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MICROSPONGE GEL FOR TOPICAL DELIVERY – RECENT REVIEW

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Abstract Microsponge is recent novel technique for control release and target specific drug delivery system. Therefore many scientist or researcher attracted towards the microsponge drug delivery system. Also Microsponge technology has been introduced in topical drug products to facilitate the controlled release of active drug into the skin in order to reduce systemic exposure and minimize local cutaneous reactions to active drugs. Microsponge consists of microporous beads loaded with active agent when applied to the skin, the microsponge releases its active ingredient on a time mode and also in response to other stimuli (rubbing, temperature, pH etc.) that are used mostly for topical and recently for oral administration. Microsponge technology has many favorable characteristics which make it a versatile drug delivery vehicle. Microsponge delivery system (MDS) can entrap wide range of drugs and then release them into the skin over a time by diffusion mechanism to the skin. Microsponges can entrapped various type of drug and incorporated in formulation such as cream, powder, gels, and lotions. Topical preparation have some disadvantages like unpleasant odor, greasiness and skin irritation and fail to reach the systemic circulation this problem is overcome by microsponges delivery system. Microsponges can entrapped various type of drug and incorporated in formulation such as cream, powder, gels, and lotions. Topical preparation have some disadvantages like unpleasant odour, greasiness and skin irritation and fail to reach the systemic circulation this problem is overcome by microsponges delivery system.

Keywords: Microsponge, Controlled releases, Topical drug delivery, Stability, Porous microspheres, Quasi-Emulsion Method.

INTRODUCTION

The drug delivery technology landscape has become highly competitive and rapidly evolving. More and more developments in delivery systems are being integrated to optimize the efficacy and cost-effectiveness of the therapy[1]. These new drugs typically cannot be effectively delivered by conventional means. Drug delivery systems (DDS) that

can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the healthcare system[2]

In the current years, the development of new drugs is not sufficient for drug treatment. But it also involves the development of a suitable drug delivery system at the site of action. The in-vivo fate of the drug is not only determined by the properties of the drug[3]. But it is also determined by the carrier system, which permits a controlled and localized release of the active drug according to the specific need of the therapy. The biggest challenge up to date is to control the delivery rate of the medicaments by various modern technologies met by extensive research[4].

It has improved the efficacy and safety of many drugs that may be better administered through the skin, but TDS is not practical for the delivery of drugs 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[5].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. The major problem
associated with TDS is most of the drugs are poorly water-soluble which poses many problems while formulating them in conventional dosage forms. One of the critical problems associated with poorly water-soluble drugs is too low bioavailability and erratic absorption[6].

Because of their inefficient delivery strategy, these vehicles require high concentrations of active drugs for effective therapy, resulting in discomfort and allergic responses. Other disadvantages of topical preparations include uncontrolled evaporation of the active ingredient, unpleasant odor, and the possibility of drug-vehicle incompatibility[7]. As a result, a system that maximizes the amount of time an active substance is present on the skin's surface or within the epidermis while decreasing its transdermal entry into the body is required[8].Today, developing new drugs is not enough for the treatment of medication. Be that as it may, it is also appropriate to DDS at the site of operation. The drug's in-vivo fate is not only by the property of the drug but also regulated by the transporter system[9].

It is a challenging area of research for the drugs which are applied on the epidermis for their controlled systemic circulation in predetermined amounts as well as their localization in the target organs. Topical delivery of drugs faces different types of problems[10]. Ointments, which are used for aesthetic purposes offer various problems such as greasy and sticky appearance, thus leading to patient incompliance. There is a need for high concentrations of active ingredients for such types of vehicles to achieve effective therapy, resulting in irritation and allergic reactions[11].

Microsponge Drug Delivery

In 1987, microsponges technology was developed, and advanced polymer systems, Inc, authorized the original patents. Microsponges with a variety of interconnected volumes ranging from 5-150 µm of particle voids. The average pore size of human skin is 5 microns, particles larger than 10 µm remain on the surface of the skin, and micro sponges with 10-40 microns will yield the best result and give a smooth touch feel[12]. Microsponges are capable of absorbing skin secretion and then reducing skin oils and shine. The article, however, is an extremely minute inert imperishable sphere that cannot pass through the skin pores and release the trapped drug into the skin slowly. Microsponges are non-collapsible structures. The length of the pore may be up to 10 ft and the volume of the pore may be up to 1 ml/g depending upon the size[13].

Microsponges can adsorb or load a high degree of active materials into the particle or onto its surface. Its large capacity for entrapment of actives up to 3 times its weight differentiates microsponges from other types of dermatological delivery systems. Recently, a microsponge delivery system (Figure 2). It has been successively addressed for the controlled release of drugs onto the epidermis with an assurance that the drug remains chiefly localized and does not enter the systemic circulation in major amounts and resulted in a new creation of highly efficacious and well-tolerated novel product[14].The vehicles of topical formulations need to contain high concentrations of active agents for effective therapy because of the low efficiency of a delivery system, consequential in irritation and allergic reactions in significant users[15].

The microsponge system will stop the excessive accumulation of ingredients inside the stratum and also the stratum. Doubtless, the microsponge system will considerably scale back the irritation of effective drugs while not reducing their effectuality[16]. The empty spheres are then washed away with subsequent cleansing. The microsponge system fulfills these needs and has resulted in a new generation of terribly well-tolerated and extremely efficacious, novel merchandise. are usually conferred to the patron in typical forms like creams, gel, or lotions, and they contain a comparatively high concentration of active ingredients[17].

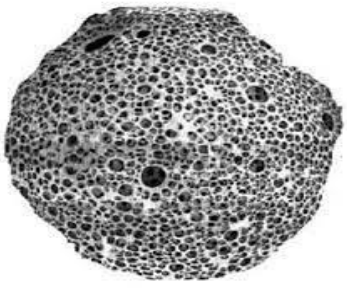

Figure 1: Highly porous.

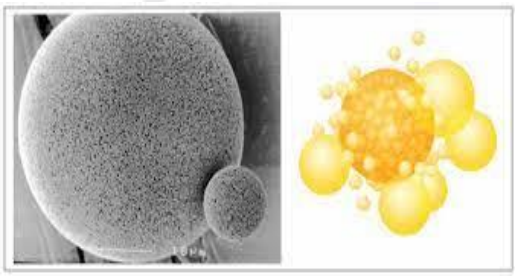

Figure 2: View of Microsponge Technology.

These vehicles require high concentrations of active agents for effective therapy because of the low efficiency of a delivery system, resulting in irritation and allergic reactions in significant users. Other drawbacks of topical

formulations are uncontrolled evaporation of active ingredients, unpleasant odor, and potential incompatibility of drugs with the vehicles. Thus, there exists the need for the 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[18].

Characteristic of Microsponge drug delivery systems.

1) It should be either fully miscible in the monomer or capable of being made miscible by the addition of a small amount of a water-immiscible solvent.
2) It should be water-immiscible or at most only slightly soluble.
3) It should be inert to monomers.
4) It should be stable in contact with the polymerization catalyst and conditions of polymerization.
5) Micro sponges are stable over the extended Ph range from 1 to 11 and constant up to 130 c temperature.
6) Micro sponges are friendly with many excipients and do not require sterilization.
7) About 50 to 60 % of drugs may be entrapped in micro sponges, which gives good flowing properties[19].

Advantages of microsponge drug delivery systems.

1) These are performed as controlled drug delivery systems.
2) Drug directly applies to target organs.
3) It increases the stability of the drug.
4) Drug loading capability is higher compared with other topical formulations.
5) These are able of absorbing skin secretions and reduce oiliness.
6) Microcapsules cannot frequently control the release rate of active pharmaceutical ingredients[20].

Characteristics of Materials to be Entrapped in Micro sponges:

Active ingredients which can be entrapped in microsponge can be incorporated into different products such as powders, creams, lotions, gels, and soaps.
Some requirements must exist in material that will get entrapped in microsponge such as:

1. It should not be water miscible or roughly only slightly soluble.
2. It should be inert to monomers.
3. During formulation, it should not raise the viscosity of the mixture
4. It should not cause the spherical structure of the microsponges to collapse.
5. It should be fully miscible with the monomer as well as be able to make them miscible by adding a small amount of water-immiscible solvent.
6. Materials that are entrapped in the vehicle must be of restricted solubility to avoid problems in cosmetic preparations. The vehicles might consume microsponge before the application if solubility is not restricted[21].

Applications of Microsponge Systems.

1) Topical Delivery.

These agents are a mainstay in cosmetics and the treatment of dermatological disorders. However, they are associated with substantial skin irritancy, especially in sensitive patients. The rapid release and subsequent accumulation of the active ingredients of the topical agents have been associated with this irritancy.

2) Oral Delivery.

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

3) Cardiovascular engineering using microsponge technology.

Biodegradable materials with autologous cell seeding require a complicated and invasive procedure that carries the risk of infection. A biodegradable graft material containing collagen microsponge that would permit the regeneration of autologous vessel tissue has developed. The ability of this material to accelerate in-situ cellularization with autologous endothelial and smooth muscle cells was tested with and without pre-cellularization.

4) Microsponges for Biopharmaceuticals Delivery.

The microsponge delivery system is employed both in the delivery of biopharmaceuticals as well as in tissue engineering. Dai 2010 et al developed 3D scaffold hybrid structures that have the advantages of natural type I collagen and synthetic PLGA knitted mesh. The collagen microsponges facilitated cell seeding and tissue formation and mechanically strong PLGA mesh served as a skeleton.

The scaffolds were divided into three groups:

a) Thin: collagen microsponge formed in interstices of PLGA mesh
b) Semi: collagen microsponge formed on one side of PLGA mesh
c) Sandwich: collagen sponge formed on both sides of PLGA mesh[22].

Microsponge release mechanism

1) Pressure-triggered systems:

Microsponge system releases the entrapped material when pressurized/rubbed; the amount released depends upon the special characteristics of the sponge. The microsponge best suited for a given application may be optimized by varying the type of material and different process variables.

2) Temperature-triggered systems:

Some active ingredients loaded in micro sponges can be too viscous at room temperature to flow spontaneously into the skin. The flow rate can be increased by increasing the skin temperature and hence release. So, it is possible to regulate the release of substances from the micro sponge by modulation of temperature[23].

3) PH-triggered system: Modifying the coating on the microsponge can be used to trigger the active's ph-based release. This has a wide range of uses in drug delivery**.**

4) Solubility-triggered systems:

In the presence of water, microsponges containing water-miscible chemicals such as antiseptics and antiperspirants will release the component. Diffusion can also be used to activate the release, however, the partition coefficient of the ingredient between the micro sponges and the external must be taken into account[24].

Method of Preparation of Microsponge Drug Delivery System

1. **Liquid–liquid suspension polymerization**[25].

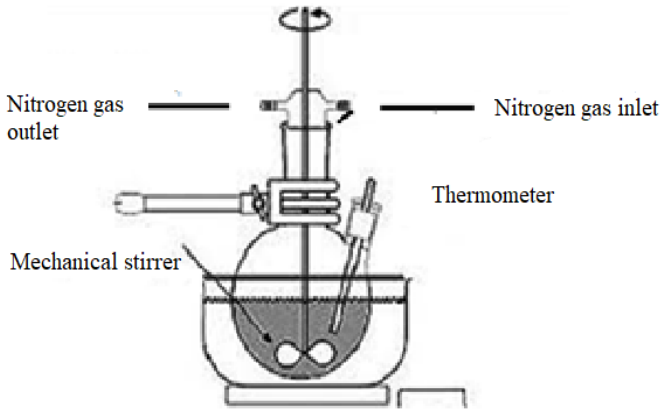

Figure 3: Liquid – Liquid suspension polymerization.

Immiscible monomers and active ingredient are dissolved in suitable solvent monomers.

Dispersed in aqueous phases which consist of additives like surfactant, suspending agent.

Polymerization is activated by increasing temperature or irradiation or by adding catalyst.

Polymerization process is continues the formation of spherical structure.

After the process solvent is removed and formed spherical porous microsponges.

2) Quasi-emulsion solvent diffusion method

When the drug is sensitive to the polymerization conditions, a two-step process is used. Microsponges are prepared by a quasi-emulsion solvent diffusion method using different polymer quantities. In the emulsion solvent diffusion, the affinity between the drug and the good solvent is stronger than that of the good solvent and the poor solvent. The drug is dissolved in the good solvent, and the solution is dispersed into the poor solvent, producing emulsion (quasi) droplets, even though the pure solvents solvent phase and the poor solvent diffuse into the droplets by which the drug crystallizes inside the droplets are miscible. The good solvent diffuses gradually out of the emulsion droplets into the surrounding poor solvent diffuses into the droplets by which the drug crystallizes inside the droplets[26].

Preparation[27]

Polymer like Eudragit RS 100 was dissolve in Dichloro methane (inner phase).

Then the drug is added in solution and dissolved in Ultrasonication at 35 0C.

Inner phase was poured into PVA solution in water (outer phase).

Continuously stirring 3-4 hour and after that filtered.

Dried in oven at 40°Cand microsponge was formed.

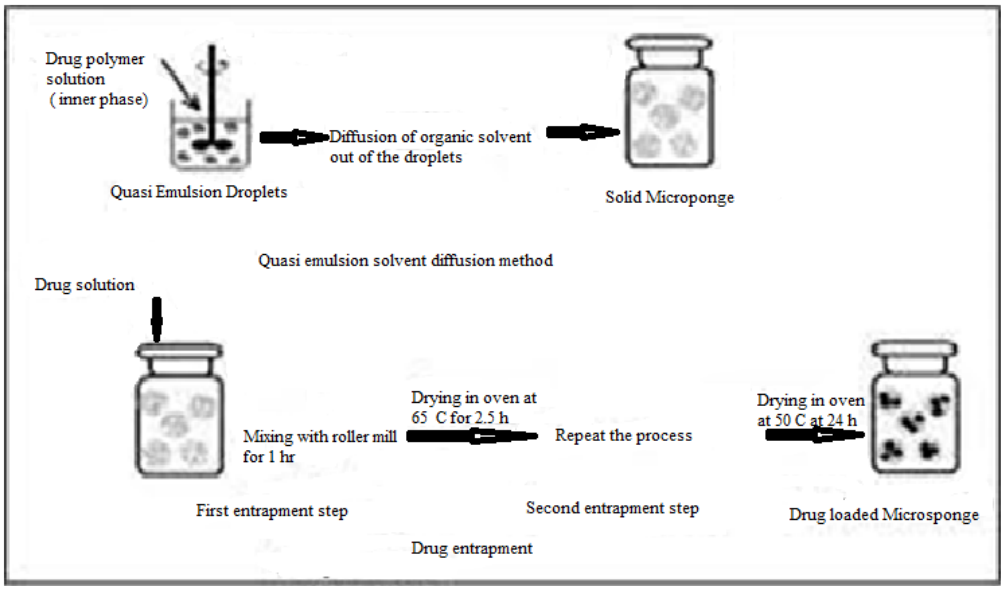

Figure 4: Quasi-emulsion solvent diffusion method.

Evaluation Parameters of microsponges

1) Particle size (Microscopy)
2) Scanning Electron Microscope (SEM) study.
3) Loading efficiency and production yield.
4) Compatibility Studies.
5) Polymer/Monomer Composition.
6) Dissolution studies.
7) *In- vitro* diffusion studies.

1) Particle size determination:

Particle size analysis is performed by laser light diffractometry or any other suitable method. Free-flowing powders with fine aesthetic attributes are possible to obtain by controlling the size of particles during polymerization. The values (d50) can be expressed for all formulations as a mean size range. The cumulative percentage of drug release from microsponges of different particle sizes will be plotted against time to study the effect of particle size on drug release. Particles larger than 30µm can impart a gritty feeling and hence particles of sizes between 10 and 25µm are preferred to use in the final topical formulation.

2) Scanning Electron Microscope (SEM) study:

For morphology and surface topography, prepared 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 by scanning electron microscopy (SEM). SEM of a fractured microsponge particle can also be taken to illustrate its ultra structure[28].

3) Loading efficiency and production yield:

The loading efficiency (%) of the microsponges can be calculated according to the following equation:

$$\text{Loading efficiency} = \frac{\text{Actual Drug Content In Microsponge} \times 100}{\text{Theoretical Drug Content}}$$

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[29].

$$\text{Production Yield (PY)} = \frac{\text{Practical Mass of Microsponge} \times 100}{\text{Theoretical mass}}$$

4) Compatibility Studies:

The compatibility of the drug with reaction adjuncts can be studied by thin layer chromatography (TLC) and Fourier Transform Infra-red spectroscopy (FT-IR). The effect of polymerization on the crystallinity of the drug

can be studied by powder X-ray diffraction (XRD) and Differential Scanning Colorimetry (DSC). For DSC approximately 5mg samples can be accurately weighed into aluminum pans and sealed and can be run at a heating rate of 15 0 C/min over a temperature range of 25–430 0C in an atmosphere of nitrogen[30].

5) Polymer/Monomer Composition:

Factors such as microsponge size, drug loading, and polymer composition govern the drug release from microsponges. The polymer composition of the MDS can affect the partition coefficient of the entrapped drug between the vehicle and the microsponge system and hence have a direct influence on the release rate of the entrapped drug. The release of drugs from microsponge systems of different polymer compositions can be studied by plotting cumulative % drug release against time. The release rate and total amount of drug released from the system composed of methyl methacrylate/ethylene glycol dimethacrylate is slower than the styrene/divinyl benzene system[31].

6) Dissolution Studies:

The dissolution profile of microsponges can be studied by use of dissolution apparatus with a modified basket consisting of 5µm stainless steel mesh. The speed of the rotation is 150 rpm. The dissolution medium is selected while considering the solubility of actives to ensure sink conditions. Samples from the dissolution medium can be analyzed by suitable analytical methods at various intervals.

7) *In-vitro* diffusion studies:

The in vitro diffusion studies of prepared microsponge gel were carried out in Keshary– Chien diffusion cell using a cellophane membrane. 100 ml of phosphate buffer was used as the receptor compartment, and then 500 mg of gel containing 10 mg of the drug was spread uniformly on the membrane. The donor compartment was kept in contact with a receptor compartment and the temperature was maintained at 37±0.50. The solution on the receptor side was stirred by externally driven Teflon-coated magnetic bars at predetermined time intervals, pipette out 5 ml of solution from the receptor compartment and immediately replaced with the fresh 5 ml phosphate buffer. The drug concentration on the receptor fluid was determined spectro-photometrically against the appropriate blank. The experiment was carried out in triplicate[32]

Table 1: Summary of Recent advances in micro sponge drug delivery system.

SL no	Drug	Polymer	Results
1	Betamethasone	Ethyl cellulose and Eudragit RS 100.	In FTIR spectra of characteristic C=O stretching at 1607 cm-1, C-O of phenol stretching at 1253 cm-1 were observed. The percentage yield of stable formulations F5 to F8 was from 87.23% to 69.23% and ranged from 55 to 64%. [33]
2	Curcumin	Ethyl cellulose and polyvinyl alcohol.	The curcumin microsponges loaded in the carbopol gel showed 77.5% of drug release in 24 h. The amount of drug that remained in the skin was found to be 207.61 ± 5.03 µg/cm2. [34]
3	Fluconazole	Polyvinyl alcohol and Eudragit RS 100	The spectrum of pure FLZ showed characteristic peaks at 3120.82cm-1, 1620.21cm-1, and 1209.37cm-1. The spectrum of the drug and PVA indicates no chemical interaction. [35]
4	Nystatin	polyvinyl alcohol, propylene glycol, Ethyl cellulose.	The microsponge formulation gel, F3 showed viscosity3465.84cps, spreadability of 26.22g cm/s, and drug content of 89.65%. The drug release profile. F3 released 81.03% of the drug at 12 hours. [36]

5	Clarithromycin	Ethylcellulose and Xanthan Gum	Microsponges were transparent, homogenous, and exhibited a pH of 6.8 ± 0.02, spreadability of 9.92 ± 0.44 g/cm, and viscosity of 35370.17 ±493.09centipoises. The CLRMS-F3 gel released 82.13 ± 0.47% drug in 12 hrs using a zero-order kinetic. [37]
6	Terbinafine HCl	Ethylcellulose and Dichloromethane	Among the four microsponge gel formulations, THMG II showed better results like pH 6.2, a viscosity of 3960 cps, spreadability of 18.1 g cm/s, drug content of 87.6%, and drug release showed a fiction release pattern. [38]
7	Miconazole	Carbopol 940,propylene glycol and Eudragit RS 100	The exact mechanism of drug release, to the Korsemeyer-Peppas equation. The value of N = 0.86 which shows non-fiction in nature as shown in Table 3 Optimized microsponges shows the maximum zone of 17mm of miconazole nitrate.[39]
8	Oxybenzon	Dichloromethane Polyvinyl alcohol and Ethyl cellulose-N10.	The microsponges were spherical with pore sizes in the range of 0.10–0.22 μm. The optimized formulation possesses the particle size and entrapment efficiency of 72 ± 0.77 μm and 96.9 ± 0.52%, respectively. [40]
9	Oxiconazole nitrate	Eudragit S-100, And polyvinyl alcohol	The production yield of 61.44% to 80.45% and The highest drug release for F3 and F9 formulation was found to be 87.77 % and 83.24 % respectively for the 8 h. [41]
10	Havan Ash	Eudragit RL100 Ethanol, dichloromethane and Eudragit RL 100	The formulation has its pH 6.3, Spreadabilty (g.cm/sec) 14.4 ± 0.77 7and viscosity (cps) 18251 50.12, have good result of psychometric analysis. [42]
11	Clobetasol Propionate	EthylCellulose, Dichloromethane and Carbopol-934 LR	The microsponges gel results the formulation with 1:1 drug–polymer ratioand the release upto 75.75 % at the end of 12 h. [43]
12	Roxithromycin	EudragitRL100 and Carbopol980,Dic hloromethae.	The pH of the gel has average pH of 6.3 ± 0.2 the range of 17.4 to 25.10 showing good characteristics of spreading, the cumulative release of the formulations are in the range of 61.1% to 75.4%. [44]
13	Clindamycin	Polyvinyl Alcohol , Carbopol 934 Ethyl cellulose Dichloromethanea Ethanol	The entrapment efficacy and production yield of CLN-free base were 73.72 ± 0.07% and 58.37 ± 0.27%. [45]
14	Dithranol	Potassium di-hydrogen phosphate Acetonitrile , methanol, ethyl cellulose.	The Percentage yield was found to be 66.28%, whereas encapsulation efficiency was ranged between 71.33% to 49.21%. It produce prolonged efficacy without producing toxicities to the skin. [46]

15	Oregano oil	Carbopol, ethylcellulose, propylparaben and dichloromethane	The prepared microsponges of particle size and production yield. Results revealed micro size range 19.87 mm to 248.13 mm with a good production yield 72.85% of M6. [47]
16	Diclofenac Sodium	Polyvinyl Alcohol , Carbopol 934 Ethyl cellulose Dichloromethanea Ethanol	The average particle size of all formulations ranges from 28.7 µm to 45.9 µm. Percentage yield 26.21 ± 1.02 %, Drug content 63.02 ± 2.16 mg, Spreadability 14.4 ± 0.77, pH 7.4 ± 0.2, Viscosity 2564 cps, Cumulative Release 49.89 % in 24 hour.[48]

Conclusion

Microsponge drug delivery system has become highly competitive and rapidly evolving technology and more and more research are carrying out for cost-effective therapy. MDS holds a promising future in various pharmaceutical applications in the coming years as they have unique properties like enhanced product performance and elegancy. Microsponge can be effectively incorporated into topical drug delivery system for retention of dosage form on skin, and also use for oral delivery of drugs using bio-erodible polymers, especially for colon specific delivery and controlled release drug delivery system thus improving patient compliance by providing site specific drug delivery system and prolonging dosage intervals.

Microsponges have a distinct advantage over the existing conventional topical dosage forms for the treatment of tropical diseases; it is a unique technology for the controlled release of topical agents also use for oral as well as biopharmaceutical drug delivery. This shows advantageous over other products by non mutagenic, non toxic, non irritant. There is a very high demand in international market for new and very efficient Pharmaceutical and Cosmetic products. The market requires potential and versatility for Micro sponge technology. During formulation consideration formulator can realize the full capabilities of these unique materials which provide improved stability, enhanced safety, reduction in side effects from API, enhanced multi functionality and improved ingredient compatibility. Therefore, microsponge has got a lot of potential and is a very emerging field which is needed to be explored. Microsponges constitute a significant part by virtue of their small size and efficient carrier characteristics. So microsponge drug delivery system has got a lot of potential and is a very emerging field which is needed to be explored in the future with most research study.

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