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MICREOSPONGE DELIVERY SYSTEM: AN OVERVIEW

Shikha Deshwal* and Ashwin Kumar Saxena

Department of Pharmaceutics, IFTM University -Delhi Road, Moradabad, 244001, India.

ABSTRACT

The delivery of active material which has final target to skin is not suitable for Transdermal drug delivery system. Conventional dermatological products typically provide active ingredients in relatively high concentrations but with a short duration of action. This may lead to a cycle of short term over medication followed by long term under medication. In contrast, microsponge technology allows an even and sustained rate of release, reducing irritation while maintaining efficacy. Microsponge drug delivery systems are uniform, tiny sponge like spherical polymer particles composed of porous microspheres. Microsponges have the property of absorbing skin secretions, therefore reducing oiliness and shine from the skin. Microsponge products are differing from other types of dermatological drug delivery systems. Microsponges are mostly used as topical formulation and recently used as oral formulation. It gives the opportunity to the formulator a range of alternatives to develop drug and cosmetic products. Micro-sponges 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. This review article covers a brief outline of features of microsponge, advantages of microsponges, Microsponge-manufacturing process, applications in pharmaceutical field, release mechanism ,evaluation Parameters of Microsponges.

Key words: Transdermal drug delivery system, Dermatological, Concentrations, Microsponge, Topical formulation, Release mechanism.

INTRODUCTION

Transdermal delivery system (TDS) delivered the drug in to systemic circulation via skin (Mandava SS, Thavva V, 2012). It has boost up the efficacy and safety of many drugs that may be better administered via skin. But transdermal delivery system is improbable for delivery of materials whose final target is skin itself (Kydonieus AF, Berner B, 1987). No proficient vehicles have been developed for controlled and localized delivery of drugs entity into the stratum corneum and underlying skin layers and not beyond the epidermis. Conventional formulations of topical drugs are proposed to work on the outer layers of the skin. Typically, such products release drug upon application, producing a highly concentrated layer of active medicament that is rapidly absorbed. Furthermore, the significance of topical drugs suffers from various problems like greasiness, stickiness associated with the ointments and so on, that often result in lack of patient compliance In topical formulations, the vehicles should contain high concentrations of active agents for effective therapy because of the low efficiency of delivery system, resulting into irritation and allergic reactions when applied on to the skin. Topical formulations have following drawback as uncontrolled evaporation of active ingredient, unpleasant odor and potential in-compatibility of drugs with the vehicles. Due to the drawback of topical formulation there is a need 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 microsponges meet with these requirements (Chowdary KPR & Rao YS, 2004).

Corresponding Author

Shikha Deshwal
E-mail: shikhadesh128@gmail.com

Microsponge drug delivery systems are uniform, tiny sponge like spherical polymer particles composed of porous microspheres (Figure-1) and this technology was developed by Won in 1987. Microsponges have high degree of cross-linking due to this property their particles that are insoluble, inert particles that are made of synthetic polymers, and of sufficient strength to stand up to the high shear commonly used in manufacturing of creams, lotions, and powders (Kaity S, 2010). Microsponges have the capacity to adsorb or "load" a high degree of medicament into the particle and on to its surface. Microsponges have the property of absorbing skin secretions, therefore reducing oiliness and shine from the skin. Microsponge products are differ from other types of dermatological drug delivery systems because Microsponge entrap large no. of pharmaceutical and cosmetic active ingredients to enhance their performance in topical dermatology products up to three times its weight. Furthermore.The entrapped medicament protected from physical and environmental degradation by microsponge particles (Shaha V *et al*., 2010).

Microsponges are 10-25 microns in diameter, loaded with active entity. For the controlled release of topical agent, the microsponge technology is unique. The microsponge technology releases its active compound on a time mode and also in response to other stimuli like rubbing, temperature, pH, etc on applying to the skin (Vyas SP, Khar RK, 1987). MDS technology is being used in cosmetics, over-the-counter skin care, sunscreens and prescription products. Various formulations can be used microsponge technology, but microsponge drug delivery system is more frequently manufactured as gels. Microsponges slowly release the active medicament when applied on the skin. Minimum dose of pharmaceutically active compound may delivered through Microsponges. Microsponge technology designed to enhance medicament stability, reduce side effects of medicament, and modify drug release profiles. FDA has approved these characteristics for Retin-A Micro® (0.1% or 0.04% tretinoin) and Carac (0.5% 5-flurouracil) products for acne treatment and actinic keratoses, respectively.

The microsponge technology was developed by Won in 1987 and the original patents were assigned to Advanced Polymer Systems. Several predictable and reliable systems were developed for systemic delivered through skin under the title of transdermal delivery system (TDS). It has improved the efficacy and safety of many drugs that may be better administered via skin. But transdermal delivery system is unrealistic for delivery of materials whose final target is skin itself (Chadawar V, Shaji J, 2007).

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. 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 that is rapidly absorbed (Nacht S, Katz M, 1990). Furthermore, the significance of topical drugs suffers from various problems like greasiness, stickiness associated with the ointments and so on, that often result in lack of patient compliance. These vehicles necessitate a high concentration 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. The fundamental appeal of the microsponge technology stems from these difficulties experienced with conventional formulations in releasing active ingredients over an extended period of time. Conventional dermatological products typically provide active ingredients in relatively high concentrations but with a short duration of action. This may lead to a cycle of short term over medication followed by long term under medication. In contrast, microsponge technology allows an even and sustained rate of release, reducing irritation while maintaining efficacy (Parikh BN *et al*., 2010).

Features of Microsponges

a) Microsponge formulations are stable at the temperature up to 130˚C
b) Microsponge formulations are compatible with most vehicles and ingredients
c) These are stable over range of PH 1 to 11
d) These are self sterilizing as their average pore size is 0.25μm where bacteria cannot penetrate
e) Microsponge formulations have higher payload (50 to 60%), still free flowing and can be cost effective (Chandramouli Y *et al*., 2012)

Advantages of Microsponge Delivery System

a) Microsponge can absorb oil up to 6 times its weight without drying.
b) Microsponge provides continuous action up to 12 hours i.e. extended release.
c) It Improved product elegancy.
d) It minimizes the irritation and it gives better tolerance which leads to improved patient compliance.
e) It can also enhance efficacy in treatment.
f) They have better thermal, physical and chemical stability.
g) These are non-irritating, non-mutagenic, non-allergenic and non-toxic.
h) Microsponge technology allows the incorporation of immiscible products.

i) Microsponge develop novel product due to its flexibility nature.
j) In contrast to other technologies like microencapsulation and liposomes, MDS has wide range of chemical stability, higher payload and are easy to formulate.
k) Liquids can be converted in to powders improving material processing (Aritomi H *et al*., 1996; Tansel C, Baykara T, 2002).

Characteristics of substances that is entrapped in microsponge

Most liquid or soluble ingredients can be entrapped in the microsponge particles. Active ingredients should be either fully miscible in monomer or capable of being made miscible by addition of small amount of a water immiscible solvent.

a) Active ingredients should be inert to monomers.
b) Active ingredients should be water immiscible or at most only slightly soluble.
c) Active ingredients should be stable in contact with polymerization catalyst and conditions of polymerization.
d) The solubility of actives in the vehicle must be limited to avoid cosmetic problems, not more than 10 to 12% w/w microsponges must be incorporated into the vehicle. Otherwise the vehicle will deplete the microsponges before the application.
e) Polymer design and payload of the microsponges for the active must be optimized for required release rate for given time period.

These standards act as porogen or pore forming agent. Such active substance can be entrapped while polymerization takes place by one-step process. While when the drug substance is sensitive to the polymerization conditions, polymerization is performed using substitute porogen. Microsponge delivery system can be incorporated into conventional dosage forms such as creams, lotions, gels, ointments, and powder and share a broad package of benefits (Kawashima Y *et al*., 1992; D'souza JI *et al*., 2005).

Microsponge-manufacturing process

Microsponges entrap active medicament, entrapment of active entity can take place in two ways, based on physicochemical properties of medicament. Liquid-liquid suspension polymerization which is one step process and quasi emulsion solvent diffusion techniques which is two-step process are used for entrapment of drug in microsponges. When drug create the porous structure it is called porogen, for porogen character, drug should behave as typically an inert non-polar material. 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

It is also called as Bottom-up approach (starting with monomer). In general, a solution phase is made containing of monomers and the active entity (non polar). This solution phase is then suspended with agitation in an aqueous phase compromising additives such as surfactants and dispersing agents. Once the suspension is formed with discrete droplets of desired size, polymerization is effected by activating the monomers either by catalysis, increased temperature or irradiation. (Figure 2) (Anonymous 1)

The polymerization process leads the formation of a reservoir type of system with spherical structure. After the polymerization process the solvent is removed leaving the spherical structured porous microspheres, i.e., microsponges. The particles are then washed and processed until they are substantially ready for use. The various steps involved in the preparation of microsponges are summarized in scheme 1 (Anderson DL *et al*., 1994) as follow:

Quasi-emulsion solvent diffusion

Quasi-emulsion solvent diffusion method (Top-down approach) also named as two-step process is used for those drugs which are sensitive to the polymerization conditions. In quasi-emulsion solvent diffusion method, the microsponges formed using an internal phase containing polymer such as eudragit RS 100 which is dissolved in ethyl alcohol. Then, the drug is slowly added to the polymer solution and dissolved under ultrasonication at 35˚ C and plasticizer such as triethylcitrate (TEC) was added in order to aid the plasticity. In this, the external phase consists of 200 ml distilled water and 40 mg polyvinyl alcohol (PVA). The inner phase was poured into the PVA solution in water (outer phase). After emulsification, the mixture was continuously stirred for 2 hours. Then the mixture was filtered to separate the microsponges. The product was washed and dried by vacuum oven at 40°C for 24 hours. (Shown in fig. 3)

Release Mechanism

Vehicle contain active ingredient in an entrapped form. The particles of microsponge delivery system are an open structure in nature, so the active intity is free to diffuse in and out from the particles and into the vehicle until equilibrium is reached. When microsponge product is applied to the skin, the drug that is present in vehicle will be absorbed into the skin, depleting the vehicle, which will become unsaturated, therefore, disturbing the equilibrium. This will begin a flow of the drug 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 drug to the skin,

providing prolonged release over time. Release can also be controlled through diffusion or other external triggers such as pressure, temperature and solubility (Embil K, Nacht S, 1996; Khopade AJ *et al*., 1996; Shah VP, 1989).

Pressure

Pressure/ Rubbing applied can release drug from microsponge onto skin.

Temperature change

Flow rate of active entity increase with increase in temperature.At room temperature, few entrapped active ingredients can be too viscous to flow suddenly from microsponges onto the skin.

Solubility

The microsponge composed with water-soluble ingredients like anti-perspirants and antiseptics will release the ingredient in the presence of water. Thus the ability of external medium plays a significant role to dissolve the active ingredient, the concentration gradient varies or the ability to swell the microsponge network.

Applications of microsponge systems

Microsponges are mostly used as topical formulation and recently used as oral formulation. It gives the opportunity to the formulator a range of alternatives to develop drug and cosmetic products. Micro-sponges 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. (Table-1) (Barkai A *et al*., 1990)

Marketed Formulations: Microsponge delivery systems are used for topical prescription, over-the-counter (OTC) and personal care products. Products under development or in the marketplace utilize the topical microsponge system in three primary ways (The marketed products are shown in table 2).

- As reservoirs releasing active ingredients over an extended period of time
- As receptacles for adsorbing undesirable substances, such as excess skin oils
- As closed containers holding ingredients away from the skin for superficial action

Evaluation Parameters of Microsponges

Drug release from microsponges affected by various factors. Microsponges can be evaluated by following factors.

Particle Size Determination

Particle size analysis of microsponges can be performed by laser light diffractometry or any other suitable method. The values of particle size (d50) can be expressed for all formulations as mean size range. Particle size of microsponge effect the drug release. Cumulative percentage drug release from microsponges of different particle size will be plotted against time to study effect of particle size on drug release. Particles larger than 30 μm can impart gritty feeling and hence particles of sizes between 10 and 25 μm are preferred to use in final topical formulation (Martin A *et al*., 1991).

Morphology and Surface Topography of Microsponges

Scanning electron microscopy (SEM) was conducted to studied drug morphology and surface topography, of prepared microsponges. For SEM study, Microsponges can be coated with gold–palladium under an argon atmosphere at room temperature and then the surface morphology of the microsponges can be studied.SEM of a fractured microsponge particle can also be taken to illustrate its ultra structure (Emanuele AD, Dinarvand R, 1995).

Determination of Loading Efficiency and Production Yield

The loading efficiency (%) of the microsponges can be calculated according to the following equation .The production yield of the microsponges can be determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponge obtained (Kilicarslan M, Baykara T, 2003).

Determination of True Density

The true density of microsponges was measured using an ultra-pycnometer under helium gas and was calculated from a mean of repeated determinations (Barkai A *et al*., 1990).

Characterization of pore structure

Pore volume and diameter play a vital role in controlling the intensity and duration of effectiveness of the drug. Pore diameter also affects the migration of active ingredients from microsponges into the vehicle in which the active medicament is dispersed. Mercury intrusion porosimetry can be employed to study effect of pore diameter and volume with rate of drug release from microsponges. Porosity parameters of microsponges such as intrusion–extrusion isotherms pore size distribution, total pore surface area, average pore diameters, shape and morphology of the pores, bulk and apparent density can be determined by using mercury intrusion porosimetry (Anonymous 2).

Compatibility studies

Thin layer chromatography (TLC) and Fourier Transform Infra-red spectroscopy (FT-IR) are used to suggested the Compatibility of drug with reaction adjuncts .powder X-ray diffraction (XRD) and Differential Scanning Colorimetry (DSC) are used to studied Effect of polymerization on crystallinity of the

drug. For DSC approximately 5 mg samples can be accurately weighed into aluminum pans and sealed and can be run at a heating rate of 15oC/min over a temperature range 25–430oC in atmosphere of nitrogen.

Polymer / Monomer Composition

In microsponge delivery system, the drug entrapped between the vehicle and the microsponge system. Polymers of MDS can affect partition coefficient of the entrapped drug and have direct influence on the release rate of entrapped drug. Release of drug from microspongel systems of different polymer compositions can be studied by plotting cumulative % drug release against time. Monomer should be suitable with vehicle into which it will be dispersed and characteristics of drug to be entrapped.

Resiliency

Resiliency (visco-elastic properties) Increased cross-linking in microsponge system which 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 (Dsouza JI *et al*., 2004).

Dissolution Tests

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

Determination of loading efficiency and production yield

The loading efficiency (%) of the microsponges can be calculated according to the following equation: Loading efficiency = Theoretical Drug Content/Actual Drug Content in Microsponges X 100.

The production yield of the microparticles can be determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponge obtained. Production Yield (PY) = Theoretical Mass (polymer drug) /Practical Mass of Microsponges X 100

Table 1. Applications of Microsponge system

S.No.	Active agents	Applications
1	Sunscreens	Long lasting product efficacy, with improved protection against sunburns and sun related injuries even at elevated concentration and with reduced irritancy and sensitization.
2	Anti-acne e.g. Benzoyl peroxide	Maintained efficacy with decreased skin irritation and sensitization.
3	Anti-inflammatory e.g. hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatoses.
4	Anti-fungals	Sustained release of actives.
5	Anti-dandruffs e.g. zinc pyrithione, sele-nium sulfide	Reduced unpleasant odour with lowered irritation with extended safety and efficacy.
6	Antipruritics	Extended and improved activity.
7	Skin depigmenting agents e.g. hydroquinone	Improved stabilization against oxidation with improved efficacy and aesthetic appeal.
8	Rubefacients	Prolonged activity with reduced irritancy greasiness and odour.

Table 2. Marketed products based on MDS

Product Name	Advantages	Manufacturer
Retin-A-Micro	0.1 And 0.04% tretinoin entrapped in MDS, for topical treatment of acne vulgaris. This formulation uses patented methyl methacrylate / glycol+8 dimethacrylate cross-polymer porous microspheres.	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.	Dermik Laboratories, Inc.Berwyn,PA19312 USA
Line eliminator dual retinol facial treatment	Lightweight cream with a retinol (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	Biomedic

	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.	
Retinol 15 night cream	A night time treatment cream with Microsponge system. The formula contain of pure retinol. Continuous use of Retinol 15 will result in the visible diminishment of fine lines and wrinkles, and improve in skin discolorations.	Biomedic,sothys
Epi Quin micro	The Microsponge® system entraps hydroquinone and retinol. The microsponges release these ingredients into the skin gradually throughout the day, which may minimize skin irritation	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	Embil Pharmaceutical.
Salicylic peel 20 and 30	Deep BHA peeling agent: Salicylic acid 20% and 30%, 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
Micro peel plus	The Micro Peel® Plus, stimulates cell turnover through the application of salicylic acid in the form of microcrystals using Microsponge® technology. The Micro Peel® 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 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. Oil-free formula contains soothing Green Tea to help calm inflammation caused by breakouts. Cornstarch and Vinyl Dimethicone/Methicone Silsesquioxane Cross-polymer act as microsponges to absorb excess surface oils on skin.	Dermatological
Oil control lotion	Feature-light lotion 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. The natural-antibiotic Skin Response Complex soothes inflammation and tightness to promote healing, Acne-Prone, oily skin conditions	Fountain Cosmetics
Lactrex™ 12% moisturizing cream	It contains 12% lactic acid as the neutral ammonium salt and ammonium lactate. Lactrex™ also contains water and glycerin, a natural humectant, to soften and help moisturize dry, flaky, cracked skin.	SDR Pharmaceuticals, Inc., Andover, NJ, .S.A. 07821
Dermalogica oil control lotion	It 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	Scott Paper

Fig 1. Microsponge System (Porous Microspheres)

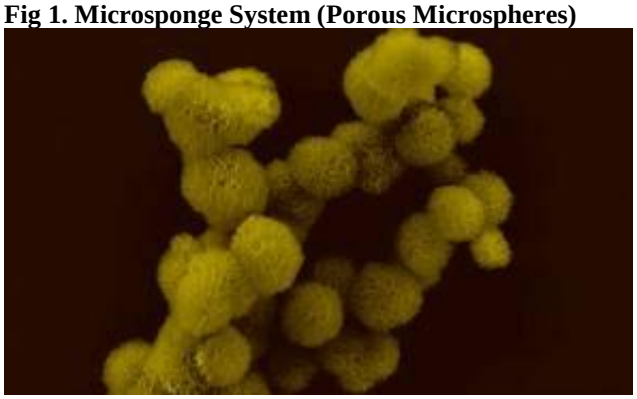


Fig 2. Reaction vessel for microsponge preparation by liquid-liquid suspension method

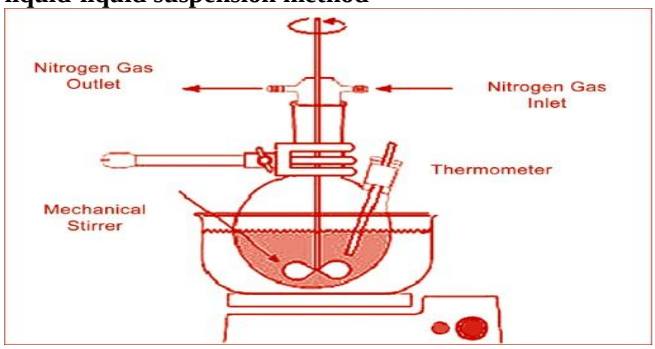
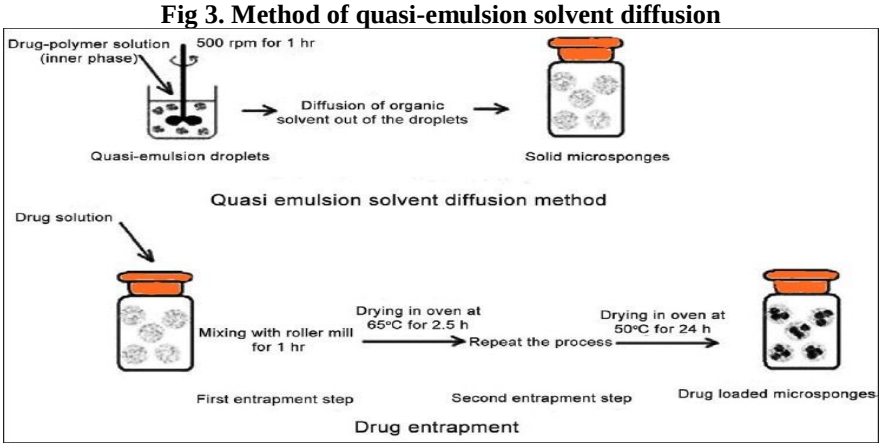


Fig 3. Method of quasi-emulsion solvent diffusion



CONCLUSION

This review suggests that, Microsponge products are differ from other types of dermatological drug delivery systems because Microsponge entraps large no. of pharmaceutical and cosmetic active ingredients to enhance their performance in topical dermatology products up to three times its weight. Microsponges are 10-25 microns in diameter, loaded with active entity. For the controlled release of topical agent, the microsponge technology is unique. The microsponge technology releases its active compound on a time mode and also in response to other stimuli like rubbing, temperature, pH, etc on applying to the skin. The various criteria of drug which are include in transdermal patches such as Active ingredients should be inert to monomers. Active ingredients should be water immiscible or at most only slightly soluble. Active ingredients should be stable in contact with polymerization catalyst and conditions of polymerization.

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