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Microsponge: An Innovative and Novel Strategy for Drug Delivery System

Buddhabhushan V. Bansod, Roshani B. Khairnar, Kajal L. Sonawane, Shailesh S. Chalikwar*

**Department of Pharmaceutical Quality Assurance,
R. C. Patel Institute of Pharmaceutical Education & Research, Shirpur - 425 405, Maharashtra, India.**

Abstract : Microsponge approach has become highly competitive and rapidly evolving technology. They are porous, polymeric microsphere that can be effectively incorporated into topical drug delivery system for the purpose of retention of dosage form on skin. Microsponge systems are non-irritating, non-mutagenic, non-allergenic and non-toxic. Microsponges are generally used for oral delivery of drugs, especially for colon specific delivery and controlled release drug delivery system to improve patient compliance by providing site specific drug delivery system and prolonging dosage intervals. Microsponges are generally prepared by several methods i.e. Liquid-liquid suspension polymerization and quasi emulsion solvent diffusion method. The present review introduces Microsponge methodology along with its principle, characterization such as Particle size and its distribution, surface morphology, porosity, density, parameters and release mechanism and drugs incorporated in MDS.
Key Words : Microsponge, Microsponge Delivery System; Control release; Microsponge Preparation Methods; Drugs used in MDS.

INTRODUCTION

The drug delivery methodology area has become highly challenging and rapidly developing. To optimize of efficacy and cost effectiveness of therapy the large amount of developments in drug delivery system are incorporated. Drug delivery systems (DDS) that can exactly control the rate of release to a specific site of body that have a tremendous affects over the health care system[1]. Tablets, capsules, gels, lotions and creams are conventional dosage forms with immediate release, are unsuspicious and show a large number of inadequacy alike poor bioavailability, adverse reaction, skin and gastric irritation and toxicological results of effective agents. Therefore for contribution to both human being and animal health the modified drug release approach depict one of the most important areas of Pharmaceutical sciences[2]. To attain targeted and controlled release of drugs the novel drug delivery systems had been increasingly explorated that require high concentrations of effective agents to be integrated for effective therapy due to their low efficiency.

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The biggest challenges faced by every drug industry are to control the release rate of active agents to a fixed site in human body. Transdermal drug delivery system (TDDS) has enhanced the efficacy and safety of various drugs that may be better delivered through skin. But this system is not applicable for delivery of those materials whose final target is skin itself. Therefore drugs for topical application having many problems for example ointments, which are frequently aesthetically unpleasant, oily, adhesiveness etc. that often results into inadequacy of patient compliance. Thus these vehicles need active agents with high concentration for efficient treatment because of their small effectiveness of delivery system no longer drug can be absorb form skin. This problem can be fulfills by the microsponges delivery system. Microsponges require low drug content but having the longtime of contact with skin results into no irritation and no sensitive reaction are observed in a few patients[3,4].

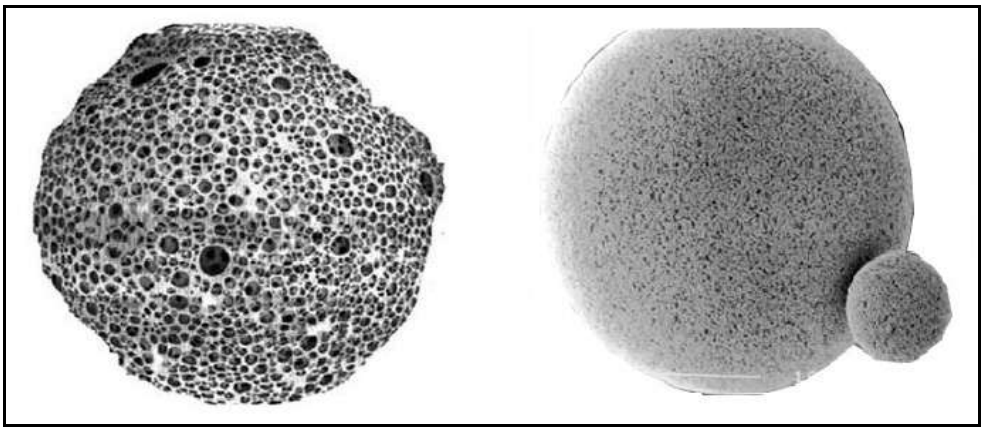


Fig. 1: Porous nature of Microsponge[3, 6]

The Microsponge Drug Delivery System (MDDS) **Figure 1,** also called as *'Solid phase porous microsphere'* is a novel drug delivery system which is highly cross-linked, porous, minute sponge-like spherical particle and patented polymeric system composed of spongy and porous microspheres[5]**.** The scientist Won has developed this microsponge drug delivery technology in 1987 and the original patents were assigned to Advanced Polymer Systems, Inc. The microsponges particle size varies from 5 to 300 µm in diameter loaded with active ingredient, typically 10-25 µm sphere size particle having 250000 pores and its internal pore structure length upto 10 feet. Microsponge delivers its active ingredients on a time mode and in response to temperature, rubbing, pH etc[1,6]. It composed of porous surface non-collapsible structures in which active components are liberated in controlled manner. At the recent time, this MDS technique has been generally used in the preparation of topical products[7]**.** Further these microsponge porous particles are incorporated into various formulations like creams, powders, lotion, and sunscreen, anti-inflammatory and anti-fungal[8,9]**.** Accordingly, this MDS system has been commercially employed for chronotherapy of topical drug delivery and considered for oral, parenteral and pulmonary drug delivery. In the oral drug delivery, arena microsponges were mostly investigated for colon drug delivery system[10]**.**

Characteristics of microsponge delivery system

The microsponge delivers its active ingredients slowly into the skin when applied over the skin in response to burnished, temperature and pH effect etc. with perfect efficacy and fewest irritations[1, 11].

1. Microsponge preparations are stable between the long pH ranges from 1 to 11.
2. They are constant at the temperature upto 130^{o}C.
3. They are united with most of the instruments and ingredients.
4. Common pore size of microsponge 0.25 µ, therefore there is absence of sterilization.
5. Microsponge show free flowing characteristics and should be cost effective.
6. The drug entrapment efficiency in microsponge up to 50-60%.
7. Microsponges are difficult to absorb into the skin due to their large particle size.
8. Microsponges are inert molecules without producing any allergy, irritation and toxicity.

9. These can soak oil up to 6 times their weight without drying.
10. It gives extended release up to 12 h.
11. Microsponges formulations are flexible.

Advantage of microsponge delivery system[6,12]

- It controls oil; soak up to 6 times of its weight without drying.
- It improved product elegancy.
- These delivery system permits the incorporation of immiscible products.
- It provides extended release up to 12 h.
- It reduced irritation formulas.
- They are also permits novel product form.
- These are non-irritating, non-mutagenic, non-allergenic and non-toxic.
- It also improved product attractiveness.
- It gives better compliance means wide consumer acceptance.
- It also gives product a majestic feel.
- MDS enhance the physical and chemical stability.
- It gives permission for incarnation of immiscible products.
- It converted liquid material to powder.
- It can improve effectiveness of treatment.
- It enhances the control of condition.
- It can also improve bioavailability of same drugs.

Advantages of microsponge over other formulations

There are several advantages of microsponge over other formulations present in the market.

Advantages over conventional formulations:[13]

- Conventional formulations of topical drugs are design to working on the outermost layers of the skin.
- Such formulations discharge their active ingredients after application by producing a layer of concentrated active ingredient that is absorbed with a great speed.
- This conclusion gives excessive cumulating of ingredients inside the epidermis and the dermis when compare to the microsponge delivery system which are then prevented by microsponge.
- Microsponge system can lower the side issues of the drug parallel as irritation without reducing its efficacy.
- For examples, Microsponges of Benzoyl peroxide preparation which have acceptable efficacy with minimum irritation.
-

Advantages over microencapsulation and liposome formulations:[9]

- The MDS has specific advantages on the other system such as microencapsulation and liposomes.
- The rate of release of actives generally cannot control in microcapsules.
- The actives within the microcapsules will be liberated when the wall is burst.
- Liposomes meet to lower burden, complicated formulation, narrow chemical stability and microbial instability.
- While microsponge delivery system in differs to the liposomal systems are steady within the range of temperature up to 130 ^{o}C, pH 1 to 11, compatible with most instruments and ingredients, average pore size is 0.25 µm where bacteria cannot pierce.

Advantages over ointments:[3,13]

- Patient compliance with ointment is lowered due to its unpleasing, viscid and oily nature.

- These determinants require highly concentrations of active ingredients for effective and potent treatment because of ointments have low efficacy as drug delivery systems, therefore they produce irritation and sensitization.
- The poor odor, evaporation of active ingredient with uncontrolled and potential inconsistency of drugs with vehicles are the another disadvantage of topical formulations.
- Microsponge system enlarges the period of time where an active ingredient is found besides on a surface of skin or in the epidermis, while reducing its transdermal permeation into the body.

Limitations of microsponge delivery system[12]

1. The organic solvents are usually uses as porogen for microsponge preparation method, which shows an environmental hazard, may be highly inflammable, showing a safety hazard.
2. In some materiality, a very small amount of residual monomers which may be toxic and hazardous to life have been monitored.

Requirements of material entrapped in microsponge delivery system

Microsponge can be assimilated into various different products like powders, lotions, gels, creams and soaps which can be entrapped with active pharmaceutical ingredients.

Following some requirements must subsist in material that will get entrapped in microsponge such as:[12,6]

1. It should be water immiscible or only minutely soluble.
2. Material should be inactive to monomers.
3. It should not increase viscosity of the mixture throughout formulation.
4. The globular skeleton of the microsponges should not cause by material to collapse.
5. After the adding of a little quantity of solvent of water immiscible, the material will be completely miscible with the monomer.
6. In the contact with polymerization catalysts and polymerization condition, the material should be constant.
7. Materials that are loaded in the medium must be of restricted solubility to keep away from problems in cosmetic preparations.
8. The volume of microsponge and polymer design for materials must be optimized for desired release rate for a limited period of time.
9. Design of polymer and payload of the microsponges should be optimized for required rate of release for certain period of time period.

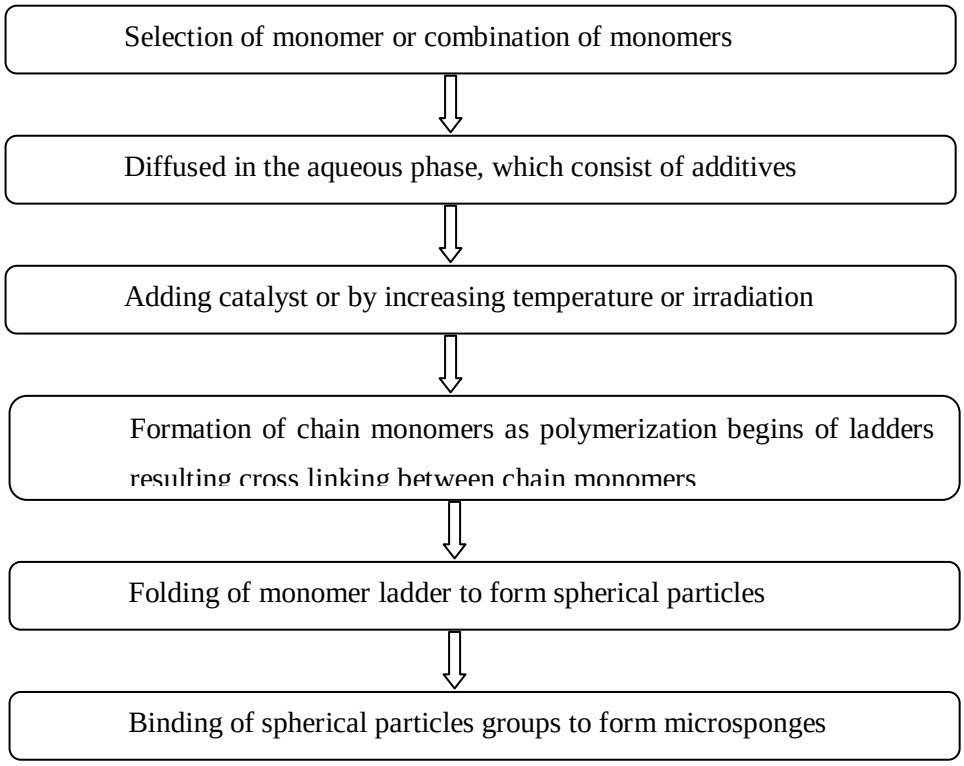
Microsponge delivery system: Preparation methods

A particular encapsulation method is selected on the basis of solubility properties of the drug and polymer[1]. **Patil et al,** have reported the preparation of microsponge drug delivery system can be carried out using two methods: first method is liquid-liquid suspension polymerization and another is quasi emulsion solvent diffusion techniques. These methods are based on physical as well as chemical properties of loaded drug. If the loaded drug is usually an inert non-polar material, will generate the pervious structure known as "porogen". Porogen drug is uncompleted to hinder the polymerization and to become it activated[6]. **Srivastava and Pathak** have been found out that other than above methods, lyophilization, water in oil in water (w/o/w) emulsion solvent diffusion and oil in oil (o/o) emulsion solvent diffusion[10]**.**

A. Liquid-liquid suspension polymerization:[4]

1) Microsponges are formulated by suspension polymerization method based on free radical suspension polymerization technique shown in Figure 2.

2) In this method, the process was takes place in three naked round bottom flask with stirrer, connected with water condenser and thermometer is used to determine the temperature.



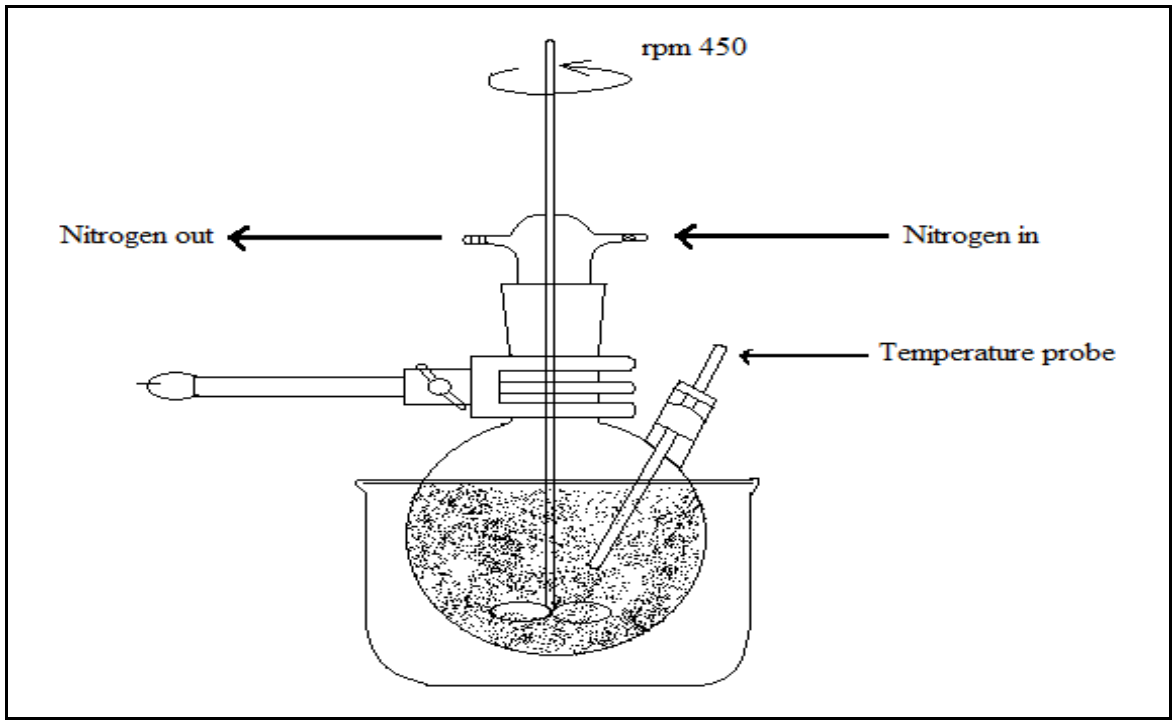


Fig. 2: Reaction vessel for microsponge preparation by liquid-liquid suspension polymerization[3]

B. Quasi-emulsion solvent diffusion:[6]

1) This is the widely used technique of microsponge preparation.
2) Microsponge were also prepared by second technique i.e. Quasi-emulsion solvent diffusion technique.
3) In this technique, the inner phase containing Eudragit polymer i.e. Eudragit RS 100 were dissolved in ethanol.
4) After preparation of internal phase, the drug is added slowly into solution and then it dissolved under ultrasonication at temperature 35^{o}C.

5) Triethylcitrate was then added as a plasticizer to asset the plasticity.
6) After that the prepared inner phase is poured into a solution of polyvinyl acid (PVA) in water. This is referred as 'outer phase' shown in **Figure 3.**
7) For the separation of microsponge, these combinations of inner and outer phase solution are then stir for next 60 min and filtered it.
8) The obtained microsponges are dried at 40°C for 12 h in an air heated oven and at last weighed it to calculate production yield.

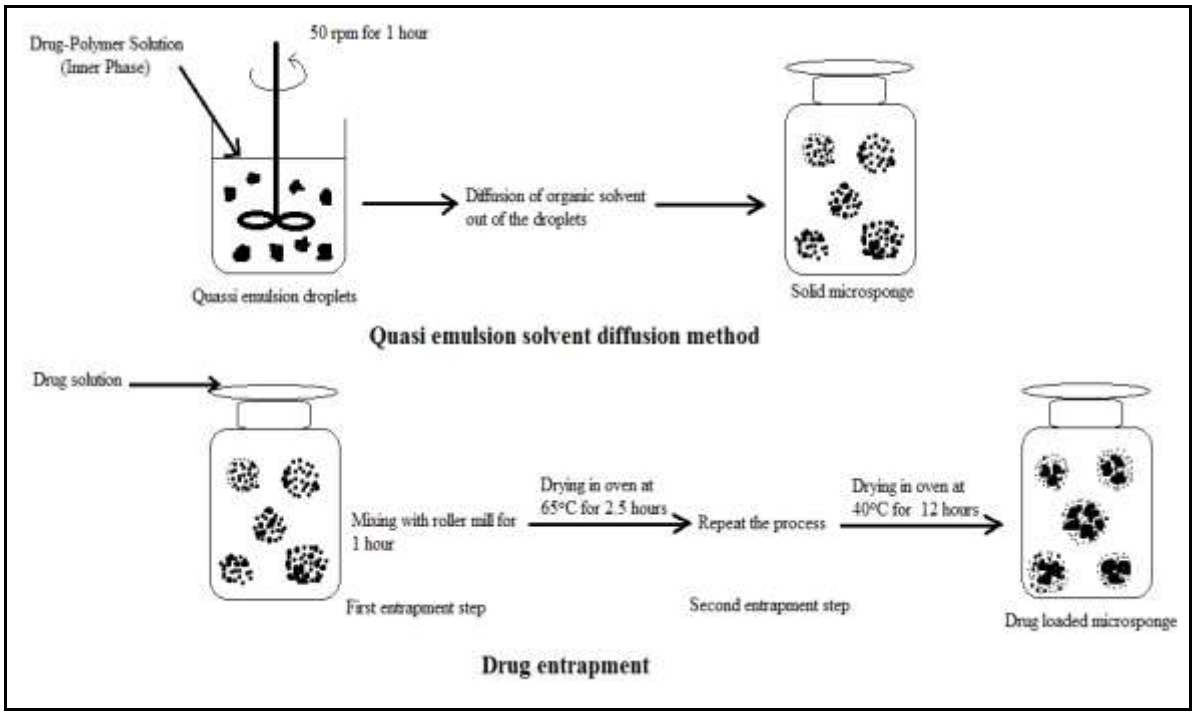


Fig. 3: Preparation of microsponges by quasi emulsion solvent diffusion[7]

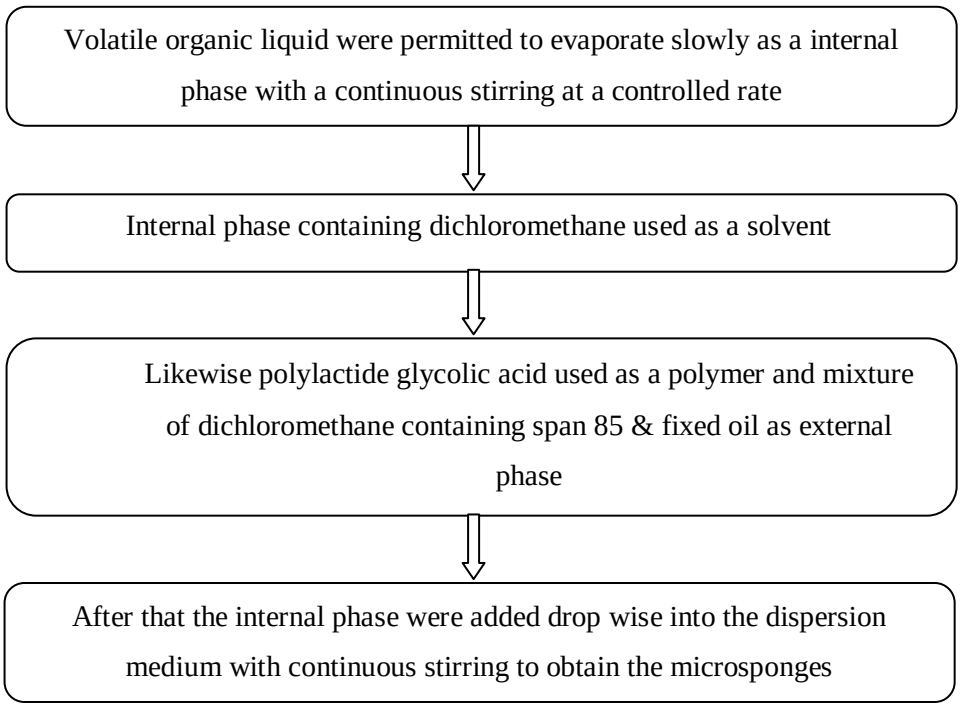
C. Lyophilization

Lyophilization is novel technique was prepared by gelation technique used for converting the microspheres to porous microspheres. In this technology, the microparticles were incubated in the Chitosan HCl solution and lyophilized[14]. Rapid elimination of solvent leads to formation of pores in the microphores. This method is quick and rapid. But due to rapid elimination of solvent, there are broken or shrunken microparticles are produced. This is the disadvantage of lyophilization method.

D. Water in oil in water (w/o/w) emulsion solvent diffusion

Another novel technique named w/o/w emulsion solvent diffusion was developed to prepare biodegradable porous microparticles. In this method, an internal water phase was dispersed in organic polymeric solution. The internal phase consists of an emulsifying agent such as span, stearylamine and polyethyleneimine. After that, this w/o emulsion was again dispersed in external aqueous phase which contain PVA to form a double emulsion. The advantage of this method is the entrapment of both water soluble and water insoluble drugs[10].

E. Oil in oil (o/o) emulsion solvent diffusion



This technique was employed for development of hydroxyzine HCl-loaded Eudragit RS-100 microsponges using acetone as dispersing solvent and liquid paraffin as the continuous medium[15,16,10].

Hypothetical mechanism of microsponge delivery system

The entrapped form of active ingredient is added to the medium. As the microsponge particles do not have a continuous membrane surrounding them have an open structure, the active is free to move in and out from the particles and into the vehicle until equilibrium is reached, when the vehicle becomes saturated. The active that is previously in the medium when the finished product is applied to the skin which will be immersed into the skin, deducting the medium become unsaturated, thus equilibrium will disturbing. The flow of active will be start from the microsponge particle into the medium and from medium to the skin to the medium is dried. The particles of microsponge are kept on the stratum corneum surface after drying or absorbed medium. These will continue to release the active to the skin with little amount, providing extend release over time. This suggested mechanism of action emphasizes the importance of formulating vehicles for use with microsponge entrapments[1].

Release mechanism of microsponge delivery system

Microsponge drug delivery system composed of a multitude of highly porous microparticles that contain a composite network of interconnecting emptiness with a non-collapsible structure[17]. On the basis of several adaptable factors, the release rate of the active constituents can be found before they are loaded in the microparticles/microspheres. These flexible factors made up of the pore diameter, the difference in concentration of the active constituents between the microparticles/microspheres, the extent of cross-linking of the polymers and the vehicle in which these spheres reside. The MDS of topical agent preparation can be performed in several different forms, for example a cream, gel, or lotion. Once the MDS formulation is topically applied onto the preferred region of the skin, the active constituents spread out of the microspheres into the medium and then onto the skin[18,19]. Microsponges can be organized to deliver specific quantity of active ingredients over time in regards to equal to one or more than one outside triggers[13].

1. Solubility

In presence of water, microsponges entrapped with water-miscible constituents such as antiperspirants and antiseptics will discharge the ingredient. The discharge can also be achieved by diffusion taking into account the partition coefficient of the constituents between the external system and microsponges[20].

2. Pressure

Pressure or rubbing applied can discharge active constituents from microsponges onto skin. The MDS were suitable for a topical application may be improved by changing the type of material and different various process variables[21,22].

3. Temperature

The release of active constituents from microsponges can be activated by temperature triggered system.Some loaded actives can be very thick and sticky at room temperature to flow suddenly from microsponges on to the skin. When the skin temperature increased it will leads to increased flow rate and thus release[18].

4. pH

The discharge of the active constituents based on pH triggered system can be accomplished by altering the coating on the microsponge. This has numerous advantages and uses in drug delivery[3]. The pH triggered studies were performed by using USP spindal dissolution apparatus[18].

Evaluation parameters of microsponge delivery system

Various methods are used for the physical characterization of MDS:

1) Particle size analysis

Most useful methods i.e. an optical microscopy or an electron microscopy methods are used for the evaluation of particle size and size distribution. As the size of the particles greatly affects the appearance of the final formulation and its stability, it becomes extremely critical step. During polymerization processes, the free-flowing properties of microsponge powders with fine attractive properties can be created by controlling the particles size. Particle size has significantly affects the drug loading and drug release profile. By using Laser light diffractometry method or any other possible methods the particle size of loaded and unloaded microsponges can be analyzed. The d_{50} value can be stated for all formulations as mean size range. Microsponge's particle size more than 30 μm can gives gritty feeling and that's why the range of particles size between 10-25 μm is preferred for final topical formulation. The concentration of emulsifying agent and drug:polymer ratio are factors that significantly affects the particle size of formulation. If the ratio of drug:polymer is increases the small particles are obtained. While increasing the concentration of emulsifying agent results in formation of larger size microsponge[1,10].

2) Morphology and surface topography

The morphological study of microsponge showed that the presence of pores on the carrier surface[10]. For the determination of morphology and surface topography of microsponges, the prepared final microsponges can be coated with gold-palladium at room temperature i.e. 37 ± 0.5°C temperature under an argon atmosphere then these gold-palladium coated microsponges are studied for the surface morphology with the help of scanning electron microscopy (SEM) technique[23].

3) Loading efficiency and production yield

Passive loading and active loading are the two ways which can be made for drug loading based on the physical and chemical properties of the drug to be loaded. Passive loading is one-step process while active loading is two-step process. Passive loading is more convenient and efficient than active loading and it is easier than active loading. Therefore, the passive loading of drug can be selected as a method of choice. An increase in the ratio of drug:polymer and decrease in the particle size, increases drug loading efficiency and production yield[10].

The drug loading efficiency and production yield can be determined by using following equation no. 1, and 2[6]:

$$\text{Loading effficiency} = \frac{\text{Actual Drug Content in Microsponge}}{\text{Therotical Drug Content}}$$ ……. Equation No. 1

$$\text{Production Yield} = \frac{\text{Practical Mass of Microsponges}}{\text{Therotical Mass}} \times 100$$ ……. Equation No. 2

4) Determination of true density

Ultra-psyncometer apparatus is used for the determination of microsponge true density under helium gas[24].

5) Angle of repose

The angle of repose is used for the determination of flow properties of the powder. Funnel was placed 2 cm above the horizontal surface. The powdered sample was then allowed to flow from the funnel, so the pile of the powder was obtained. The diameter of the pile was determined and then radius of pile was calculated[25].

The angle of repose is calculated by using equation no. 3 as

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$ ……. Equation No. 3

Where,
Θ = angle of repose
h = height of the pile
r = radius of the pile

6) Bulk density

The mass of powder divided by bulk volume of powder is termed as bulk density. Weigh accurately 10 g of sample powder which was previously passed through 20 # sieve and transfer in 50 mL graduated cylinder. Cautiously level the powder without compacting and note the unsettled apparent volume (V_0). Calculate the apparent bulk density in gm/mL by the following equation no. 4[12].

$$\text{Bulk density} = \frac{\text{Weight of sample}}{\text{Volume of sample}}$$ ……. Equation No. 4

7) Tapped density

Accurately weigh 10 g of sample powder and transferred into 50 mL graduated measuring cylinder. Then mechanically tap the cylinder containing the sample and allowing it to fall under its own weight via mechanically tapped density tester that provides a fixed drop of 14 ± 3 mm at a nominal rate of 300 drops/min. Tapped the cylinder for 500 times at first and determine the tapped volume (V1) to the adjacent graduated units, repeat the tapping an additional 750 times and determine the tapped volume (V2) to the adjacent graduated units. If the difference between the two volume is less than 2% then final the volume (V2) is taken as tapped volume and tapped density is calculated using equation no. 5[12].

$$\text{Tapped density} = \frac{\text{Weight of sample}}{\text{Tapped volume}}$$ ……. Equation No. 5

8) Scanning electron microscopy (SEM)

Surface properties of microsponge formulation and active pharmaceutical ingredients (API) are studied by using scanning electron microscopy by placing a sample on a brass tube and coated with the layer of gold and SEM image are taken[25]. It gives information about shape of microspanges along with surface properties.

9) Monomer/Polymer composition

Size of microsphere, drug loading and monomer composition are the factors which govern the release of drug from microspheres. Monomer composition of the microsponge delivery system can influence the partition

coefficient between the medium and the microsponge delivery system and thus it direct affects on the release rate of entrapped drug. Discharge of drug from different polymer compositions can be studied by plotting cumulative % drug release vs. time[26].

10) Resiliency

Resiliency is also termed as 'Viscoelastic properties'. This property affects the collapsible characteristic and drug release profile of the microsponges. It is very essential to optimize the inflexibility of the microsponges that can be done by optimizing the cross-linking to delay the rate of drug release [10,11].

11) Pore diameter and volume

Void volume (Pore volume) evaluates the amount of active substance that can be integrated in the Microsponge system. Both void volume and diameter are essential in calculating the intensity and duration of effectiveness of the active component. Pore diameter also influences the movement of the active component from the Microsponge into the medium in which the substance is dispersed. Accordingly, the diameter of the pores can have direct affects on the stability of the final formulations[18].

12) Compatibility study

Compatibility of drug in the company of reaction is done through the thin layer chromatography and Fourier Transform Infra-red spectroscopy methods. With the help of X-ray diffraction and Differential Scanning Colorimetry, the consequence of polymerization on crystallinity of the drug can be observed[26].

13) Dissolution study

Dissolution profile of MDS can be studied using USP XXIII dissolution apparatus with a redesigned basket consisted of 5 µm stainless steel mesh at 37 ± 0.5°C in 150 rpm. The dissolution vehicle (official methods) is selected and considering solubility of drug to make sink conditions. The by suitable analytical methods are involved in analyzing samples from the dissolution medium at different intervals[23].

Microsponge drug delivery systems reported in literature

Drugs which are fabricated in microspongedrug delivery system (MDDS) as per literature are reported in **Table 1.**

Table 1: Drugs explored in microsponge drug delivery systems

Sr. No.	Name of Drugs	Method used	Polymer used	Benefits	References
1.	Albendazole	Oil in oil emulsion solvent diffusion	Eudragit RS 100	Parasitic worms treatment in sustained release oral dosage form.	**27**
2.	Fluconazole (FLZ)	Quasi-emulsion solvent diffusion	Ethyl cellulose (EC) and Eudragit RS 100	Topical formulation for controlled release of the drug and consequently avoiding its oral side effects	**28**
3.	Mupirocin	Emulsion solvent diffusion	Ethyl cellulose in dichloromethane	Topical delivery system for sustained release and enhanced drug deposition in the skin	**29**
				Enhanced retention in the skin indicating better potential of the delivery system for treatment of primary and secondary skin infections, such as impetigo, eczema, and atopic dermatitis	
4.	Curcumin	Quasi emulsion solvent diffusion	Ethyl cellulose and Eudragit S 100	Treatment of gastric cancer	**30**

5.	Flutrimazole	Quasi-emulsion solvent diffusion	Eudragit RS 100	To control the release of drug to the skin and topical treatment of superficial mycoses of the skin	**31**
6.	Eberconazole nitrate (EB)	Quasi-emulsion solvent diffusion	Ethyl cellulose, Polyvinyl alcohol and Dichloromethane	Potential carrier for EB in topical fungal therapy	**32**
				Prevent the excessive accumulation of the drug in the skin, control its side effects, improve its efficacy and decrease the frequency of application and the systemic absorption	**32**
7.	Ketoprofen	Quasi-emulsion solvent diffusion	Eudragit RS 100	Study effects of pressure and direct compression on tabletting of microsponges	**33**
8.	Ketoprofen	Quasi-emulsion solvent diffusion	Eudragit RS 100	Physical characteristics of the microsponges and the *in-vitro* release rate of the drug from the microsponges were studied.	**34**
9.	Valsartan	Quasi-emulsion solvent diffusion	Ethyl cellulose, Polyvinyl alcohol and Dichloromethane	Enhance its therapeutic benefits and minimize its side effects, while improving the management of the disease condition.	**35**
10.	Nateglinide	w/o/o double emulsion solvent diffusion	Ethyl cellulose and hydroxy propyl methyl cellulose	Effective in the treatment of Type-2 (non-insulin dependent) Diabetes mellitus.	**36**
11.	Fluconazole	Quasi-emulsion solvent diffusion	Ethyl cellulose, Polyvinyl alcohol	Fluconazole Loaded Microsponge Gel For Topical Sustained Delivery	**37**

12.	Hydroxyzine hydrochloride	Oil in oil emulsion solvent diffusion	Methocel 10000 cps and in combination with Eudragit –S 100, Eudragit-L 100, Eudragit-RL 100 and Eudragit-RS 100	Treatment of urticaria and pruritus	**38**
13.	Clotrimazole	Quasi-emulsion solvent diffusion	Ethyl cellulose and PVA	Potential of clotrimazole Microsponge loaded carbopol gel as a local depot for sustained drug release	**39**
14.	Miconazole nitrate	Quasi-emulsion solvent diffusion	Ethyl cellulose, Polyvinyl alcohol and dichloromethane	Treatment of diaper dermatitis for enhanced therapeutic effect	**40**
15.	5-fluorouracil (5-FU)	Quasi-emulsion solvent diffusion	Eudragit-L100 (Ed-L100) and/or Eudragit-S100 (Ed-S100)	Developed Colon-targeted drug delivery system proved to be more patient compliant by providing a better mode of treatment over the present intermittent chemotherapy by injection or infusion.	**41**
16.	Temisartan	Quasi-emulsion solvent diffusion	Eudragit E or eudragit L in organic solution as internal phase and aqueous solution of polyvinyl povidone as external phase	Tablet formulations proved to show better release profile in all aspects as compared to marketed (Micardis®) tablet	**42**

17.	Dicyclomine	Quasi-emulsion solvent diffusion	Eudragit S-100	Develop microsponge-based novel colon-specific drug delivery system containing dicyclomine using natural polysacchrides (pectin) for the treatment of IBS	**43**
18.	Benzoyl peroxide (BPO)	Quasi-emulsion solvent diffusion	Ethyl cellulose and dichloromethane	Control the release of BPO to the skin	**44**
19.	Ibuprofen	Quasi-emulsion solvent diffusion	Acrylic and Eudragit RS	Extensive stress relaxation of microsponges after compression was responsible for their excellent compressibility	**45**
20.	Metronidazole	w/o/w emulsion solvent evaporation	Ethyl cellulose	Delayed release 42 microsponge based gels for treatment of skin infections and disorders.	**46**
21.	Silver sulfadiazine	w/o/w emulsion solvent evaporation	Carbopol 934 and Ethyl cellulose (18–22 cps viscosity grade) (EC)	Optimize gel for partial thickness (second degree) burn wounds	**47**
22.	Prednisolone	Quasi-emulsion solvent diffusion	Eudragit S 100 (ES)	Management of colon ailments such as inflammatory bowel disease.	**48**
23.	Paeonol	Quasi-emulsion solvent diffusion	Ethyl cellulose-M70	Increase paeonol permeation rate but also minimize transdermal penetration of the drug into the body, which should increase drug bioavailability at the level of the skin and reduce side-effects when treating skin disease	**49**

24.	Levonorgestrel	Quasi-emulsion solvent diffusion	Carbopol 934	Helps to improve the bioavailability of drug, and gives sustain and control release effect which will ultimately improve the birth control.	**(50)**
25.	Indomethacin	Quasi-emulsion solvent diffusion	Eudragit RS 100	Minimize frequent dosing, prolong the pharmacological effect and improve patient compliance	**51**
26.	Mitiglinide calcium (MTG)	Quasi-emulsion solvent diffusion	Eudragit RS100, ethyl cellulose	Improve diabetic patients compliance by eliminating the Necessity of frequent dosing thus attaining better diabetes control	**52**
27.	Betamethasone	Quasi-emulsion solvent diffusion	Eudragit RS 100	Topical gel for anti -inflammatory action	**53**
28.	Bupropion HCl	Quasi-emulsion solvent diffusion	Ethyl Cellulose, Polyvinyl Alcohol and Dichloromethane	Treatment of psychosis	**54**
29.	Flurbiprofen (FLB)	Quasi-emulsion solvent diffusion	Eudragit RS 100	Potential for colonic drug delivery	**55**
30.	Diclofenac diethylamine	Quasi-emulsion solvent diffusion	Eudragit RS 100	Treatment of arthritis and musculoskeletal disorders	**56**
31.	Domperidone	Quasi-emulsion solvent diffusion	Eudragit RS 100	Therapy of gastroparesis, emesis and alike gastric ailments	**57**
32.	5-Fluorouracil (5-FU)	Oil in oil emulsion solvent diffusion	Eudragit RS 100	Treatment of Colon Cancer	**58**
33.	Nebivolol	Oil in oil emulsion solvent diffusion	Eudragit RS 100 and Carbopol 934	Significant and fast wound healing and closure in diabetic rats	**59**

34.	Fluconazole	Quasi-emulsion solvent diffusion	Carbopol 934	Microsponge gel for topical delivery of fluconazole for fungal therapy	**60**
35.	Nicorandil	Quasi-emulsion solvent diffusion	Eudragit - RSPO and HPMC K100M	Used in cardiovascular diseases	**61**
36.	Oxybenzone	Quasi-emulsion solvent diffusion	Ethyl cellulose and Dichloromethane	Enhanced sun protection factor with reduced toxicity and irritation	**62**
37.	Cinnarizine	Quasi-emulsion solvent diffusion	Ethyl cellulose	Cinnarizine employing capmul GMO as bioadhesive coating material and confirmed the viability of acconon MC 8‑2EP/NF As bioadhesive raw material for sustained targeted delivery of drug	**63**
38.	Naproxen	Quasi-emulsion solvent diffusion	Eudragit (RS-100) and Carbapol	Naproxen gel formulations for transdermal delivery	**64**
39.	Ketoprofen	Quasi-emulsion solvent diffusion	-	For spatial and temporal delivery and to treat various colonic diseases	**65**
40.	Benzyol peroxide	Quasi-emulsion solvent diffusion	Ethyl cellulose and Eudragit RS 100	Shown better entrapment efficiency with porous nature and used for treatment of acne	**66**
41.	Hydroxyzine HCL	Oil in oil emulsion solvent diffusion	Eudragit RS-100	Effects of different variables affecting microencapsulation were studied	**15**
42.	Ketoconazole	Quasi-emulsion solvent diffusion	Carbapol 940 and Eudragit RS 100	Showed better antifungal Activity on fungal induced guinea pig skin and bring remarkable decrease on gel application for fungal treatment	**67**
43.	Miconazole (MCZ)	Quasi-emulsion solvent diffusion	Eudragit RS 100	Miconazole (MCZ) microsponges gel as an attractive dosage form for vaginal candidiasis	**68**

44.	Fenoprofen	Quasi-emulsion solvent diffusion	Eudragit RS 100 and Chitosan & HPMC for tablet preparation	For colon specific and sustained drug delivery	**69**
45.	Loratadine	Quasi-emulsion solvent diffusion	Ethyl cellulose and PVA	Confirmed the bioadhesive characteristics of Acconon MC 8-2 EP/NF for development of controlled release biaodhesive floating microsponges	**70**
46.	Meloxicam (MLX)	Quasi-emulsion solvent diffusion	Eudragit RS 100	Developing calcium-pectinate matrix tablet for colon-targeted delivery and potential for use as an adjuvant therapy for colorectal cancer	**71**
47.	Paracetamol	Quasi-emulsion solvent diffusion	Eudragit RS 100	Developing PCM microsponge based novel colon specific drug delivery system	**72**
48.	Babchi essential oil (BEO)	Quasi-emulsion solvent diffusion	Encapsulate BEO in ethyl cellulose (EC)	Potential for the treatment of dermatological disorders and help to overcome Skin irritation problems by preventing direct contact of Babchi oil and skin.	**73**

Applications of microsponge DDS[4,21,9]

1) Microsponges are widely used for the topical delivery which can reduce the irritation of effective drugs and further it can incorporated into various products such as creams, gel, lotion etc.
2) It is recently used for oral delivery system- It reduces the solubilization rate of poorly aqueous drugs.
3) It is used as an anti-fungal to sustained release of active ingredients.
4) Microsponge technique also used in bone-tissue engineering.
5) It also used in cardiovascular engineering.
6) Microsponge technology is used as an anti-inflammatory, antifungal, anti-acne, anti-ulcer, anti-dandruff agent etc.
7) MDDS used in the treatment of Actinic Keratoses.
8) It is used in sunscreen to reduce skin irritation and sensitization.

Marketed formulations of microsponge delivery system

Various marketed formulations of MDS are used for the topical, oral and over-the-counter (OTC) and personal care products shown in **Table 2.**

Table 2: Various marketed products of MDS

Sr. No.	Product Name	Pharmaceutical Uses	Manufacturers	References
1.	Retin A Micro	Acne vulgaris	Ortho-McNeil Pharmaceutical, Inc.	**1**
2.	Retinol cream	Helps maintain healthy skin	Biomedic	**22**
3.	Retinol 15 Night cream	Anti-wrinkles	Sothys	**25**
4.	Glycolic Acid Moisturizer w/SPF 15	Anti-Wrinkles, soothing	AMCOL Health & Beauty Solution	**74**
5.	Ultra Guard	Protects baby‟s skin	Scott Paper Company	**23**
6.	Salicylic Peel 20	Excellent exfoliation	Biophora	**10**
7.	Lactrex™ (12%) Moisturizing Cream	Moisturizer	SDR Pharmaceuticals, Inc.	**25**
8.	EpiQuin Micro	Hyper pigmentation	Skin Medica Inc.	**75**
9.	Sports cream RS and XS	Anti-inflammatory	Embil Pharmaceutical Co. Ltd.	**75**

CONCLUSION

The detailed data summarized in this article suggest that many various pharmaceutical drugs are explored in microsponge delivery system. MDS holds major potential in both pharmaceutical industries due to its novel release methodology and its ease of administration with fewer side effects. It is a peculiar and novel methodology for the controlled release of topical agents which can entrap the actives that are releases onto the skin over a time. Various literatures have reported that the microsponges systems are non-irritating or soothing, non-allergic, non-mutagenic and non-toxic. MDS technique is used currently in over-the-counter skin care products, sunscreens, prescription and cosmetic products. Therefore, microsponge has got a lot of prospective and is a very rising field which is needed to be examined and it is probable to become a precious drug delivery matrix substance used for different therapeutic applications in the upcoming future.

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