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Microsponge Drug Delivery: An Overview

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ABSTRACT

Microsponge drug delivery system is an important part of the field of novel drug systems due to the controlled release profile and targeted delivery. These systems made up of microspheres having pores, having size of 10-25 microns and the active ingredient is entrapped in it. These are having non-collapsible structures, spherical particles same as a sponge, made up of a group of interconnecting voids having large porous surfaces due to which controlled release profile is obtained. These are effective for topical drug delivery as well as gastro-retentive drug delivery system. Microsponge is one of the better approaches for gastric retention where oral drug delivery is inappropriate due to non-uniformity in absorption profile, the inadequate release of active ingredients, short time of residence in the stomach. This drug delivery system is having various advantages such as non-toxic,non-irritating,non-allergic, can entrap a wide variety of active ingredients and these are formulated into various topical formulations such as cream, gel, liquid or powder. It bypasses the disadvantages of other formulations such as dosing frequency, drug interaction, and incompatibility with the environment. The present review describes versatile microsponge technology including its formulation preparation, characterization, method of evaluations, recent developments in this technology, and prospects.

INTRODUCTION

Drug delivery systems (DDS) that can control the rate of release at the target site reducing unwanted systemic side effects are important. Carrier technology having microsponges, nanoparticles, liposomes offers the same, including regulation of the release and absorption characteristics. The Microsponge is promising drug delivery in terms of the controlled release of drugs restricted to the epidermis so that no entry in entering the systemic circulation. Conventional topical formulations have various drawbacks like uncontrolled evaporation of active ingredient, unpleasant odor, and potential incompatibility of drugs with the vehicles. The microsponge delivery system bypasses these drawbacks.[**Error! Reference source not found.**, 2, 3]

Microsponges are made up of polymers and having a porous structure. They are tiny, having non-collapsible structure, and having porous surfaces. Size of microsponges is ranging from 5-150µm. Wide ranges of active ingredients are used in microsponge drug delivery e.g. antifungal drugs, essential oil, anti-infective agents, fragrances, sunscreens, etc. Further these microsponges are incorporated into suitable formulations such as creams, lotions, and powders.[4]

A typical microsponge having size 25µm can have up to 250000 pores and having an internal pore structure nearly equivalent to 10 feet in length and due to this system behaves as a reservoir type drug delivery system. This system can be incorporated with active ingredients equivalent to its weight. The microsponge particles are not absorbed through the skin due to too large size as compared to skin pores.[5, 6, 7]

History of microsponge drug delivery system[8,9]

The microsponge technology was invented by Won in the year 1987. The original patents were taken by Advanced Polymer Systems, Inc. in California, US (Redwood City). This Company developed a large number of variations in the formulation procedures. Those were applied to the cosmetic, over-the-counter (OTC) and prescription pharmaceutical products. At present, this technology has been licensed by Cardinal Health, Inc., and used for topical products especially for the controlled release of active drug.[8,9]

Properties of the **drug for loading into microsponge**[5,9]

Most liquid or soluble ingredients can be used to entrap into the microparticles. Active substances that can be entrapped in microsponges must meet the following characteristics,

1. It should be fully miscible in monomer otherwise should be made miscible by the addition of a small amount of a water-immiscible solvent.

2. It should be immiscible in water or at the most slightly soluble in water.

3. It should be inert concerning the monomer.

4. To avoid cosmetic problems, the solubility of active ingredients in the vehicle must be checked.

5. The spherical structure of microsponge should not collapse.

6. It must be compatible with polymerization catalysts and states of polymerization.

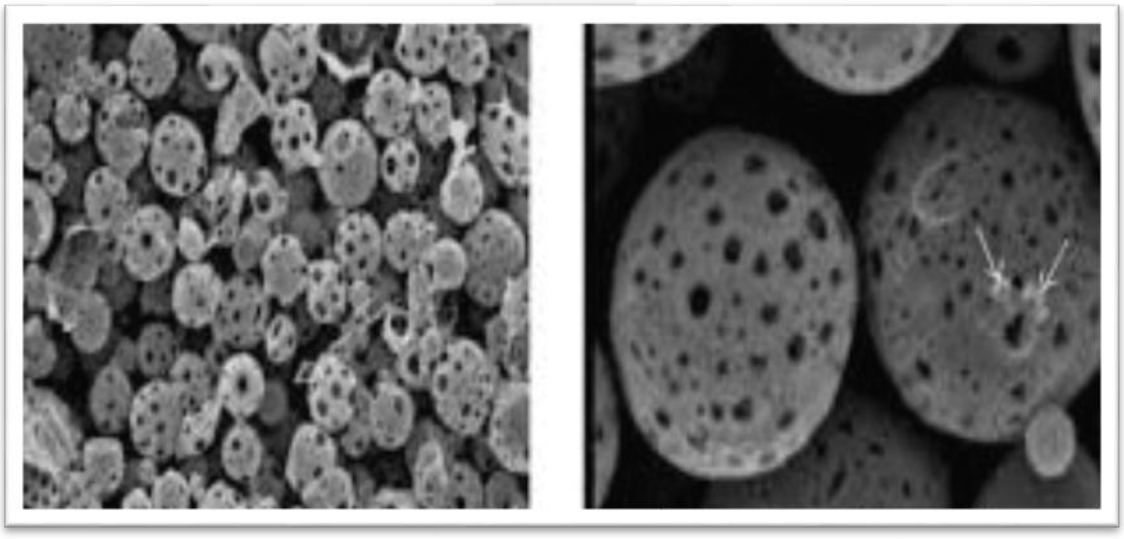

Figure No. 1: Structure of microsponge[10]

Advantages of microsponges [11-14]

1. Formulations have stability over range of pH 1 to 11.

2. Formulations have stability the temperature up to 1300C.

3. They are most compatible with various vehicles and ingredients.

4. Microsponge formulations are having average pore size is about 0.25µm so act as self-sterilizing as bacteria are unable to penetrate pores.

5. Entrapment efficiency is about 50 to 60%.

6. Microsponge formulations are cost-effective.

7. .microsponges can absorb large amounts of oil i.e. up to 6 times.

8. Microsponge particles themselves are too large so they are difficult to be absorbed into the skin and this adds a measure of safety to these microsponge materials by avoiding the side effects of the microsponge adjutants.

9. Sustained-release formulations can be prepared.

10. They are having superior formulation flexibility.

Limitations of microsponge formulations[11]

The use of organic solvents in preparation methods is progeny, which is responsible for environmental hazard because some solvents may be inflammable, providing a safety hazard. The traces of monomers in the formulation are toxic and dangerous to health.[11]

Types of Release systems of Microsponges[13,15]

1) Pressure Modulated Systems

Upon applying pressure microsponge system releases the entrapped material and the released amount depends upon various characteristics of the sponge. When the type of material and different process variables are varied then the microsponge best suited for a given application may be optimized.

2) Temperature Modulated Systems

This system uses temperature modulation to control of release from microsponge, this system is explained with an example, when sunscreen exposed to higher temperature show higher release.

3) pH Modulated Systems

PH Triggered systems use a coating of pH-sensitive polymers on the microsponge system.

4) Solubility Modulated Systems

Due to an aqueous medium such as perspiration can trigger the release rate of active moieties entrapped in microsponges.E.g. antiseptics, antiperspirants, and deodorant formulations Release depend on the dissolution of active component in the external medium.

Methods for preparation of microsponges:

1. Liquid-liquid suspension polymerization[11,16,17]

Liquid-liquid systems are used in this technique and porous structures are formed. In this method, miscible monomers are first dissolved along with active ingredients in a suitable solvent. The prepared solution is then dispersed in the aqueous phases having additives like surfactant, suspending agents that facilitate formation of suspension. Temperature is increased or the addition of a catalyst is done to activate polymerization. Reservoir type of system with spherical structure is formed by polymerization process. The solvent is removed to achieve porous and spherical structured microsponges.

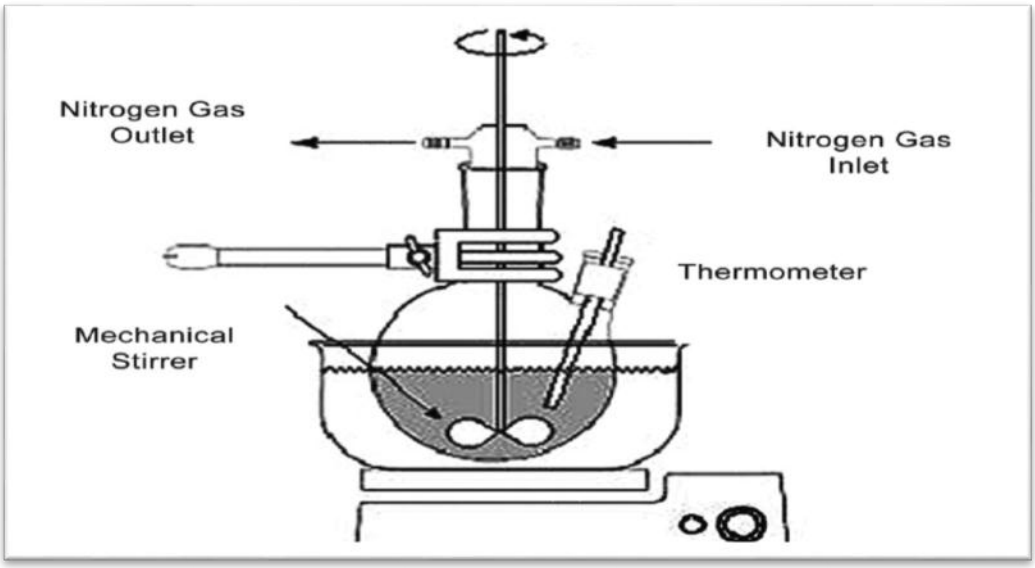

Figure No. 2: Liquid-liquid suspension polymerization[11]

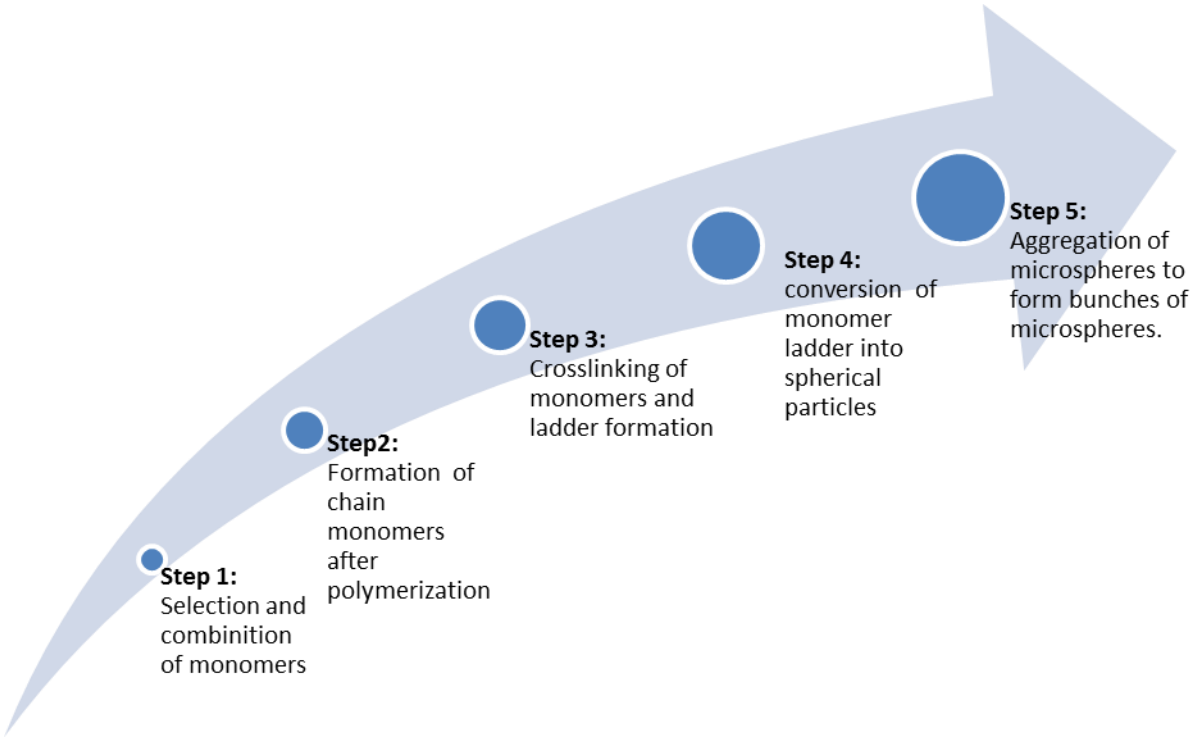

Figure No. 3: Summary of different steps involved in the liquid suspension polymerization

2. Quasi-Emulsion Solvent Diffusion Method[11,16,17]

Quasi-Emulsion Solvent Diffusion Method consists of an external phase and internal phase. It is a two-step process, where an internal phase consists of drugs and polymers such as Eudragit RS 100 or ethyl cellulose. Other constituents such as ethyl alcohol, Triethyl citrate, or trichloromethane are also used. Firstly polymer is dissolved in a suitable solvent. Then, the drug is added to the above-prepared solution and ultrasonication is done at 35˚C. Plasticizer such as triethyl-citrate is used to aid the plasticity. The internal phase is then added into the external phase having polyvinyl alcohol and distilled water. The stirring is also required for optimized hours. Then, the mixture was filtered to separate the microsponges. The obtained product is washed and dried in a heated oven at temp 40°C.

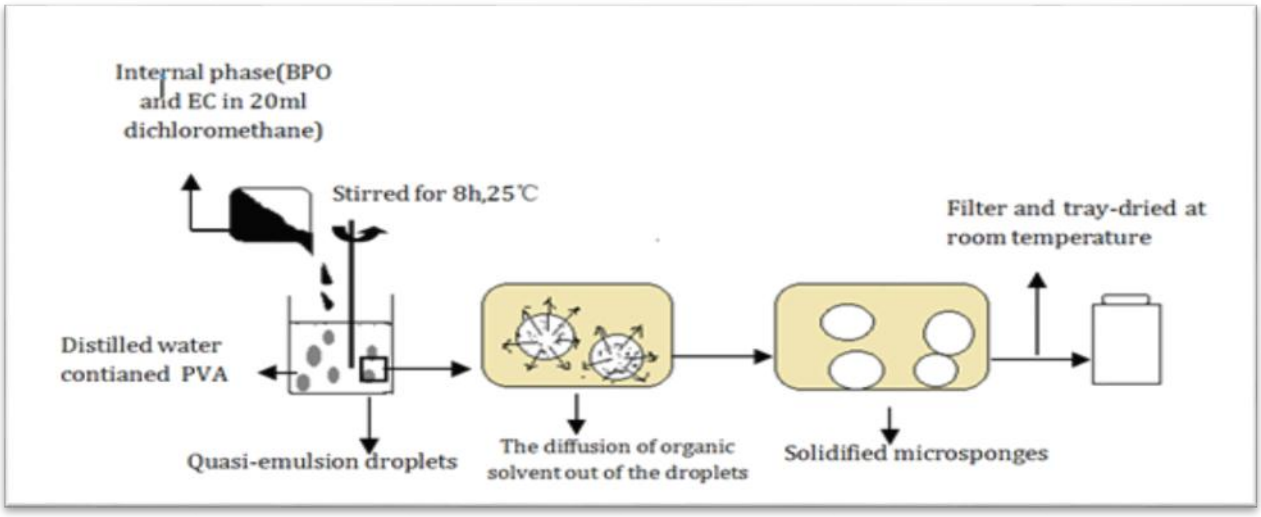

Figure No. 4: Quasi Emulsion Solvent Diffusion Method (Schematic Diagram)[18]

Table No. 1: Summary Stages of Quasi Emulsion Solvent Diffusion Method

Sr. No.	Description of Step
Step No:1	Internal phase=Polymer + Solvent
Step No:2	External Phase=Dist water + PVA
Step No:3	Addition of Internal phase into External phase along with stirring
Step No:4	Formation of microsponges
Step No:5	Drying of microsponge

Parameters influencing formulation[16]

Microsponges have primary parameters such as are Particle size, the structure of pore, diameter, the volume of microsponges and release characteristics. Its components and polymerization conditions are altered by predesigning the above parameters.

1. Size of particle:

The free-flowing property of the powders can be modified by controlling the size of the microspheres at the time of formulation. The microsponges having diameters of 5 to 300 micrometers are freely flowable. Smaller particles are not desirable. Larger particle size should formulate if desire. The release rate of the active ingredient is greatly influenced by Particle size and diameter of the same. If smaller the size of the microsponges slower release rate is obtained.

2. Pore Diameter and Volume:

Pore volume (Void volume) is important to incorporate active substances into microsponge. Both diameter and pore volume are crucial in the modulation of intensity and effectiveness duration of the active components entrapped. Pore diameter determines the movement of the active ingredient from the structure of Microsponge into the medium in which active moiety is dispersed. So the stability of a formulation is affected by the diameter of the pores.

3. Property of Resiliency:

The proportion of crosslinking of polymer in the process of polymerization is varied to get beads having a softer or harder nature. 10% cross-linking is optimum for giving them strength and shape and hence the release of active moiety from pores. Release rate slows down as an increase in the cross-linking.

4. Monomer Composition:

Active components and vehicle used are major factors that affect the selection of the monomer. Other Factors are the hydrophilicity or lipophilicity may be modulated to obtain control on the release of components such as vitamins, lipids, sunscreens, fragrances, humectants, Antifungals, etc.

Hypothetical mechanism of action for topical drug delivery[6,18,19]

The active ingredient is entrapped into the structure of microsponge. As these particles have a porous structure, the active moiety is freely moved in and out from the particles and inside the surrounding vehicle until equilibrium is obtained, so the vehicle gets saturated. Once the finished formulation is applied on the skin, the active moiety present in the vehicle will be transferred on the skin. As depletion of the vehicle takes place, unsaturation between both systems takes place and equilibrium gets disturbed. This will start again flow of active ingredient from microsponge to vehicle and finally to the skin. This process continues until the vehicle is either dried or absorbed. Even after that, the release from microsponge particles on the surface of the skin will continue gradually, so prolonged-release is obtained over time. If the active drug which we have to incorporate into microsponge is too soluble, the desired sustained release is not obtained.

The gradual release is obtained if the drug added in a vehicle is in free form. So it is necessary to choose a vehicle that has minimum solubility for an active constituent. This concept is opposite to conventional topical formulations in which maximum solubility of the active drug is done. Solubility of active in a vehicle is acceptable to some extent because this will provide initial loading dose until release mechanism due to equilibrium takes place. The rate of release of active constituents depends on the partition coefficient of the drug between vehicle and polymer and characteristics of beads, for example, pore diameter and surface area. Release can also be modified by diffusion or other systems such as temperature, pH friction, moisture.

Mechanism of action for oral formulation[19]

Microsponges having a particle size less than 200 µm are effectively taken by macrophages in the colon. Due to this localized action in the colon is achieved. These formulations can increase absorption lag time for colon and entrapment takes place at the targeted site. In this way, release mechanism for oral formulations of microsponges can explained.

Parameters related to safety[16]

As Microsponge drug delivery systems are composed of polymers which are biologically inert, more than 30 safety parameters are taken into consideration such as skin irritation on rabbits and humans, eye irritation testing in rabbits, oral toxicity in rats, mutagenicity in bacteria, and allergenicity in guinea pigs. Such parameters indicate that the polymers taken are safe for human use. preliminary data shows that upon application of injection into the skin, some Microsponge drug delivery systems are not recognized by defense mechanism of body as foreign substance and hence cause no response in the due to their presence.

Marketed formulations[6,20]

Table No. 2: Marketed formulation

Sr. No.	Product Name	Pharmaceutical Uses	Manufacturer
1	Glycolic Acid Moisturizer w/SPF 15	Anti-Wrinkles, soothing	AMCOL Health & Beauty Solution
2	Retin A Micro	Acne vulgaris	Ortho-McNeil Pharmaceutical, Inc
3	Carac Cream, 0.5%	Actinic keratoses	Dermik Laboratories, Inc.
4	Line Eliminator Dual Retinol Facial Treatment	Anti-wrinkle	Avon
5	Retinol 15 Night cream	Anti-wrinkles	Sothys
6	Retinol cream	Helps maintain healthy skin	Biomedic
7	EpiQuin Micro	Hyper pigmentation	SkinMedica Inc
8	Sports cream RS and XS	Anti-inflammatory	Embil Pharmaceutical Co. Ltd.
9	Salicylic Peel 20	Excellent exfoliation	Biophora
10	Oil-free matte block SPF 20	Sunscreen	Dermalogica
11	Lactrex™ 12% Moisturizing Cream	Moisturizer	SDR Pharmaceuticals, Inc
12	Dermalogica Oil Control Lotion	Skin protectant	John and Ginger Dermalogica Skin Care Products
13	Ultra-Guard	Protects baby‟s skin	Scott Paper Company

Evaluation of microsponge formulation:

1. Particle size analysis and morphology[9,11,21]

Conventional light microscopy and scanning electron microscopy are common techniques used for visualizing microsponges. Both techniques are used to study the particle size and distribution of the size of microspheres. For visualization of double-walled microparticles light microscopy is used as coating parameters can be controlled. Structures before coating and structures after coating are visualized to do the same. Higher resolution technique to analyze particle size is Scanning Electron Microscopy. Microparticles surfaces are

investigated and also cross-section is studied so also used for double-walled systems. For microparticles having multiple walled structures Confocal Fluorescence Microscopy is used. Other methods are coulter counter and Laser light scattering for determination of morphology of microsponges.

2. Pore structure analysis[13,22]

For modifying the release of the microsponges the size of the pores plays an important role. It is measured by parameters such as pore diameter and volume of microparticles. Mercury intrusion porosimetry is used to calculate these parameters, which correlates pore-volume and diameter with the release of drug from microsponges. Intrusion extrusion isotherms can determine parameters such as the distribution of pore-size, total pore-surface area, and diameter of microsponges.[6]

3. Determination of true density[4]

An Ultrapycnometer is used to calculate the true density of microspheres under helium gas. Mean is taken from repeated observations.

4. Surface topography of Microsponges and Morphology[4,23]

Various techniques are used like photon correlation Spectroscopy, Scanning electron microscopy, transmission electron microscopy etc.are used to study surface topography of microsponge. Scanning Electron Microscopy is the most widely used technique in which Microsponges are coated with gold-palladium and then the surface topography of the Microspheres is studied.

5. Production yield[9,11,24]

The following equation is used to calculate the production of the microsponges.

Production Yield (PY) = [Practical Mass of Microsponges / Theoretical Mass (Polymer + Drug)] *100

6. Determination of loading efficiency[25]

The following equation is used to calculate the loading efficiency of the microsponges. It is based on the initial weight of the raw materials taken and the final weight of the obtained microsponges.

$$\text{Actual Drug content (\%)} = (M_{act} / M_{ms}) * 100$$

$$\text{Encapsulation Efficiency} = (M_{act} / M_{the}) * 100$$

Where, M_{act} = actual DDEA content in weighed quantity of microsponges,

M_{ms} = weighed quantity of microsponges

M_{the} = theoretical DDEA content in microsponges

7. Determination of pH[4]

The pH meter is used to determine the pH of the microsponges loaded gel. The readings are taken for 3 samples and the average is taken.

8. Rheological characterization[26]

The rheological measurement of a microsponge loaded gel is done with a rheometer in controlled stress. A fresh sample of gel loaded with microspheres or viscous systems is used for the determination of rheology at different temperatures.

9. Diffusion study evaluation(Ex- vivo diffusion)[26]

For *ex-vivo* diffusion, the study is done with sacrificing full-thickness skin male Wistar albino rats obtained from the abdomen. Subcutaneous fat is removed and cut into pieces. Pieces are larger than the effective diffusion cell surface area. These skin pieces are immersed in normal saline. These pieces are mounted between donor and receptor chambers of Franz diffusion cell. In this way study conditions and analytical methods are developed as identical as in-vitro release evaluation.

10. Dissolution Test[9,27]

Dissolution release rate of microsponges can be evaluated by making use of dissolution apparatus USP XXIII containing a modified basket having stainless steel mesh of 5µm. Suitable dissolution medium is selected by considering the solubility of active drugs to ensure sink conditions. At various intervals, the samples are taken analyzed.

11. Resiliency(Viscoelastic Properties)[26]

It is one of the viscoelastic properties. Higher amount of cross-linking affects the rate of release that is it slows down the release rate.

12. Compatibility Studies[28]

There should be no reactivity between drugs and recipients or there should inert nature of recipients with Apathies is done with Thin Layer Chromatography and Fourier Transform Infra-Red spectroscopy. Powder X-ray diffraction and Differential Scanning Colorimetry techniques are the techniques that are used to study thermal analysis and polymerization effect on crystallinity.

13. Stability study[28]

Stability study of microsponge loaded system can be performed at different storage conditions as per the guidelines of ICH (International Conference on Harmonization). It is done by subjecting them to different specific conditions like 40˚C/75% RH, 25˚C/ 60% RH, 30˚C/ 65% RH, and 2–8˚C for a predetermined time. The sample is evaluated for changes withdrawn at different time intervals for changes such as pH change, change in drug content, physical appearance, rheological properties, and drug release from the system, etc.

Recent developments in the microsponge drug delivery system[6,29]

Various advances such as nano ferrosponges, Nanosponges, and microbeads are formulations developed by modifying the preparation method of microsponges. β - CD nanosponges by using β – CD is useful for entrapment of hydrophilic as well as hydrophobic drugs. These systems were used for the delivery of various drugs such as Flurbiprofen, dexamethasone, doxorubicin, itraconazole, serum albumin by the oral route. These nanosponges are prepared by the cross-linking reaction of the β -CD molecule with biphenyl carbonate. These

nanosponge carrier drug delivery systems are specially used in targeted drug delivery for cancerous cells so useful for the incorporation of cytotoxic drugs.

Future prospects[6]

We can develop peptide delivery for the oral route of administration. This technology uses biodegradable polymers so it enables safe delivery of the drug. Due to porous structure, it can give release in the scarce of dissolution media so it can be useful in pulmonary as well as colon drug delivery systems. This drug delivery is also useful in routes like parenteral. These carriers can also be used in the culture media of cells and so useful in microbiological aspects. It has an application in cosmetics in oral form to retard the release of volatile active ingredients. Microsponges can be incorporated in toothpaste or mouthwashes for a specific purpose. It has applications in long-lasting cosmetics such as lipsticks so that it is helpful in uniform covering and spreading. So Microsponge drug delivery system is promising drug delivery systems in various applications in the upcoming future having unique properties such as good product performance and better elegance, extended-release profile, predetermined drug release profile, reduced irritation due to various actives, improved stability, higher flexibility to develop the novel formulation.

CONCLUSION

Microsponge drug delivery has become highly evolving technology and research is going on to optimize the cost of formulation and usefulness of the therapy. Due to high efficiency and highly innovative technology, it has wide applications in pharmaceutical as well as cosmetics. The market has considerable potential for Microsponge technology and the versatility offered by it. Formulators work on new and creative methods to deliver active substances and can realize the full capabilities of these unique materials to provide improved safety, enhanced stability, fewer side effects from the active substance, improved multifunctionality, and better ingredient compatibility. Microsponge delivery system can be a better strategy for a new generation of Pharmaceutical and Cosmetic products. Microsponges possess a distinct advantage over the various conventional topical dosage forms for the topical diseases, it is a unique technique for the controlled release of topical agents, also used for oral as well as biopharmaceutical drug delivery. This drug delivery is advantageous over other products by non- mutagenic, non- toxic, non-irritant nature. So the microsponge drug delivery system has

got a lot of potentials and is a versatile delivery system which is needed to be explored in the future with maximum research study.

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