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REVIEW ON MICROSPONGE DRUG DELIVERY SYSTEM

Reshma.s.vijay*, Mrs. Remya S.B, Dr. Proshobh G.R., Ms. Hephziba Blassan, Ms. Haripriya

Sree Krishna College of Pharmacy and Research Center, Parassala, Thiruvananthapuram Dist. Kerala.

Abstract:

Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge-like spherical particles with a large porous surface. Moreover, they may enhance stability, reduce side effects and modify drug release favorably. Microsponge delivery technology has many favorable characteristics, which make it a versatile drug delivery vehicle. Microsponge systems are based on microscopic, polymer based microspheres that can suspended or entrap a wide variety of substances, and can then be incorporated into a formulated product such as gel, cream, liquid or powder. The outer surface is typically porous, allowing a sustained flow of substance out of the sphere. Microsponges are porous, polymeric microspheres that are used mostly for topical use and have recently been used for oral administration. Microsponges are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effect, and modify drug release.

Corresponding author:

Reshma S Vijay,

7th semester B. Pharm student

Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram Dist. Kerala

Email: reshmasvijay7@gmail.com

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1.1INTRODUCTION:

Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge- like spherical particles with a large porous surface. Microsponge is recent novel technique for control release and target specific drug delivery system. They are desire to deliver API efficiently at the minimum dose and also to enhance stability, reduce side effect and modify drug release. Typically in 5-25µm in diameter

Topical Delivery Systems (TDS) The purpose of topical dosage form is to conveniently deliver drugs across a localized area of the skin. To develop an ideal dosage form one must take into account the flux of drug across skin, retention of the dosage form and the patient acceptability of the formulation. The problem of formulating a drug is complex because of the wide diversity of drug solubility in vehicle components and the vast range in cutaneous fluxes. When it comes to the delivery of a drug to a specific site, topical formulations are probably among the most challenging products to develop. An effective topical formulation needs to provide a stable chemical environment in order to accommodate multiple compounds that may have different, if not incompatible, physicochemical characteristics. Once applied, a topical formulation must interact with the skin environment, which can influence the rate of the release of the compound in order to achieve adequate skin absorption. The excipients themselves will exert additional physical effects on the skin, such as drying, occluding, or moisturizing. These insights have resulted in new delivery systems that are capable of enhancing the efficacy, tolerability, and cosmetic acceptability of topical formulations.[1]

1.2 ANATOMY

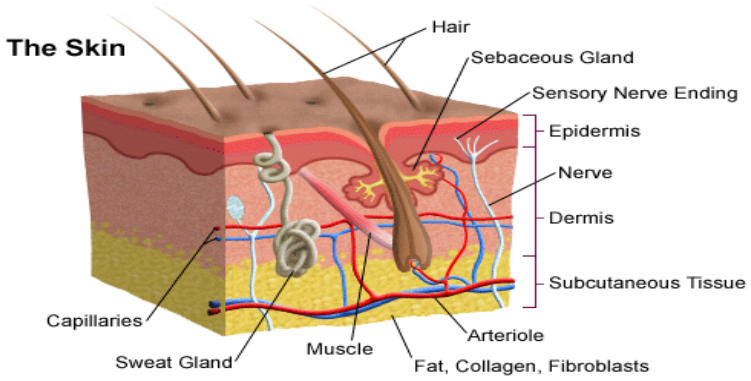

Figure 1: **Microsponge as Topical drug delivery**

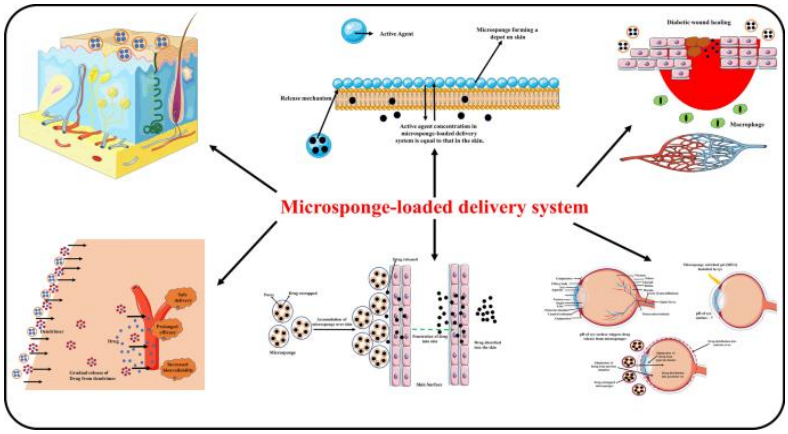

Figure 2: Anatomy of skin

- The human skin is a large and complex organ that protects internal tissues from environmental exposure. As the interface between the organism and the external world, the skin is susceptible to injuries organisms.
- Topical drug delivery systems are formulated either to give local effect or to enter in to the systematic circulation, where skin serves as the portal of entry to the drug and various formulations made available in the market are creams, gels, lotions, ointments etc.
- Main drawbacks of topical pre-formulations for local action are they may readily absorbed and hence, less duration of action and decrease activity.
- Similarly topical preparations for systemic action have drawback like drug doesn't reaches the systemic circulation in sufficient amounts.[2]

To overcome this problem MDS technique plays important role

- A Microsponge Delivery System (MDS) is patented, highly cross-linked, porous polymeric microspheres that can entrap wide range of actives and then release them with desired rate. This system is applicable for the improvement of performance of topically applied drugs.
- When Microsponge delivery system applied to the skin, the release of drug can be controlled through diffusion or other variety of triggers, including rubbing, moisture, pH, friction, and skin temperature.
- Thus the Microsponge should remain maximum time at the skin and below the epidermis and release the medicament slowly.[3]

Needs for microsponges drug delivery system

- Microsponges consist of non-collapsible structure with porous surface through which active ingredients are released in a controlled manner.
- Their characteristics feature is the capacity to adsorb or 'load' a high degree of active materials into the particle and on to its surface.
- To prevent excessive accumulation of ingredients within the epidermis and the dermis.
- Controlled release of drug on to epidermis does not enter the systemic circulation in significant amounts.[4]

Characteristic of Micro sponge drug delivery systems

1. Microsponges are stable over the extended ph. range from 1 to 11 and constant up 130˚C temperature.
2. Microsponges are friendly with many of excipients and no require of sterilization.
3. About 50 to 60 % drug may possibly be entrapped in microsponges, and gives good flowing properties.
4. These are still molecules without any allergy, irritation and toxicity.
5. It must be either fully miscible in a monomer or capable of being made miscible by the addition of a small amount of a water-immiscible solvent.
6. It must be water immiscible or at most only slightly soluble.
7. It must be inert to monomers and should not increase the viscosity of the mixture throughout formulation.
8. It must be stable when in contact with the polymerization catalyst and under environment of polymerization.
9. The spherical structure of the micro sponges must not collapse.[5]

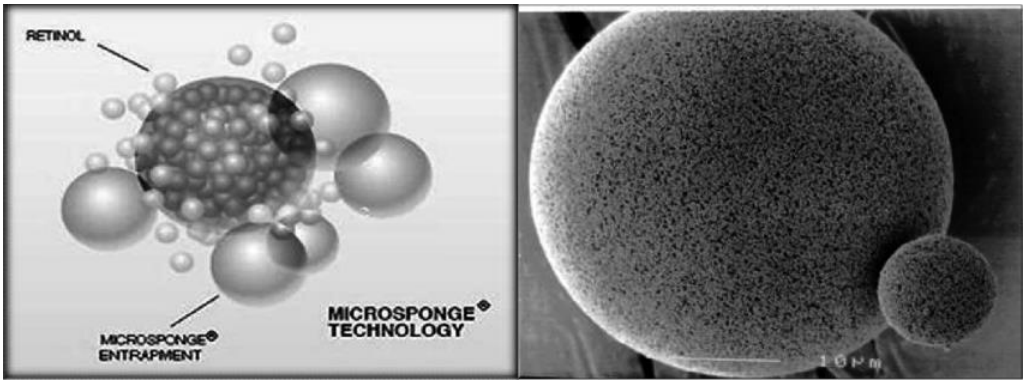

Fig 3: Characteristics of Microsponges

1.3 ADVANTAGES

- These are performing as controlled drug delivery system.
- Drug directly applies on target organs.
- It increases stability of drug.
- Drug loading capability is higher compare with other topical formulations.
- These are able of absorbing skin secretions and reduce oiliness.
- Microcapsules cannot frequently control the release rate of the active pharmaceutical ingredients. Once the wall is ruptured the active ingredients contained within the microcapsules will be released.
- Liposomes suffer from a lower pay load, complicated formulation, limited chemical stability, and microbial instability. Do the MDS have a wide range of chemical stability and are they easy to formulate.
- Micro DS have stability over a pH range of 1 – 11.
- Stable up to temperature 130°C.
- Pay load is up to 50 – 60%.
- Free flow and cost efficient.
- Microsponges are microscopic spheres competent of absorbing skin secretions, as a result Reducing oiliness and shine from the skin.[6]

1.4 DISADVANTAGES

- Unpleasant odor
- Greasiness and skin irritation
- Fail to reach the systemic circulation[7]

Benefits of Microsponges drug delivery systems

- Enhanced product performance.
- Extended release.
- Diminish irritation and hence enhanced patient Compliance
- Improved product elegancy.
- Improved oil control as it can absorb oil up to 6 times its weight without drying.
- Allows for novel product forms.
- Improves efficacy in treatment.
- Cure or control confirm more promptly.
- Improve control of condition.
- Improve bioavailability of same drugs
- Flexibility to develop novel product forms.
- Non-irritating, non-mutagenic, non-allergenic and non-toxic
- Improves stability, thermal, physical and chemical stability
- Allows incorporation of immiscible products.
- Improves material processing e.g. liquid can be converted to powders[8]

1.5 APPLICATIONS

- It has been used for the study of colon targeting of drugs and genes.
- It has been used in sunscreen, cosmetics and over-the-counter (OTC) products.
- Microsponge used for topical delivery(such as cream, gel, liquid or powder)
- Microsponge used as oral delivery
- Microsponge used for Bone and Tissue Engineering[9]

Applications of MDS

Microsponges technology in cosmetics

Microsponge technology has an intriguing use in oral cosmetics, such as sustaining the release of volatile chemicals, therefore enhancing the duration of the 'fresh feel'. Such volatile substances can be easily integrated into dental pastes or mouth washes as MDS. MDS can be used in a range of coloured cosmetic items, such as rouge or lipsticks, to extend the life of the product by trapping the colour in the Microsponge. MDS aids in the disintegration of uniformity and boosts the covering power. Hence, the colourful cosmetics made with MDS will be incredibly exquisite as a result[10]

MDS for topical delivery

The action of traditional topical drug formulations is thought to be limited to the outermost layers of the skin. When these traditional items are put to the skin, they release their pharmaceutically active medicine, resulting in an extraordinarily concentrated film of pharmaceutically active drug that is rapidly absorbed. This excessive build-up of active components in the epidermis and dermis layers of the skin can be avoided by packaging the medicine in a microsponge drug delivery system. This microsponge technology can significantly reduce drug irritation while maintaining its effectiveness. Furthermore, these drug-containing porous microspheres can be incorporated into dosage forms such as creams, gels, powders, and lotions.[11]

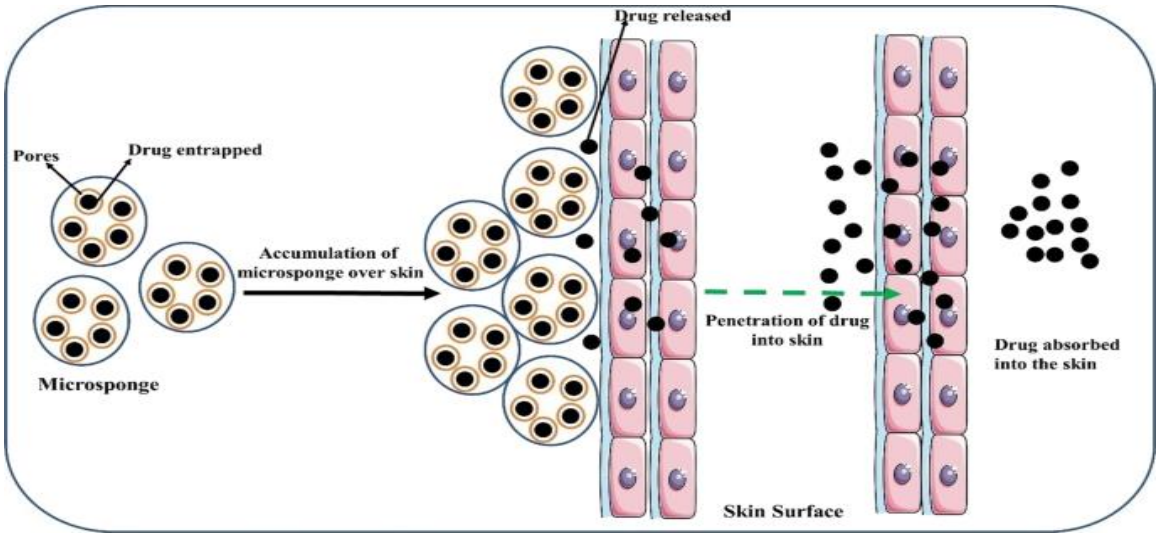

Figure 4: Mechanisms of drug release from topical microsponges

MDS for oral drug delivery

The oral administration of drug using MDS is appropriate because this technology has the ability to increase the release rate of drugs that are poorly soluble in water by entrapping these compounds in the pore system of the microsponges. The pH of the microsponge oral drug administration is regulated by it.

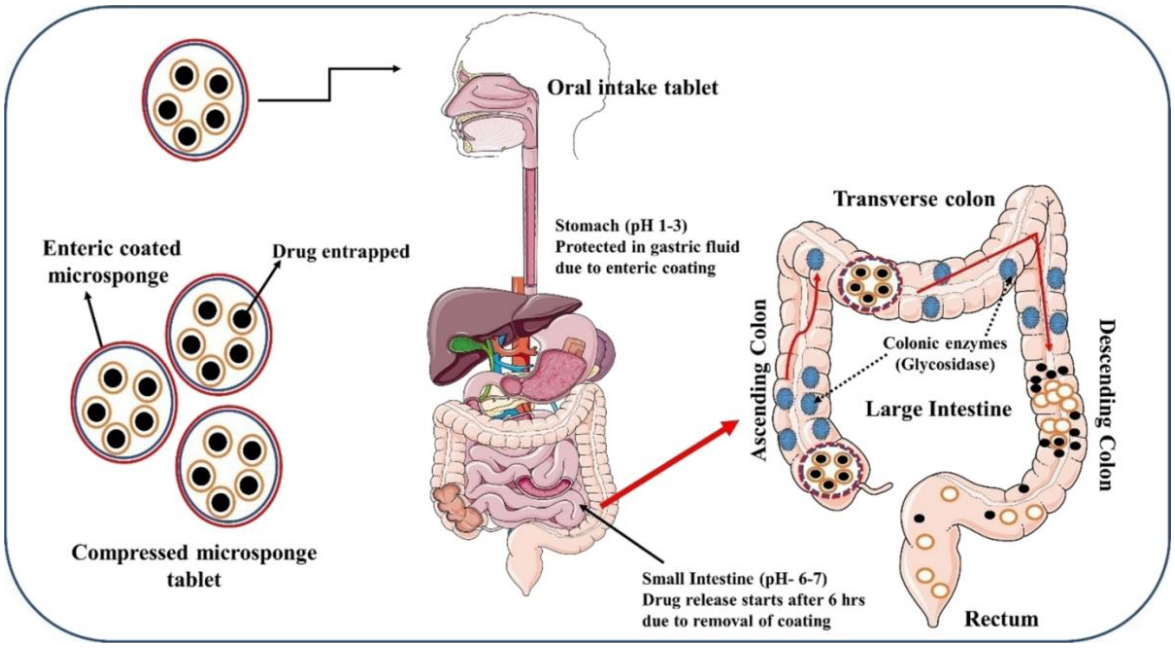

Figure 5: Drug release mechanisms from microsponges for an oral drug delivery system

The microsponge delivery technology also has the potential to embrace drugs in a restricted environment and to transfer active ingredients to the lower region of the GIT in a regulated way. The fundamental reason for using the microsponges system as a carrier for colonic administration is that actives with a size of less than 200 µm can be easily taken up by macrophages in the colonic tissues, resulting in effective localized drug action at the targeted spot.[12]

Ocular delivery

Water-soluble drugs can be applied topically as an ointment or an aqueous suspension, whereas water-

insoluble pharmaceuticals can be applied topically as an ointment or an aqueous suspension. The pharmacokinetics of drug in the eye is a complicated process. Following that, the drug is carried into the anterior chamber across the blood–aqueous barrier. The drug is transported from the anterior chamber to the Schlemm's canal and trabecular meshwork, where it is removed through aqueous humour turnover. Through the blood–aqueous barrier, the medicine is also removed from the aqueous humour and into the systemic circulation. Finally, a drug molecule in the blood crosses the blood–retina barrier and reaches the eye's posterior chamber[13]

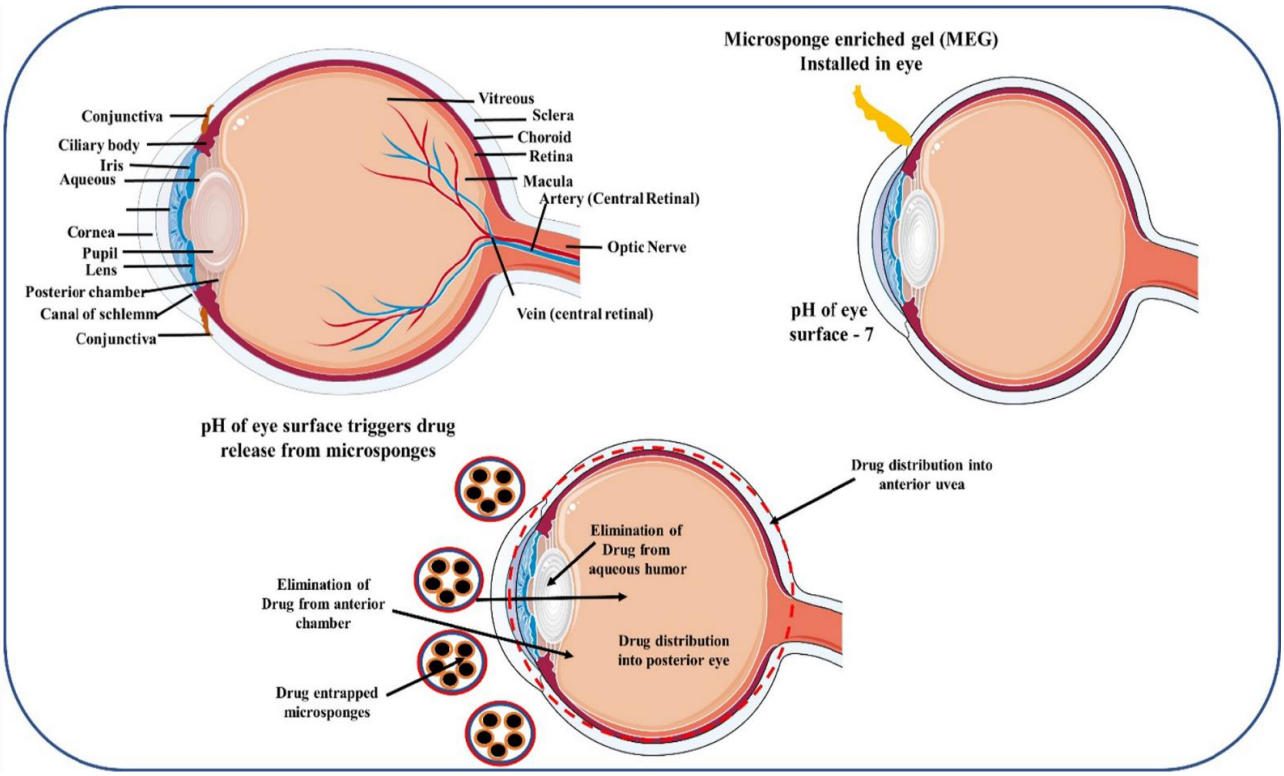

Figure 6: Drug release mechanisms from microsponges for ocular drug delivery

MDS in cosmetics and dermatology

Won's initial patents for microsponge technology were issued to Advanced Polymer Systems, Inc. in 1987. Microsponge technology was used in cosmetics, over-the-counter (OTC), and prescription medicinal goods by this firm. MDS ensures drug localization on the skin's surface and inside the epidermis, bridging the gap between systemic and local cutaneous side effects. Only the technological aspects of MDS for dermatological and cosmetic products differ. Cosmetic items have a lot shorter manufacture, marketing, and introduction period than dermatological products due to minimal regulatory restrictions.

Furthermore, skin targeting with microsponges drug delivery devices is possible, preventing excessive drug absorption into the percutaneous blood circulation.[14]

MDS in arthritis

The use of microsponge to dispense diclofenac has been studied in the treatment of arthritis. Diclofenac is the most often prescribed non-steroidal anti-inflammatory drug (NSAID) for the alleviation of pain and swelling associated with arthritis and other musculoskeletal disorders; however, it has been related to gastrointestinal irritation and first-pass metabolism. A topical treatment containing diclofenac MDS can be used to alleviate these concerns. Quasi-emulsion solvent diffusion technique to manufacture MDS gels containing diclofenac diethyl-amine to achieve a prolonged release for arthritis therapy. They compared their findings to the commercial Voltaren Emulgel 1.16 percent w/w. The gel only released 81.11 percent of the medicine in 4 h, but the microsponges-based gel released the drug over 8h produced MDS containing lornoxicam as the active component for treating arthritis and integrated them into tablet form, finding that the drug was released for a long duration, ranging from 86% to 96 percent to 12h[15].

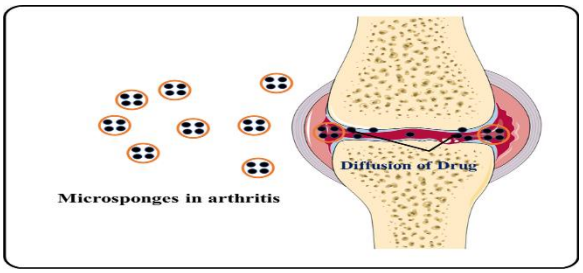

Figure 7: microsponges in arthritis

2.1. INSTRUMENTS HANDLED

(1) Liquid-liquid Suspension Polymerization

(2)Quasi emulsion solvent diffusion method

2.1.1. **Liquid-liquid suspension polymerization**

Principle

Suspension polymerization is a process in which monomers, relatively insoluble in water, is dispersed as liquid droplets with steric stabilizer and vigorous stirring to produce polymer particles as a dispersed solid phase.

Working

During polymerization, smaller molecules, called monomers or building blocks, are chemically combined to create larger molecules or a macromolecule. Hundreds of such macromolecules collectively form a polymer.

Use

Suspension polymerization is used to make a number of thermoplastic polimers.in suspension polymerization; all reactions are carried out in relatively large droplets or in polymer particles stabilized by a small amount of water-soluble gum. Organic peroxide initiators are used to generate radicals within the droplets.[16]

2.1.2. **Quasi Emulsion Solvent diffusion method**

Principle

In this method there is a formation of two different phases one is internal and second is external phase like an emulsion. Internal phase consist of solution of drug and polymer made with volatile solvents like ethanol, acetone, dichloromethane. This phase is added in second phase i.e. external phase which consist of aqueous polyvinyl alcohol with vigorous stirring. Also triethylcitrate is added in concentration of 20 % to facilitate plasticity.

Working

Quasi emulsion solvent diffusion method consists of the emulsification of organic solution of drug which is miscible with water and it also contains stabilizers. On shifting a temporary O/W emulsion into water, droplets solidify promptly as a result of the diffusion of the organic solvent out of the droplets to the external phase.[17]

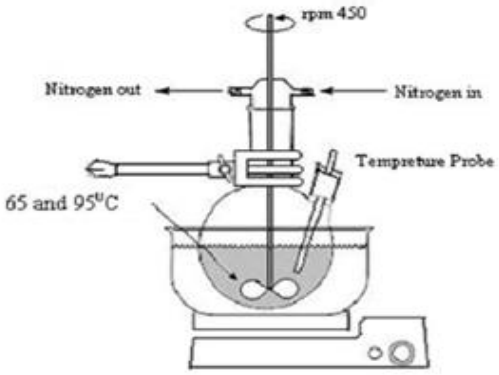

Figure 8: quasi emulsion solvent diffusion

3.1. PREPARATION METHOD

- **Multiple-emulsion solvent diffusion method**

The approach was developed to create porous and biodegradable microspheres. An aqueous inner phase was used with the addition of stearyl-amine, and the span was distributed in solution. This w/o emulsion is then dispersed again in an aqueous phase with polyvinyl alcohol to generate (w/o/w) double emulsion. This method reveals the advantage of capturing both soluble and insoluble actives. This method may also be used to entrap thermolabile compounds like proteins

- **Lyophilization**

The produced microspheres from the gelation procedure were converted into porous microspheres using this approach. After that, the microspheres were incubated in chitosan hydrochloride solution and stored for lyophilization. This approach produces microsphere holes as a result of the quick solvent removal. Because of the quick elimination of solvent, the lyophilization process of producing MDS has the disadvantage of creating shrunken or otherwise fragmented microparticles

- **Ultrasound-assisted production**

This approach was created by modifying the liquid–liquid suspension polymerization process for MDS generation. This approach uses beta-cyclodextrin monomer and diphenyl carbonate as a cross-linking agent to create MDS. To regulate the size of the microparticles, the reaction mixture is heated and sonicated. The mixture was cooled and powdered, which was then washed with distilled water before being washed with ethanol as illustrated. This technique of production is also insufficient in terms of entrapping harmful cross-linking agent residue[18]

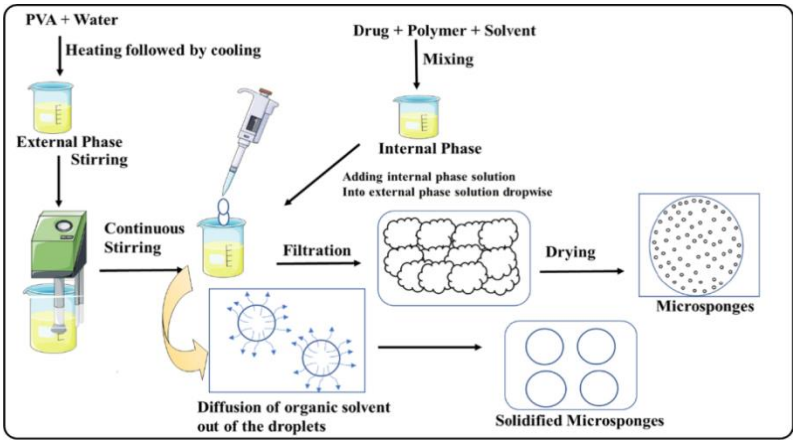

Figure 9: preparation method of microsponge

3.2. DRUGS EXPLORED IN MDS

- ✓ Ketoprofen
- ✓ Benzyl peroxide
- ✓ Retinol
- ✓ Fluconazole
- ✓ Ibuprofen
- ✓ Tretinoin
- ✓ Trolamine[19]

3.3. EVALUATION TEST

The microsponges are characterized by FTIR, DSC, XRD and SEM studies followed by determination of total drug content and entrapment efficiency. The prepared microsponges were further filled in hard gelatin capsule shell and then loaded in Carbopol gel to evaluate its potential in oral and topical drug delivery.

Evaluation of oxiconazole nitrate microsponges

1. Determination of production yield

The production yield of the microsponges was determined by calculating accurately the initial weight of the raw materials and the final weight of the microsponges obtained.

$$\% \text{ Production yield} = \frac{practical\ mass\ of\ microsponge}{theorotical\ mass(polymer+drug)} \times 100$$

2. Actual drug content and encapsulation efficiency

The drug content and encapsulation efficiency were calculated using the following formula

$$\% \text{ Encapsulation efficiency} = \frac{actual\ drug\ content\ in\ microsponge}{theorotical\ drug\ content} \times 100$$

$$\% \text{ Actual drug content} = \frac{Nact}{Nms} \times 100$$

Where Nact - is the actual oxiconazole nitrate content in weighed quantity of microsponges.

Nms - is the weighed quantity of powder of microsponges

3. Skin irritation test

Skin irritation test of optimized oxybenzone loaded microsponges gel was compared with the marketed and placebo gel.

4. Creep recovery test

In creep recovery, sample were subjected to a fixed stress from LVR for 100 s and then allowed to recover.

5. SPF Testing

The in vivo analysis was performed to study the effectiveness of the optimized formulation in comparison to the marketed formulation

$$SPF = \frac{MED\ (PS)}{MED\ (US)}$$

MED (PS) = minimal erythemal dose of protected skin;

MED (US) = minimal erythemal dose of unprotected skin.[20]

3.4. CLINICAL APPLICATION

1. Sunscreen - to improved protection against sunburns and related injuries
2. Anti – acne - maintained efficacy with decreased skin irritation and sensitization.
3. Anti –inflammatory -long lasting activity with reduction of skin allergic response.
4. Anti –dandruffs:- reduced unpleasant odour with lowered irritation with extended safety and efficacy
5. Anti-pruritics - extended and improved activity.
6. Anti –fungal- sustained release of active ingredients.[21]

4.1. APPROVAL PROCESS

4.1.1. List of microsponges approved for market[22]

Product name	**Active ingredient**	**Treatment**	**Manufacturer**
Retin -A- Micro	0-1% and 0.4% tretinoin in an aq. Gel.	Acne vulgaris	Ortho-McNeil pharmaceutical, Inc.
Cerac cream, 0.5%	0.5% fluorouracil	Actinic keratoses	Dermik laboratories, Inc.
oil control lotion	Natural antibiotics	Acne-prone, oily skin conditions.	Formulation cosmetics
Ultra- Guard	Dimethicone	Protect a baby's skin from diaper rash.	fountain cosmetics
Epi-Quin micro	Retinol and hydroquinone	Minimize skin irritation, reduced age spot, sun spot etc.	Avon
Lactrex™ 12% Moisturizing cream	12% lactic acid as the neutral ammonium salt, ammonium lactate.	Long lasting moisturization.	SDR Pharmaceuticals Inc., Andover, NJ U.S.A
Micro peel plus/ acne peel	Salicylic acid in forms of microcrystals.	Remove all dead cells doing no damage to skin	Biomedic.

4.2. MARKETED PREPARATIONS[23]

1. Murad moisturizing cream

Figure: 10

2. Cerac cream

Figure: 11

3. EpiQuin Micro

Figure: 12

4. Ultra Guard

Figure: 13

5. Neutrogena

Figure: 14

6. Dermalogica oil control

Figure: 15

4.3. FUTURE PROSPECT:

A microsponge delivery system (MDS) is an innovative and unique way of delivering drugs in a structured manner. Using microsponge drug delivery, regulated drug delivery may now be achieved quickly and easily.[24]

MDS comprises porous microspheres ranging in size from 5 to 300 microns, with a large porous structure and a very tiny spherical shape. MDS is normally used to deliver drugs via topical channels, but they have recently shown the potential approach to drug delivery via oral, ophthalmic and parenteral routes. MDS can easily modify the pharmaceutical release contour and improve formulation stability while minimizing the negative impact of the drug. The fundamental purpose of microsponge drug administration is to reach the highest possible peak plasma concentration in the blood. The capacity of MDS to self-sterilize is their most prominent attribute.[25]

4.4. CONCLUSIONS:

MDS is used as anti-allergic, anti-mutagenic and non-irritant in innumerable investigations. This review includes formulation, criteria for drugs to be incorporated in MDS, formulation methods, assessment parameters, and role of MDS in the management of various disorders. This review will be quite useful in the future in exploring the MDS in different disorders.

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