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MICROSPONGES: A NOVEL APPROACH FOR TOPICAL APPLICATION-A REVIEW

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ABSTRACT

Microsponges are patented porous microspheres polymeric delivery systems consisting of porous microspheres that can entrap with wide range of active pharmaceutical ingredients like as emollients, essential oils, fragrances, sunscreens, and anti-fungal, anti-infective and anti-inflammatory agents.[1] Each microsphere consists of a myriad of interconnecting voids within a non-collapsible structure having large porous surface. The microsponge technology was developed by Won at 1987, and the original patents were assigned to Advanced Polymer Systems, This company developed a large number of variations of the technique and applied those to the over-the-counter (OTC) as well as cosmetic and prescription pharmaceutical product.[2] Thus, there is a need to develop a delivery system to maximize residence time of the active pharmaceutical ingredient (API) in the skin. Such a new system would possibly increase the efficacy of the topically active agents while enhancing product safety. The microsponges are polymeric delivery devices which contain active ingredients with release API onto the skin over of time in response to a trigger. This Review contained brief introduction, structure, characteristic, advantages over different conventional formulation, material, methods and its application with marketed examples.

KEYWORD: Microsponges, over-the-counter(OTC), porousmicrospheres, microsponge technology, marketed examples.

INTRODUCTION

Over the past 40 years, the ability to control the delivery rate of active agents to a predetermined site in the human body has been one of the biggest challenges till date met by continued innovative solutions by the medical profession and drug industry. Because of this some areas of pharmaceutical research have been focused on the controlled delivery of systemic drugs.[3]

Various predictable and reliable systems have been developed for systemic drugs under the title of transdermal delivery systems using the skin as portal entry. Transdermal patches developed in 1970's improved the delivery of drugs such as nitro glycerine and scopolamine resulting in better control of therapeutic dose, simpler dosage regimens, and fewer side effects than the more traditional oral or parentral administration of the same drug. And more over these devices mimicked the intravenous administration of the drug which is not patient compliance.[4] In general, these delivery systems have improved the efficiency and safety of various drugs. Controlled release of drugs on to the epidermis assure that the drug remains primarily localized and does not enter the systemic circulation in significant amount thereby minimizing the side effects.

Although transdermal delivery systems can be efficient in supplying drugs for systemic effects they are not practical for controlling the delivery of materials whose final target is the skin itself.[5]

No efficient vehicle have been developed for the controlled and localized delivery of drugs in to the stratum corneum and underlying skin layers.

Yet there are many instance when epidermal localization of a drug is desirable, but absorption beyond the epidermis undesirable.[2]

Corticosteroids are the suitable examples for these problems. Although corticosteroids are effective for skin disorders, their topical application results in significant systemic absorption; this may leads to unwanted side effects such as adrenal suppression or interference with immune functions.

The same is true in case of cosmetics like sunscreens, winter cares and drugs for the treatment of epidermal infection and allergies like acne, eczema, hyper pigmentation etc. it is necessary to maximize/lengthen the time of residence of these active ingredienton the skin

surfaces or within the outer layers of the epidermis while minimizing its transepidermal penetration into the body.[6]

Another problem with the application of topical drug is the most of the vehicles, such as ointment, often prove aesthetically unappealing; greasiness stickiness or even discoloration in clothing can make daily ware unpleasant.[7]

This frequently results in patient incompliance, many of these conventional vehicles require high concentration of active ingredients for effective therapy because of their low efficiency as a delivery system. As a result, irritation or allergic response can be elicited in a significant percentage of users.

Other disadvantages of conventional topical delivery system are the uncontrolled evaporation of active ingredient, unpleasant odour, and the potential incompatibility of one or more drugs with each other or with the vehicle.[1]

Moreover 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 ingredients that is rapidly absorbed. This causes systemic side effects.[7]

Thus, there is a need to develop a delivery system to maximize residence time of the active pharmaceutical ingredient (API) in the skin. Such a new system would possibly increase the efficacy of the topically active agents while enhancing product safety. The microsponges are polymeric delivery devices which contain active ingredients with release API onto the skin over of time in response to a trigger.

Structure of Microsponges

The size of the microsponges is usually ranges from 5 – 300 μm in diameter, depending upon the degree of smoothness. The microsponge sphere can have upto 250000 pores and an internal pore structure equivalent to 10 ft in length, providing a total pore volume of about 1 ml/g. This shows a large reservoir within each microsponge, which can be loaded with up to its own weight of active agent. The microsponge particles it self are too large to be absorbed into the skin and this can adds a measure of safety to these microsponge materials. As the size of the pore diameter is smaller, the bacteria ranging from 0.007 to 0.2 μm can not penetrate into the tunnel structure of the microsponges.

Release of active ingredients from conventional topical formulation over an extended period of time is quite difficult. In contrast, microsponge technology allow an even and sustained rate of release of active ingredient, reducing irritation while maintaining efficacy. They have high degree of cross linking result in particles that are inert of potential strength, insoluble to stand up to the high shear mostly used in manufacturing of creams, lotion, and powder.[8]

Their characteristic feature is the capacity to adsorb or "load" a high degree of active materials into the particles and on its surface. Its large capacity for entrapment of actives agents, up to three times of its own weight, differentiate microsponge products from other types of dermatological delivered system.

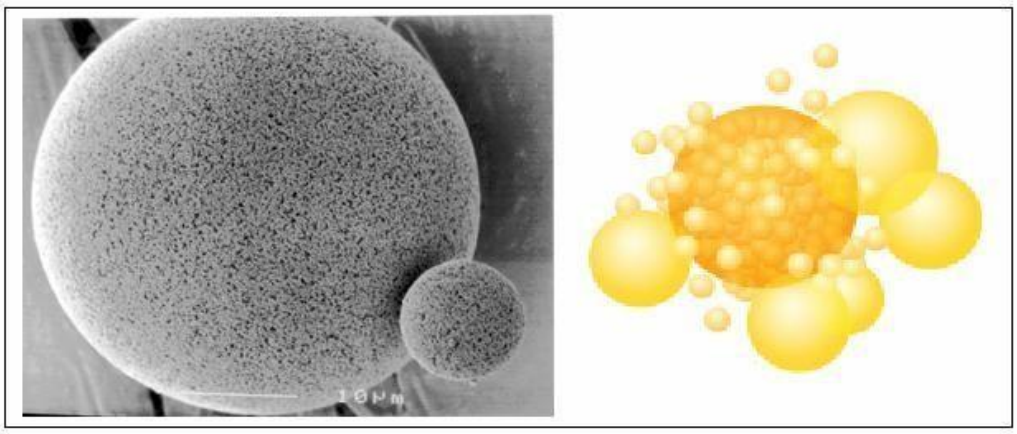

Figure: 1: Structure of Microsponges.

Characteristics of Microsponges[9,10]

- MDS have stable over ranges of pH 1 to11
- They are stable at temperature 130°C
- They are compatible with most vehicles and ingredients
- Free flowing and cost effective
- They have higher pay load is up to 50 –60%
- Microsponge formulations are self sterilizing as their average pore size is 0.25 µm threfore bacteria can not penetrate into microsponges.

Advantages of Microsponges Drug Delivary System(Mds)[11,12]

- Microsponges drug delivary system are microscopic sphere capable of absorbing skin secretions, therefor reducing oiliness and shine from the skin(absorb oil up to 6 times its weight without drying) Eg :- oil free matte block spf 20

- It provide continuous action up to 12 hrs i.e. extended release[13,14,15] Eg :- EpiQuinMicro
- The microsponge system uses microscopic reservoirs that entrap Hydroquinone and retinol.
- The MDS release these ingredients into the skin gradually throughout the day.Improve thermal, chemical, and physical stability.
- These are non-irritating, non mutagenic, non allergic and nontoxic. Eg :- carac cream, 0.5%.

Advantages over conventional formulation

Usually conventional formulations are intended to work on the epidermis layers of the skin producing a highly concentrated layer of active ingredient and that is rapidly absorbed.[16] When compare to the Microsponge system can prevent excessive accumulation of ingredients within the dermis and epidermis layer of the skin. Such products release their active ingredients upon application. Potentially, the Microsponge system can reduce significantly the irritation of effective drugs without reducing their efficacy. For example, by delivering the active ingredient gradually to the skin like MDS-Benzoyl peroxide formulation have excellent efficacy with minimalirritation.[17]

Advantages over microencapsulation and liposomes[18]

The MDS has many advantages over the other technologies like liposome and microencapsulation. Microcapsule cannot usually control the release rate of actives. Once the wall is ruptured the active contained within microcapsules will be released. Liposome does suffer from lower paylod, difficult formulation, limited chemical stability and microbial instability. While microsponge system in contrast to the microencapsulation and liposomes system are stable over wide range of pH 1 to 11 and temperature up to 130^0C compatible with most of the ingredients and vehicles, self sterilizing as average pore size is 0.25µm where bacteria cannot penetrate higher paylod (50-60%) still free flowing and can be cost effective.[19]

Advantages over ointments

Ointments are often aesthetically unappealing, greasiness, stickiness etc. that often results into lack of patient compliance. [20] These type of system require high concentrations of active agents for the maximum effectiveness because of their low efficiency of drug delivery system, resulting into allergic reactions and irritation in significant users. Other drawbacks of

topical formulations are unpleasant odour, potential incompatibility of drugs with the vehicles, uncontrolled evaporation of active ingredient and when microsponge system maximum 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.[21]

Characteristic of Actives That Is Entrapped Into Microsponges

- It should be either miscible in monomer[22] as well as capable of being made miscible by addition of small amount of a water immicible solvent.
- It should be inert to monomers and should not increase the viscosity of the mixture duringformulation.
- It should be water immiscible or nearly only slightlysoluble.
- It should not collapse spherical structure of the microsponge.
- It should be stable in contact with polymerization[23]catalyst and also in conditions of polymerization.
- Not more than 10 to 12%wlw microsponges must be incorporated in to the vehicle in order to avoid cosmeticproblems.
- Paylod and polymer design of the microsponges for active must be optimized for required release rate for given period oftime.

Common Polymers Used In Microsponge Preparation

There are various polymer, which are used in preparation of microsponges. Usually monomers like styrene, Di vinyl benzene, Ethyl vinyl benzene and methyl methacrylate are employed in liquid -liquid suspension polymerization technique. Where Eudragit RS100 and carbopol were employed for quasi emulsification technique. None of the above mentioned polymer were found to be superior to others when properties were compared. Eudragit polymers are copolymers obtained from esters of acrylic and methacrylic acid, whose physicochemical properties are determined by its functional groups. Eudragit polymer are available in a wide range of different physical forms. Eudragit RS100 is employed for quasi emulsificationtechnique.

Method of Preparation of Microsponges[24,25,26]

Based on the physiochemical properties of the drug to be incorporated in microsponge, this is divided in to two ways,

1. One step process or liquid-liquid suspension polymerization
2. Two step process or quasi- emulsion diffusion

1) Liquid-liquid suspension polymerization

In this method the monomers are firstly dissolved along with active ingredients in a suitable solvent solution of monomer and are then dispersed in the aqueous phase with agitation. Aqueous phase usually consists of additives such as dispersants (suspending agent) and surfactants etc in order to facilitate the formation of suspension. Once the suspension is established having distinct droplets of the preferred size then polymerization is initiated by increasing temperature or by the addition of catalyst as well as irradiation.[27] The polymerization method leads to the development of a reservoir type of system that opens at the surface through pores. During the polymerization, an inert liquid immiscible with water however completely miscible with monomer is used to form the pore network in some case. After polymerization process, the liquid is removed leaving the microsponges which is permeate within preformed microsponges then, incorporated the various type of active ingredients like antifungal, anti inflammatory, anti acne, etc and act as a novel carriers for topical drug delivery system.[28]

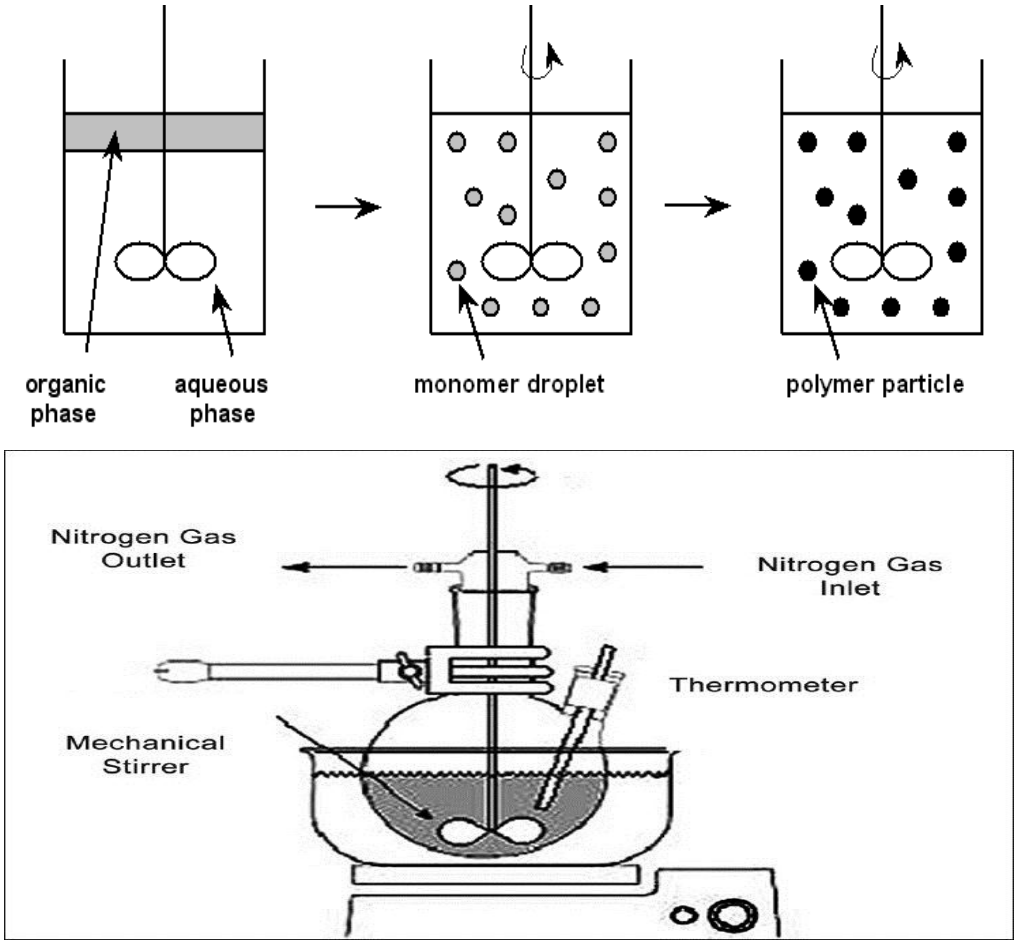

Figure 2: Liquid-liquid suspension polymerization.

The various steps involved in the preparation of microsponges are summarized as follows[29]

Step 1: Selection of monomers and combination of monomers.

Step 2: Formation of chain monomers as polymerizationstarts.

Step 3: Formation of ladders as a result of cross-linking between chainmonomers.

Step 4: Folding of monomer ladder to form sphericalparticles.

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

Step 6: Binding of bunches to produce microsponges.

2) Quasi –emulsion solvent diffusion[30]

In this method external phase and internal phase were used. The internal phase is organic phase containing drug, ethyl alcohol/ acetone (good solvent), polymer and Triethylcithrate(TEC)/ trichloro-methane /Dichloromethane (bridging liquid), which was added at an amount of 20% of the polymer in order to facilitate the plasticity. The external phase mostly consists of distilled water and polyvinyl alcohol(PVA).

Weighed amount of drug and polymer were dissolved in measured quantity of ethanol. The ethanolic solution was formed and then poured into water containing polyvinyl alcohol. The system was thermally controlled at 20°C Ethanol solution was finely dispersed in the aqueous phase as discrete droplet of the polymer solution of the drug were solidified in the aqueous phase via counter diffusion of ethanol and water out the droplets. The formed micro particle were filtered and washed with distilled water before being tray dried at room temperature.

Steps

This is a two step process where the microsponges can be prepared by quasi-emulsion solvent diffusion method using the different polymer.

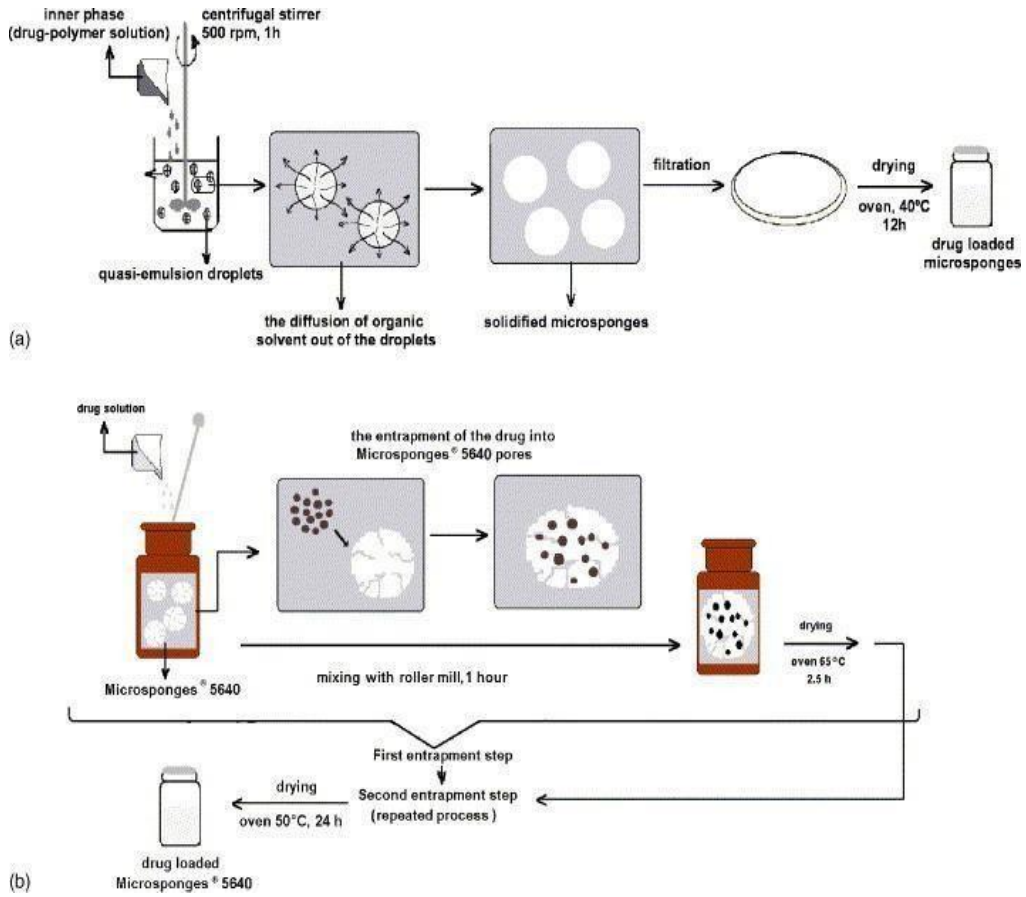

Figure 3: Quasi – emulsion solvent diffusion.

- To prepare the inner phase, Eudargit RS 100 is dissolved in ethyl alcohol.
- Then drug can be added to solution and dissolved under ultrasonication at 35°C
- The inner phase is then poured into PVA solution in water (outerphase)
- Following 60 min of stirring, the mixture is filtered to separate the microsponges.
- The microsponges are in air-heated oven at 40^0C for 12hr and weighed to determine production yield (PY).

Drug Release Mechanism[31]

Microsponges can be intenteded to release given amount of active ingredients over time in response to one or more following external triggers i.e. pressure, pH, temperature change and solubility etc which are described as follows.

Temperature changed[32]: Entrapped materials, such as sunscreens and emollient can be too viscous at room temperature to flow spontaneously from the microsponges onto the skin, when warmed by the skin temperature, the sun and the other heat source , their viscosity may decrease, resulting in an increase flow rate.

pH[33]: The pH responsive MDS involves coating of conventional microsponge delivery system with enteric coating type of material, which imparts pH responsiveness to this system.

Pressure[34]: Rubbing or pressure applied can release the active ingredients from microsponges on to skin.

Solubility[35]: Microsponges loaded with water miscible ingredients like antiseptics and anti-perspirants will release the ingredient in the presence of water. The release is also be activated throught diffusion by taking into consideration, the partition coefficient of the ingredient between the external system and the microsponges.

Effect of Formulation Variables on Physical Properties of Microsponges

a) Effect of composition of internal and external phase

It is formed that particle size of microsponges were directly propotional to the apparent viscosity of dispersed phase. Larger the difference between apparent viscosity of dispersed and contineous phase (external phase), due to the higher viscosity of the internal phase, the globules of the formed emulsion can hardly be divided in to smaller particles and bigger droplets are found resulting in a increase in mean particle size.

Good microsponges can be produce only when 3 to 5ml of internal phase is used.

When the amount of internal phase is increased from 5 to 15ml, the production yield and drug content of microsponge is found to be decreased this is due to the lower amount of the drug in the high volume of internal phase.

b) Effect of drug to polymerratio

When the amount of polymer is kept constant but the ratio of drug to polymer is varied, the drug containing capacity is not much effected by drug to polymer ratio but the production yield can be enormously changed from minimum ratio to maximum one. Another parameters which is effected from the drug polymer ratio change is particle size. It has been observed that the 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**

As the stirring rate is increased microsponge of smaller size are obtained. Increase the stirring rate decrease the production yield but the drug content get increased s 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.

Benefits[36]

The microsponge delivery system offers the following benefits:

- Liquid can be converted topowders.
- Allows for novel product forms advanced oil control – absorbs up to 6 timesits weight withoutdrying.
- Extended release – continuous up to 12hours.
- Reduced irritation – better tolerance means broader consumeracceptance.
- Improved product aesthetics – gives product an elegantfeel.

Flexibility Benefits

- Improve stability – thermal, physical, chemical.
- Allows incorporation of theimmiscible.
- Improves materialprocessing.

Application of Microsponge System[37]

Microsponges are porous polymeric microspheres. Microsponges offers the formulator arrange of alternative to develop drug and cosmetic products. Microsponges are design to deliver a active ingredient efficiently to enhance stability at the minimum dose and also, modify drug release and reduce side effects.

Table 1.

Active agents	Application
Anti inflammatory. Eg ;- hydrocortisone	Long lasting activity with lessening of skin allergic response and dermatoses
Sunscreen	Long lasting product efficacy with improved protection against sun related injuries and sunburns and even at elevated concentration and with reduced irritancy and sensitization.
Anti acne, eg ;- benzoyl peroxide	Maintained efficacy with decreased skin irritation and sensitization
Anti fungal	Sustained release of activities
Antidandruff.	Reduced unpleasant odour with extended
Anti pruritis	Extended and improved activity
Skin Agent	Improved stabilization against oxidation with improved efficacyand aesthetic appeal

Microsponges Drug Delivary System Marketed Formulation[38,39]

Table 2.

Product	Advantage	Manufacture
Retin -A- Micro	0.04% and 0.1% 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
Line eliminator dual facial treatment.	Light weight cream with a retinol (Vitamin A) in microsponges. This dual-system delivers both immediate and time released wrinkle-fighting action. Visibly diminishes appearance of fine lines, wrinkles & skin discolorations associated with aging.	Avon
Retinol cream, retinol 15 night cream	Continued use of Retinol 15 night cream will result in the visible diminishment of fine lines and wrinkles, results in improvement the skin discolorations due to aging, and then enhanced skin smoothness	Biomedic, Sothys
Sports cream RS and XS	Topical analgesic-anti- inflammatory and counterirritant actives in a Microsponge® Delivery System (MDS) for the management of muculoskeletal Condition	Embil Pharmaceutical Co. Ltd
Micropeel plus/ acne peel	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 Micro Peel Plus aggressively out performs other superficial chemical peels by freeing the skin of all dead cells while doing no damage to the skin.	Biomedic
Oil free matte block spf20	This invisible oil-free sunscreen shields the skin from damagingUV sun rays while controlling oil production, giving you a healthy matte finish. This is formulated with MDS technology, Oil Free Matte Block absorbs oil and preventing shine without any powdery residue.	Dermalogica
Oil control lation	A feature-light lotion with technically important microsponges that absorb oil on the skin surface during the whole day, in a matter finish. The naturally- antibiotic Skin Response Complex soothes inflammation and tightness to promoted healing. Acne-Prone.	Fountain cosmetics
Lactrex™ 12% moisturizing cream.	Lactrex™ 12% Moisturizing Cream contains lactic acid 12% as the neutral ammonium salt, ammonium lactate. Microsponge® technology has been included for long lasting moisturization and comfortable application. Lactrex™ also contains	SDR Pharmaceuticals, Inc., Andover , NJ, U.S.A. 07821

	water and glycerin, a natural humectant, for softening and helping moisturize dry, flaky, cracked. Skin	
Dermatologica oil control lotion	A light lotion containing microsponges to absorb oil on the skin's surface and helpfull to enhanced shine and maintain an all-day matter finish. Zinc Gluconate, Yeast Extract, Caffeine and Niacinamide purify and inhibit overactive sebaceous gland activity and soothing irritation.	John and Ginger Dermalogical Skin Care Products
Aramis fragrances	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 and 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. 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 protectance	Scott paper company.

CONCLUSION

Microsponge delivery is prominent strategy to accelerate performance of topical drug as it provides improved stability, enhanced formulation flexibility and increased elegance. Thus overall beneficial effect of Microsponge such as enhanced product performance, extended-release, reduced irritancy, ease of production, elegancy and physical stability of drug confirm the microsponge has great potential as novel approach in the topical drug delivery system.

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