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MICROSPONGES: AS A TOPICAL DRUG DELIVERY SYSTEM

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ABSTRACT: Now a day's control delivery of the drug is easily achieved by Microsponge delivery system. These microsponges are very similar to polymeric porous microspheres. In general microsponges are 5-300 micron in diameter, spherical in shape, large porous surface, tiny in structures. Microsponges generally used in the topical drug delivery system but recently they are used for oral administration of drugs. Microsponges deliver its drug on regular time intervals and also respond to the other stimulations. A microsponge has advantages that they modify the release of the drug enhances the stability and effectively reduces the side effects of the drugs. The main aim of formulation is to achieve desired concentration of the drug in the blood. When these microsponges used topically they prevent the accumulation of the drug in both dermis and epidermis. Microsponges can easily entrap and formulated into pharmaceutical product such as gels, creams, powders, liquids, and suspensions. One of the best features of microsponges is it has self-sterilization property; numerous study has confirmed that microsponges are non- mutagenic, non-irritant, non-allergic and non-toxic in nature. This article elaborates the history, advantages, preparation and evaluation and applications of microsponge.

INTRODUCTION: Drug delivery systems (DDS) that can precisely control the release rate or target drugs to a specific body site have had an enormous impact on the healthcare system. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle (such as microspheres, nanoparticles, liposomes, *etc.*) which modulates the release and absorption characteristics of the drug [1].

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In recent years, there has been considerable emphasis given to the development of novel microsponge based drug delivery systems, 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 like especially in aging or photodamaged 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 [2]. The major problem associated with TDS is most of the drugs are poorly water-soluble which pose many problems while formulating them in conventional dosage forms [3]. Another potential problem in topical drug delivery system of drugs-related is uncontrolled evaporation of the active ingredient, unpleasant odor, the use of unaesthetic vehicles which may be greasy, sticky, and may cause discolorations since this can result in the lack of patient compliance [4, 5, 6].

Microsponge History: The microsponge technology was developed by Won in 1987, and the original patents were assigned to advanced polymer system, Inc. This company developed a large number of variations of the techniques and applied those to the cosmetic as well as OTC and physician prescribed products [7].

Prospective Features of Microsponge: Microsponges are proved as a novel controlled pharmaceutical product. They can entrap a wide variety of drugs either in solid or in liquid form. They have high entrapment efficiency, they may absorb more than six times their weight. They are stable at high temperatures and pH ranging 1-11. They show good compatibility when they are suspended in other vehicles and liquid or semi-solid dosage forms. They produce elegance of the product releases the drug in controlled manner, stable and nonirritating which improve the patient compliance [8, 9, 10, 11].

Superiority over Other Pharmaceutical Formulations: Microsponge leads over-marketed pharmaceutical preparation.

A) Superior to Conventional Pharmaceutical Formulations: Generally semi-solid or biphasic liquid systems are available as topical delivery of drugs. They release the drug on the outer most layer of the skin. These conventional formulation showed rapid releases of the drug which may also absorb and accumulated in the epidermis and dermis layer of the skin. The high accumulation of the drug gives side effects, irritation, and toxicity. These problems are overcome with the microsponge drug delivery system. They release the drug gradually and in controlled manner to the skin [12, 13, 14].

B) Over Micro and Nano-formulation: The pharmaceutical companies especially those companies who prepared controlled topical dosage forms shown their keen interest toward microsponge nowadays.

Microsponges are advantageous over the microsphere, microencapsulation, niosomes, lipid nanoparticles, nanotubes, liposomes *etc*. in the terms of their compatibility with large number of drugs (Ketoprofen, benzyl peroxide, retinol, fluconazole, ibuprofen, tertinoin, trolamine, prednisolone, acyclovir sodium, ticonazole) due to high capacity of drug loading, easy formulation technique, control release, physical, chemical and microbial stability [15, 16, 17, 18, 19, 20, 21].

Formulation and Ingredient for Microsponge Preparation: Various polymers were reported to form microsponge 'cage'. Polymers studied for the fabrication of microsponges for the oral or topical purposes include Eudragit RS-100, Eudragit RS PO, Eudragit S-100, polylactide-co-glycolic acid, polylactic acid, polydivinyl benzene, and polyhydroxyl butyrate. Eudragit RS-100 formed the most widely studied polymer due to its versatility enabling the researchers to employ it in various ways. Eudragit RS PO also modulated the drug release along with enhancing the solubility of the drug by forming a solid dispersion like structure. Polylactide-co-glycolic acid and polylactic acid were studied for delivering the proteins and peptides.

Microsponges fabricated with these polymers also possessed floating ability due to the hydrophobicity of the polymer which limited the wetting of the particles with aqueous media, thus these microparticles can be employed for fabricating floating microsponges. Polydivinyl benzene was studied for fabricating the porous microparticles by polymerization technique using divinylbenzene as monomer but entrapping the drug with this process

may cause alteration in structure of drug molecule or conjugation of drug with monomer. The use of such a large variety of polymers for the fabrication of the microsponges showed that the method of preparation of microsponges can be modified as per the requirement. In addition to polymers and active ingredients, some researchers also used triethyl citrate as plasticizer that helps to stabilize the resilient property of the microsponges. During the preparation of microsponges by quasi-emulsion solvent diffusion method, it is reported that the presence of an emulsifier having tendency to maintain the viscosity of aqueous phase is compulsory. Researchers attempted the use of cellulose ethers and PVA for such role and found the use of PVA as a better emulsifier [22, 23].

List of Polymers used for the Preparation of Microsponge:

- Ethylcellulose
- Eudragit RS 100
- Eudragit RL 100
- PHEMA
- Polystyrene
- Acrylic polymer
- Carbapol 934
- Polyvinyl alcohol

Preparation Methods of Microsponge: The drug loading in microsponge drug delivery system is done in two ways, the one-step process or by two-step processed as discussed in liquid-liquid suspension polymerization and Quasi emulsion solvent diffusion method which are based upon the physicochemical properties of the drug that is loaded to be. If the drug is typically inert non- polar material, will create the porous structure it is called porogen. Porogen drug, which neither hinders the polymerization nor becomes activated by it and stable to free radicals are entrapped with one step process [24].

A) 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.

Polymerization process produced 1000 of microsponge cages which are spherical in structure interconnected with each other seems to look like a grapes bunch. On completion of polymerization produced solid particles were recovered from the suspension. Particles were washed and dried for further use [25].

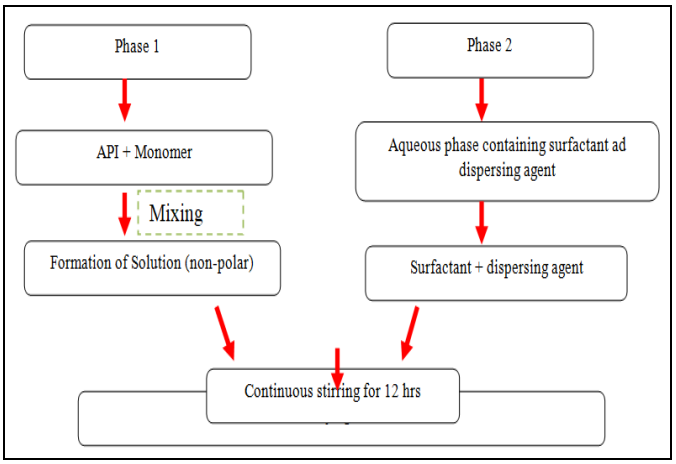

FIG. 1: PREPARATION OF SUSPENSION FOR LIQUID-LIQUID SUSPENSION POLYMERIZATION

B) Quasi-Emulsion Solvent Diffusion: This method is generally used for the preparation of oral and topical microsponges. In this method two phases were prepared, inner organic phase and outer aqueous phase.

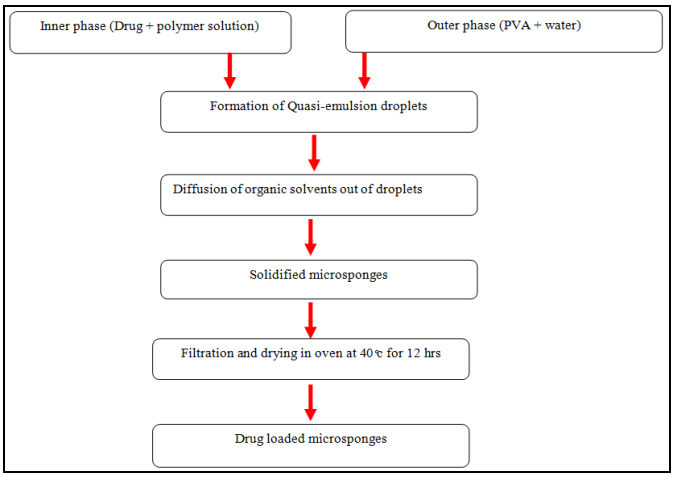

FIG. 2: QUASI-EMULSION SOLVENT DIFFUSION

In the inner organic phase polymer is dissolved in ethyl alcohol and drug is dissolved in this solution by ultrasonication at room temperature. The outer phase consists PVA solution in water. The solution

is stirred and filtered for further use. The inner phase mixed in outer phase on mechanical stirrer dropwise. On the stirring the Quasi emulsion droplet was formed which may further evaporation of organic solvent produces the solid microsponge cages. The prepared microsponges are filtered and dried in oven for 12 h [26, 27, 28].

C) Multiple-emulsion Solvent Diffusion: This novel technique was developed to prepare biodegradable porous microspheres. In this method, an internal aqueous phase containing an emulsifying agent like span, polyethyleneimine, and stearyl amine was dispersed in organic polymeric solution. Thereafter, this w/o emulsion was again dispersed in external aqueous phase containing PVA to form a double emulsion.

This method has the advantage of entrapping both water-soluble and water-insoluble drugs. It can also be used for entrapping thermolabile materials like proteins. Some authors also described the xanthan gum as an emulsifier to stabilize the internal w/o emulsion [30, 31].

D) Addition of Porogen: In this technique internal multiple emulsions was replaced by a porogen like hydrogen peroxide or sodium bicarbonate. For this, the porogen was dissolved in the polymeric solution to form a single-phase system which was redispersed in aqueous phase containing PVA. An initiator was then added to the multiple emulsion and the organic solvent was allowed to evaporate to leave the microparticles for producing microsponges [32]. The effect of incorporating hydrogen peroxide resulted in the formation of evenly distributed and interconnected pores with diameters ranging from 5 to 20 μm.

E) Oil in Oil Emulsion Solvent Diffusion: In contrast to w/o/w method, oil in oil (o/o) emulsion was prepared using volatile organic liquid as the internal phase that was allowed to evaporate slowly at a controlled rate with continuous stirring. As reported the technique used dichloromethane as the solvent for internal phase, polylactide glycolic acid as polymer and a mixture of fixed oil (corn or mineral) and dichloromethane containing span 85 as external phase. The internal phase was added dropwise to the dispersion medium with continuous stirring to get the microsponges. This technique was utilized for development of hydroxyzine HCl-loaded Eudragit RS-100 microsponges using acetone as dispersing solvent and liquid paraffin as the continuous medium. Selection of the organic solvent and external phase depend on the physicochemical properties of the drug and the polymer used for fabrication of microsponges [33, 34].

F) Lyophilization: Lyophilization as the technique was used for converting the microspheres prepared by gelation technique, to porous microspheres. In this methodology, the microspheres were incubated in the solution of chitosan hydrochloride and then lyophilized. Quick removal of solvent led to formation of pores in the microspheres. This method is quick and rapid but has the disadvantage of producing cracked or shrunken microparticles due to quick elimination of solvent [35].

G) Vibrating Orifice Aerosol Generator Method: Vibrating orifice aerosol generator (VOAG) was first reported for the preparation of lipid bilayered mesoporous silica particles. The method involved the synthesis of porous particles by evaporation-driven surfactant templating in microdroplets by a VOAG method. For the preparation of core particle tetraethylorthosilicate, ethanol, water and dilute hydrochloric acid were refluxed to prepare stock solution. The stock solution was diluted with the solvent containing surfactant and stirred to allow the formation of monodisperse droplets using VOAG. The microspheres produced were encapsulated in the liposomes. These encapsulated particles can be utilized for targeted drug delivery of actives [36].

H) Ultrasound-Assisted Production: This method was developed by modifying the liquid-liquid suspension polymerization. The microsponges are synthesis by utilizing the monomer beta-cyclodextrin (BCD) and cross-linking agent diphenyl carbonate. Size control of the microparticles was accomplished by heating and sonication of the reaction mixture. Then reaction mixture was allowed to cool, the product obtained was milled to give rough particles that were washed with distilled water and then by ethanol. The porous microparticles of cross-linked β-CD can serve as carrier for efficient loading of drugs. However, this method has the limitation of entrapment of residues of the cross-linking agents that can be potentially toxic [17].

J) Electrohydrodynamic Atomization Method: Porous microsphere of chitosan was produced by this method. Chitosan solution was sonicated to generate bubbles and the resultant bubble suspension was drawn into a syringe, perfused through a steel capillary using a syringe pump and finally subjected to electrohydrodynamic atomization. The diameter of the capillary was chosen to retain all bubbles in the suspension while it flowed through it. The voltage used in the experiments solely depends on the concentration of chitosan in the solution. The combination of flow rate and applied voltage resulted in the stable cone-jet mode in each case, except when highest concentration was used that was difficult to electrospray. The chitosan microspheres were cross-linked by 4% w/v sodium hydroxide aqueous solution [37].

Release Mechanism: The active ingredient entrapped in the microsponges may release by 4 mechanisms:

A) Pressure Triggered Release Mechanism: The entrapped drug is released from microsponge when they are pressurized or rubbed. The amount released depends upon the size and number of pore available on the sponge [38].

B) Temperature triggered Release Mechanism: The active ingredients loaded in microsponges are viscous at storage temperature. On the application onto the skin by the means of rubbing or increase in temperature reduces the viscosity the active drug may flow out vigorously the skin. Sometimes by increasing the temperature of the skin may enhance the fluidity of drug. The release of the drug is easily modulated by changing the temperature [39, 40, 41].

C) pH Triggered Release Mechanism: In this mechanism microsponge is coated with the pH-dependent polymers. On the specific pH these polymers either swelled or leached out from the microsponges. After leaching of pH-dependent polymer the drug released from the Microsponges. Coating of the microsponge increases the application of drug delivery to site-specific delivery.

D) Solubility Triggered Release Mechanism: When water-soluble drug loaded in microsponge it release only in presence of water. The rate of drug release from microsponge can be triggered by the amount of aqueous medium [42].

Applications of Microsponges Drug delivery Systems: Microsponges are designed to deliver the pharmaceutically active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects and modify drug release. Microsponges are porous, polymeric microspheres that are used mostly for topical but recently used for oral administration.

A) Microsponge 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. A single microsponge is as tiny as a particle of talcum powder, measuring less than one-thousandth of an inch in diameter. 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. Microsponge systems are made of biologically inert polymers. Extensive safety studies have demonstrated that the polymers are non-irritating, non-mutagenic, non-allergenic, non-toxic and non-biodegradable. As a result, the human body cannot convert them into other substances or break them down. Although they are microscopic in size, these systems are too large to pass through the stratum corneum when incorporated into topical products [35].

Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne, with skin irritation as a common side effect. It has been shown that the controlled release of BPO from a delivery system to the skin could reduce the side effect while reducing percutaneous absorption. Therefore, microsponge delivery of benzoyl peroxide was developed using an emulsion solvent diffusion method by adding an organic internal

phase containing benzoyl peroxide, ethylcellulose and dichloromethane into a stirred aqueous phase containing polyvinyl alcohol and by suspension polymerization of styrene and divinylbenzene. The prepared microsponges were dispersed in a gel base, and microsponge gels are evaluated for anti-bacterial and skin irritancy. The entrapped system released the drug at slower rate than the system containing free BPO. Topical delivery system with reduced irritancy was successfully developed [43-53].

B) Microsponge for Oral Drug Delivery: 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 of solubilization.

Controlled oral delivery of ibuprofen microsponges is achieved with an acrylic polymer, eudragit RS, by changing their intraparticle density [50]. Sustained release formulation of chlorpheniramine maleate, using powder-coated microsponges, is prepared by the dry impact blending method, for oral drug delivery [54]. Controlled oral delivery of Ketoprofen prepared by quasi-emulsion solvent diffusion method with Eudragit RS 100 and afterward 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 tablet [55].

C) 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 [56]. The basic fibroblast growth factor incorporated in a collagen sponge sheet was sustained release in the mouse sub-cutis according to the biodegradation of the sponge matrix and exhibited local angiogenic activity in a dose-dependent manner. Intramuscular injection of collagen microsponges incorporating fibroblast growth factor, 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 T fibroblast growth factor these results suggest the significance and therapeutic utility of the type I collagen as a reservoir of fibroblast growth factor [57].

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 [59]. A thin biodegradable hybrid mesh of synthetic poly (DL-lactic-co-glycolic acid) (PLGA) and naturally derived collagen was used for 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 [61]. A tissue-engineered patch made of our biodegradable polymer and collagen-microsponge provided well 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 [60].

Evaluation Methodology of Microsponge: [61-74]
Various evaluation tests were performed to evaluate the prepared formulations of microsponges:

A) Total Yield Percentage and Loading Efficiency: The total yield percentage of prepared Microsponge is calculated by the formula:

% Yield =Actual weight of product/total weight of product × 100

B) Scanning Electron Morphology (SEM): SEM by using the SEM the morphology surface topography and particle size diameter can be easily studied.

C) Characterization of Pore Structure: Pore volume and diameter are vital in controlling the intensity and duration of effectiveness of the active ingredient. Pore diameter also affects the migration of active ingredients from microsponges into the vehicle in which the material is dispersed. Mercury intrusion porosimetry can be employed to study effect of pore diameter and volume with the 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, interstitial void volume percent porosity, percent porosity filled, shape and morphology of the pores, bulk and apparent density can be determined by using mercury intrusion porosimetry.

D) *In-vitro* Dissolution Studies: The dissolution pattern of the active ingredient of the microsponge can be estimated by USP dissolution apparatus. 900 ml of stimulated solution at 37 ± 0.5 ºC are used to determine to dissolution behavior of the drug.

E) Stability Studies: The accelerated stability studies are carried out according to guidelines given by the International Council of Harmonization (ICH guidelines). The formulations are tested for stability at 50 ± 2 ºC, 250 ± 2 ºC/ 60 ± 5 RH, 400 ± 2 ºC/ 75 ± 5 RH. Formulations are stored in glass bottles/vials and are evaluated after every 15, 30, 45 days for their physiochemical characteristics.

F) Drug-Polymer Compatibility Studies: The sample of drug, excipients, and mixture of drug with excipients (binary (1:1) powder mixtures prepared by triturating drug with the individual excipients) was sealed in vials and kept at room temperature for not less than one month and then samples were analyzed by DSC, XRD, and FTIR.

Advancement in Microsponge Drug Delivery System: Pharmaceutical companies step ahead in the Microsponge technologies. Nowadays by modifying the method they are involved in nanosponges, nanoferrosponges, and porous microbeads. These formulations are more established and stable than the microsponges.

A) Nanosponges: Nanosponges are the nanoformulations which are used in topical drug delivery, especially the cosmetic agents passive targeting. These are helpful for absorption through the skin and extended retention in the layer of skin. These nanosponges developed by modifying the Solvent diffusion method. Either change in the agitation, amount of polymer and emulsifying agent can be easily produced nanosponges. Some researcher also showed that nanosponges are good carrier for the delivery of active ingredient which is available in gaseous form. These nanosponges carriers are also responsible for targeting cancerous cells [75-85].

B) Nanoferrospong: The nanoferrosponges are nano targeting devices consisting of ferric ions which may triggered with the help of magnet. The magnet enforces the carrier to stimulate to the deeper tissues and provide the drug at specific target site. These nanoferrosponges were prepared by co- precipitating of magnetic material with polymers. The prepared Nanoferrosponge have in high swelling index, excellent elasticity, hydrophilicity, and response to magnetism [86-90].

C) Porous Microbeads: Improved characteristics of porous microsphere produces the microbeads which have a large number of pores. Polymerization and cross-linking technologies are used to developed solid porous microbeads. These microbeads are used for topical, buccal and oral drug delivery system [91-92].

TABLE 1: LIST OF MARKETED PRODUCTS BASED ON MICROSPONGES

Product Name	Pharmaceutical uses	Manufacturer
Retinol cream	Helps maintain healthy skin	Biomedic
Salicylic Peel 20	Excellent exfoliation	Biophor
Ultra Guard	Protects baby's skin	Scott Paper Company
Oil-free matte block SPF 20	Sunscreen	Dermalogica
Benzoyl peroxide	Anti Acne	
Retin A Micro	Acne vulgaris	Ortho-McNeil-Pharmaceutical, Inc
Glycolic Acid Moisturizer w/SPF 15,	Anti-Wrinkles	AMCOL Health & Beauty Solution
EpiQuin Micro	Hyper pigmentation	SkinMedicaInc

Future Aspects of Microsponge Drug Delivery System: 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 active 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 an 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, over-the-counter skincare, sunscreens, and prescription products. This kind of drug delivery technology may lead to a better understanding of the healing of several diseases. Hence, 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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