination of true density	Ultra-pycnometer under helium gas (Displacement method)	[10]
Characterization of pore structure, Total pore volume, Material volume, Material density, Interstitial void volume, Percent porosity, Percent porosity filled, Pore volume distribution by pore size, Pore area, number of pores Pore cavity to pore throat size ratio, Pore cavity sizes, Pore throat size, Pore fractal dimensions, Pore tortuosity and tortuosity factor	Mercury intrusion porosimetry	[10-12]
Drug polymer interaction studies	Fourier transform infra-red spectroscopy (FTIR) study	[13]
Study of glass-transition temperature	Differential scanning calorimetry	[13]
Effect of polymerization on crystallinity of the drug	X-ray diffraction (XRD) studies	[14]
Compatibility studies	Thin layer chromatography (TLC)	[15]
Polymer / Monomer composition	By plotting cumulative percent drug release against time	[16-17]
Resiliency (viscoelastic properties)	By considering release as a function of cross-linking with time	[18]
Release mechanisms	By proper manipulation of the aforementioned programmable parameters	[19]
Safety considerations	Skin irritation studies in rabbits; eye irritation studies in rabbits; oral toxicity studies in rats; mutagenicity in bacteria, and allergenicity in guinea pigs	[20-21]
Drug release from the topical semi-solid formulation	Franz-type static diffusion cells	[22]

of solubilization. Controlled oral delivery of ibuprofen microsponges is achieved with an acrylic polymer, eudragit RS, by changing their intraparticle density.[31] Sustained release formulation of chlorpheniramine maleate, using powder-coated microsponges, is prepared by the dry impact blending method, for oral drug delivery.[32] Controlled oral delivery of Ketoprofen prepared by quasi-emulsion solvent diffusion method with Eudragit RS 100 and afterwards tablets of microsponges were prepared by the direct compression method. Results indicated that compressibility was much improved in the physical mixture of the drug and polymer; due to the plastic deformation of the sponge-like microsponge structure, producing mechanically strong tablets.[18] Colon-specific, controlled delivery of flurbiprofen, was conducted by using a commercial Microsponge® 5640 system. *In vitro* studies exhibited that compression-coated colon-specific tablet formulations started to release the drug at the eighth hour, corresponding to the proximal colon arrival time, due to addition of the enzyme, following a modified release pattern, while the drug release from the colon-specific formulations prepared by pore plugging the microsponges showed an increase at the eighth hour, which was the point of time when the enzyme addition was made.[33]

Microsponge-based Delivery Systems for Bone and Tissue Engineering

Bone-substitute compounds were obtained by mixing pre-polymerized powders of polymethylmethacrylate and liquid methylmethacrylate monomer with two aqueous dispersions of a-tricalcium phosphate grains and calcium-deficient hydroxyapatite powders. The final composites appeared to be porous and acted as microsponges.[34] The basic fibroblast growth factor (bFGF) incorporated in a collagen sponge sheet was sustained released in the mouse sub-cutis according to the biodegradation of the sponge matrix, and exhibited local angiogenic activity in a dose-dependent manner. Intra-muscular injection of collagen microsponges incorporating bFGF, induced a significant increase in the blood flow, in the murine ischemic hind limb, which could never have been attained by the bolus injection of bFGF. These results suggest the significance and therapeutic utility of the type I collagen as a reservoir of bFGF.[35] A biodegradable graft material containing the collagen microsponge was developed for cardiovascular tissue grafting, as it would permit the regeneration of the autologous vessel tissue.[36] A thin biodegradable hybrid mesh of synthetic poly (DL-lactic-co-glycolic acid) (PLGA) and naturally derived collagen was used for a three-dimensional culture of human skin fibroblasts. The hybrid mesh was constructed by forming web-like collagen microsponges in the openings of a PLGA-knitted mesh.[37] A tissue-engineered patch made of our biodegradable polymer and collagen-microsponge provided good *in situ* regeneration at both the venous and arterial wall, suggesting that this patch could be used as a novel surgical material for the repair of the cardiovascular system.[38]

Potential applications of microsponge systems

Microsponges are used widely to develop drug and cosmetic products for topical administration and recently for oral administration [Table 2]. These are designed to deliver the drug efficiently at the minimum dose and also to enhance stability, reduce side effects, and modify drug release.[40]

Marketed formulation based on microsponge materials

List of marketed products using microsponge drug delivery system are given in Table 3.

Future prospects

Microsponges are one of the novel drug delivery systems, which were originally developed for topical delivery of drugs. They can also be used for tissue engineering and controlled oral delivery of drugs using biodegradable polymers. It provides a wide range of formulating advantages. Liquids can be transformed into free flowing powders. Formulations can be developed with otherwise incompatible ingredients, with prolonged stability, without the use of preservatives. Therefore, microsponges will be an ideal drug delivery system related to formulations like the transdermal delivery system. As it requires vehicles at a higher concentration in order to dissolve the API for effective therapy, it causes irritation and hypersensitivity reactions in significant users. Another demerit of topical formulations is uncontrolled evaporation of the cactive ingredient, unpleasant odor, and the potential incompatibility of drugs with the vehicles. Conventional formulations of topical drugs are intended to work on the outer layers of the skin. Typically, such products release their active ingredients upon application, producing a highly concentrated layer of an active ingredient that is rapidly absorbed. Thus, the need exists for a system to maximize the amount of time that an active ingredient is present either on the skin surface or within the epidermis. Some microsponge-based products are already approved; several others are currently under development and clinical assessment.

CONCLUSION

The microsponge delivery system is a unique technology for the controlled release of macroporous beads, loaded with active agent, offering a potential reduction in side effects, while maintaining their therapeutic efficacy. The microsponge drug delivery system offers entrapment of its ingredients and is believed to contribute toward reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility. In addition, numerous studies have confirmed that microsponge systems are non-irritating, non-mutagenic, non-allergenic, and non-toxic. This technology is being used currently in cosmetics,

Table 2: Therapeutic applications of microsponges

Product name	Advantages	Manufacturer
Retin-A-Micro(TM)	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 to enable inclusion of the active ingredient, tretinoin, in an aqueous gel	Ortho-McNeil Pharmaceutical, Inc.
Carac cream, 0.5%	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, a common pre-cancerous skin condition caused by over-exposure to the sun. The product has a number of advantages over the existing topical therapies, including less irritation with shorter duration of therapy and reduced dosage frequency	Dermik Laboratories, Inc. Berwyn, PA 19312 USA
Line eliminator dual retinol facial treatment	Lightweight cream with a retinol (pure Vitamin A) in MDS, delivers both immediate and time-released wrinkle-fighting action	Avon
Retinol cream	The retinol molecule is kept in the microsponge system to protect the potency of vitamin A. This helps to maximize the retinol dosage, while reducing the possibility of irritation. Retinol is a topical vitamin A derivative, which helps maintain healthy skin, hair, and mucous membranes	Biomedic
Retinol 15 nightcream	A nighttime treatment cream with Microsponge technology using a stabilized formula of pure retinol and Vitamin A. Continued use of Retinol 15 will result in the visible diminishment of fine lines and wrinkles, a noticeable improvement in skin discolorations due to aging, and enhanced skin smoothness	Sothys
EpiQuin micro	The Microsponge® system uses microscopic reservoirs that entrap hydroquinone and retinol. The microsponges release these ingredients into the skin gradually throughout the day. This provides the skin with continuous exposure to hydroquinone and retinol over time, which may minimize skin irritation[39]	Skin Medica Inc
Sports cream RS and XS	Topical analgesic-anti-inflammatory and counterirritant actives in a Microsponge® Delivery System (MDS) for the management of musculoskeletal conditions[30]	Embil Pharmaceutical Co. Ltd.
Salicylic peel 20	Deep BHA peeling agent for (professional use only): Salicylic acid 20%, Microsponge Technology, Excellent exfoliation and stimulation of the skin for more resistant skin types or for faster results. Will dramatically improve fine lines, pigmentation, and acne concerns	Biophora
Salicylic peel 30	Deeper BHA peeling agent for (professional use only): Salicylic acid 30%, Microsponge Technology, Most powerful exfoliation and stimulation of the skin. For more resistant skin types or for faster results. Will dramatically improve fine lines, pigmentation, and acne concerns	Biophora
Micro peel plus	The MicroPeel® Plus procedure stimulates cell turnover through the application of salicylic acid in the form of microcrystals using Microsponge® technology. These microcrystals 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	Biomedic
Oil free matte block spf-20	This invisible sunscreen provides a shield for the skin from damaging UV rays and controls oil production. Microsponge technology absorbs the oil, maintaining an all-day matte finish and preventing shine without any powdery residue. Oil-free formula contains soothing Green Tea to help calm inflammation caused by breakouts. Contains no artificial fragrance or color. Cornstarch and Vinyl Dimethicone / Methicone Silsesquioxane Cross-polymer act as microsponges to absorb excess surface oils on skin	Dermalogica
Oil control lotion	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 natural-antibiotic Skin Response Complex soothes inflammation and tightness to promote healing. Acne-Prone, oily skin conditions	Fountain Cosmetics
Lactrex™ 12% moisturizing cream	Lactrex™ 12% Moisturizing cream contains 12% lactic acid as the neutral ammonium salt and 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	SDR Pharmaceuticals, Inc., Andover, NJ, U.S.A. 07821

Contd...

Table 2 (Contd...)

Product name	Advantages	Manufacturer
Dermalogica oil control lotion	Exclusive skin response complex, soothes and purifies, provides effective skin hydration, without adding excess oil; eliminates shine for hours with Dermalogica oil control lotion. The 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	John and Ginger Dermalogica skin care products
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 fragrant oil easily, while maintaining a free-flowing powder characteristic where release is controlled due to moisture and temperature	Aramis Inc.
Ultra guard	Microsponge system that contains dimethicone to help protect a baby's skin from diaper rash	Scott Paper Company

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

Active agents	Applications
Sunscreens	Long-lasting product efficacy, with improved protection against sunburns and sun-related injuries, even at elevated concentration and with reduced irritancy and sensitization
Anti-acne, e.g., Benzoyl peroxide	Maintained efficacy with decreased skin irritation and sensitization
Anti-inflammatory e.g. hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatoses
Anti-fungals	Sustained release of actives
Anti-dandruffs, e.g., zinc pyrithione, selenium sulfide	Reduced unpleasant odor with lowered irritation and extended safety and efficacy
Antipruritics	Extended and improved activity
Skin depigmenting agents, e.g., hydroquinone	Improved stabilization against oxidation with improved efficacy and aesthetic appeal
Rubefacients	Prolonged activity with reduced irritancy greasiness and odor

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.

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