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Recent Advancement Of Oral And Topical Drug Release For Microsponges: A Comprehensive Review

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Abstract

Dermatological conditions greatly disrupt patients lives and have a profound emotional impact. Topical therapy is essential for the treatment of these conditions. Traditional topical delivery methods cause over- or under-medication, which has negative consequences and lowers the effectiveness of treatment. For which, numerous traditional and innovative carrier systems are available for topical treatment against different skin conditions. One of the more innovative carriers in recent times is microsponge technology. Basically microsponges are porous microsphere-based polymeric, tiny, globular particles with a sponge-like shape and a sizable porous surface. The control drug release of Microsponges are achieved by preparing them through liquid-liquid suspension polymerization, Quasi -emulsion solvent diffusion technique with a variety of different types of polymers like Ethylcellulose, ERS 100, EL100, ES100, EC etc. This paper offers a comprehensive explanation of the innovative state-of-the-art at this time, important factors affecting the mechanism and efficacy of drug release from topically applied microsponges, and characterization techniques. These formulations increased patient compliance by offering site-specific medication delivery and reduction in irritability, greater stability, and increased therapeutic efficacy.

Key Words: Microsponge, Recent advancement, preparation techniques, patent, application.

INTRODUCTION

One of the key issues facing by researchers today is creating a formulation that can control the rate at which active compounds are delivered to a certain place within the human body at a predetermined rate. This formulation needs to be more efficient and cost-effective, but in the current environment, getting the desired

results is not always easy. The human skin is nowadays a crucial target area for medicinal treatment of dermatological issues. Topical drug administration is a suitable strategy for treating skin problems since it reduces systemic adverse effects and limits the therapeutic effect on the affected area. The stratum corneum (SC), the skin's outermost layer, acts as a strong barrier against outside substances, including medications. This intrinsic stratum corneum characteristic presents a substantial challenge to formulation scientists, and this barrier needs to be broken in order to provide therapeutically appropriate drug concentrations in different skin layers. Lipid-based colloidal carriers have been investigated extensively and shown to be useful in enabling medication administration in the modern day. This is supported by the fact that the lipids used in these formulations are similar to physiological lipids. Given this, lipid-based colloidal systems present a profitable alternative for the delivery of dermatological actives by enabling enhanced skin penetration. Their capacity to stick to the skin's surface, their increased moisture and the ability to replace epidermal lipids by permitting lipid exchange amidst the colloidal carriers and the outermost layer of the epidermis makes them well-suited for dermal applications. The prevalent use of ingredients like - hydroxy acids and vitamins in topical products, have comprehensive benefits especially in ageing or photo damaged skin. This encouraged consumers to show interest in skin care and skin treatment products. Despite being helpful, these substances can cause irritation, which is often felt as burning, stinging, or redness and specially in people with sensitive skin. The formulators attempted to overcome this issue by using one of the two techniques. They immolate efficacy in order to reduce the strength of these substances and to make them more soothing or skin-friendly [13]. The majority of medications are not well soluble in water, which causes significant issues when preparing them in conventional dosage forms [14]. This is the main issue with TDS. Unmanageable volatilization of the active ingredient, unavoidable odour, and use of unattractive vehicles are potential issues with conventional topical drug delivery systems of drugs [15, 16, 17]. To divert and control the release behaviour of medications, there has been a lot of focus on the creation of innovative microsponge-based drug delivery systems in recent years [8]. Microsponges are porous, non-collapsible, strongly cross-linked polymeric microspheres with particle diameters ranging from 5 to 300 µm. They can entangle a range of active chemicals and gradually release them [1]. By virtue of their sponge-like structure, microsponges have special compression as well as dissolving characteristics [2]. They are very effective, stable, non-irritating, non-toxic, non-allergic, and non-mutagenic, with less adverse effects and improved patient compliance [3]. Microsponges are created by using a variety of polymers, including Eudragit RS100, Eudragit L100, Eudragit S100, ethylcellulose, polystyrene, PHEMA, and others. Additionally, these active microsponges have extensive range of advantages and can also be added in formulation of capsules, gel, and powders [4–8].

Drug confinement within the epidermis as well as on the skin's surface is guaranteed by microsponge-based delivery systems (MDS), which also reduce cutaneous adversities both locally and systemically. They are biologically safe and have the benefit of programmable release. This method also offers a significant number of advantages viz greater formulation flexibility, reduced side effects, improved elegance and stability [9–12].

Figure 1 represents as view of microsponge.

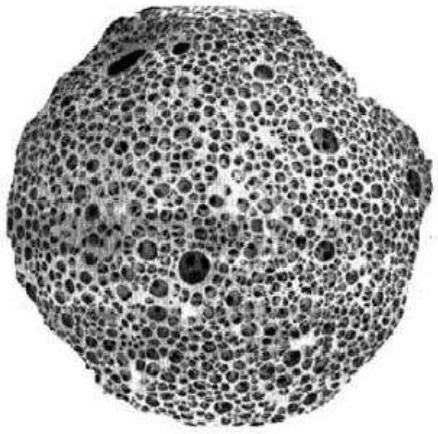

Fig 1: View of Microsponge

In addition to topical application, MDDS has demonstrated utility in numerous other domains, such as oral drug delivery systems for colon targeting, bone substitutes, biopharmaceutical delivery, tissue engineering,

disease diagnosis, and RNA silencing. However, topical application is the most common use for MDDS. The MDDS system may successfully reduce skin irritation rather than diminish its efficacy.

Features of microsponge medication systems

Microsponges work well with a wide range of vehicles and materials. They exhibit a free-flowing properties and good entrapment efficiency. Microsponges have remarkable stability throughout the pH range of 1 to 11 and at elevated temperatures, reaching up to 130°C. Because microsponges have tiny pores that prevent germs from passing through, they have the ability to self-sanitize, negating the need for additional preservatives. Microsponges do not cause allergies, rashes, or mutations. They can absorb oil six times its own weight without drying out. **[18, 19, 20]**

The characteristics of the active molecules confined within Microsponges [22, 23]

The characteristic of drug molecule were pictorially represented in fig 2

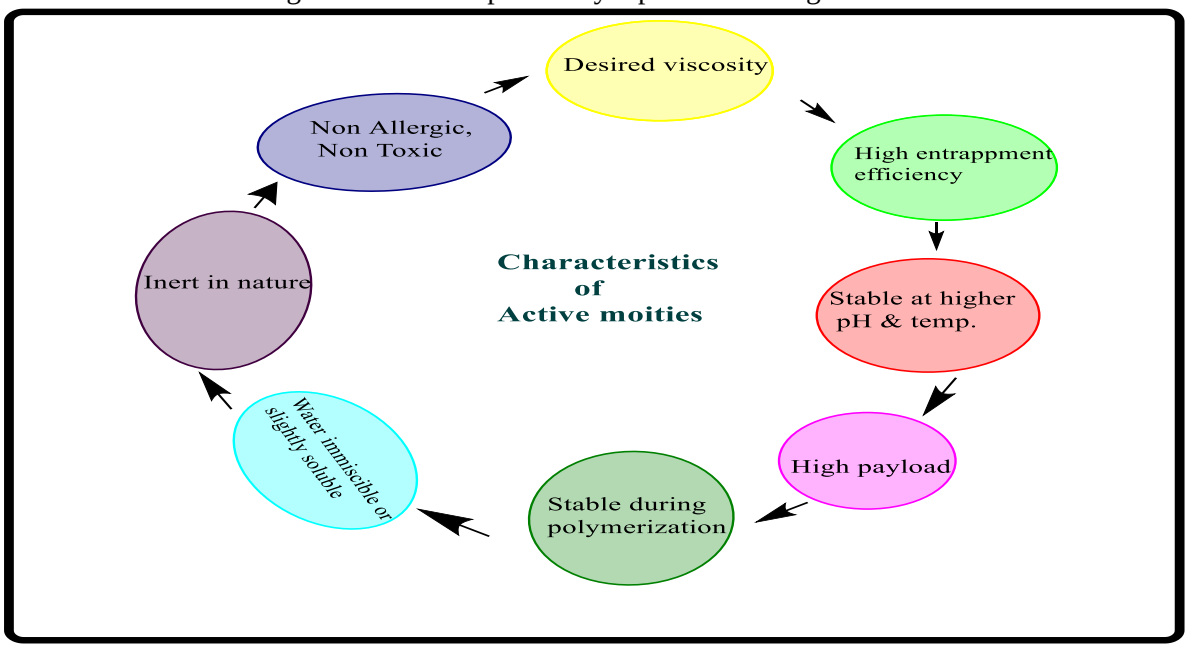

Fig 2: Characteristics of Active moieties incorporated in Microsponges

Applications of Microsponges [24-34]

Because of their special qualities, microsponges are frequently utilised as a drug delivery method in the pharmaceutical industry and have a wide range of applications. The utilisation of microsponges as a versatile tool for drug delivery, focused therapy, and controlled drug release has been demonstrated in a number of diseases and situations. Following are a few examples of how microsponges are used in the pharmaceutical industry shown in figure 5.

1. **Sustained and Controlled Drug Delivery:** Microsponges can be utilised as a drug delivery system that can sustain and regulate the release of medications. They can be filled with active pharmaceutical ingredients (APIs). Microsponges' porous shape enables the medicine to release gradually over time, resulting in a prolonged effect and lowering the frequency of dosing [24].
2. **Topical transport Systems:** To improve the transport of APIs to the skin, microsponges can be added to topical formulations including creams, gels, and lotions. They can enhance skin penetration, prevent drug deterioration, and control drug release [25]**.**
3. **Taste-Masking Agents:** Microsponges can be used as a taste-masking agent for bitter or unpleasant-tasting drugs. The drug can be loaded into microsponges and then coated with a taste-masking material to improve the taste and patient compliance [26].
4. **Oral medication Delivery:** To increase medication solubility, bioavailability, and stability, oral drug delivery can make use of microsponges. By lowering the frequency of administration, they can help prevent the medicine from degrading in the digestive tract and increase patient compliance [26].
5. **Targeted medication Delivery:** Microsponges can be modified with ligands or antibodies to focus on particular cells or tissues, enabling targeted medication delivery and lowering systemic toxicity [25].
6. **Dermatological problems:** Acne, psoriasis, and rosacea are just a few of the dermatological problems that can be treated with microsponges. They can be stuffed full of potent pharmacological substances and

used to topical formulations to deliver drugs to the skin more effectively and over a longer period of time [27].

7. **Cancer:** Microsponges can be functionalized with targeting ligands and loaded with chemotherapeutic agents for targeted therapy in cancer treatment. The microsponges can specifically target cancer cells, reducing systemic toxicity and improving drug efficacy [28].
8. **Cardiovascular illnesses:** Drugs for the treatment of cardiovascular illnesses such hypertension, atherosclerosis, and thrombosis can be delivered via microsponges. They are able to deliver controlled release and targeted drug delivery to the afflicted site by being loaded with antihypertensive, statin, and antiplatelet drugs [29].
9. **Disorders of the Central Nervous System (CNS):** Drugs for the treatment of CNS conditions like Parkinson's disease, dementia, Alzheimer's disease, and epilepsy can be treated via microsponges. In order to increase treatment effectiveness and lessen side effects, they might be loaded with medications that have a low bioavailability and are difficult to penetrate the blood-brain barrier [30].
10. **Infectious Diseases:** To treat infectious diseases like bacterial infections, fungal infections, and viral infections, microsponges can be loaded with antimicrobial medicines. They can offer better drug administration and prolonged release, which can lower dosage frequency and boost patient compliance [31].
11. **Rheumatoid Arthritis:** Microsponges can be used to deliver anti-inflammatory agents to the joints for the treatment of arthritis. The controlled release of these agents from microsponges can reduce inflammation and pain, improving patient outcomes [32].
12. **Alzheimer's Disease**: Drugs to treat symptoms of Alzheimer's illness can be delivered to the brain via microsponges. Microsponges' porous design enables the regulated release of medications in the brain, minimising adverse effects and enhancing patient outcomes [33].
13. **Ocular medication delivery**: Microsponges are gaining popularity because they can increase a medicine's bioavailability, lessen its toxicity, and extend its time in the body before wearing off. First off, microsponges can prolong the time the drug stays in the eye, boosting drug absorption and lowering the frequency of delivery. Second, they can obviate the need for preservatives by shielding the medicine from deterioration. Thirdly, by lowering the chance of adverse reactions and toxicity, microsponges can increase the safety of ocular drug administration. They can be included in a variety of eye-administered formulations, including ointments, gels, and suspensions [34].

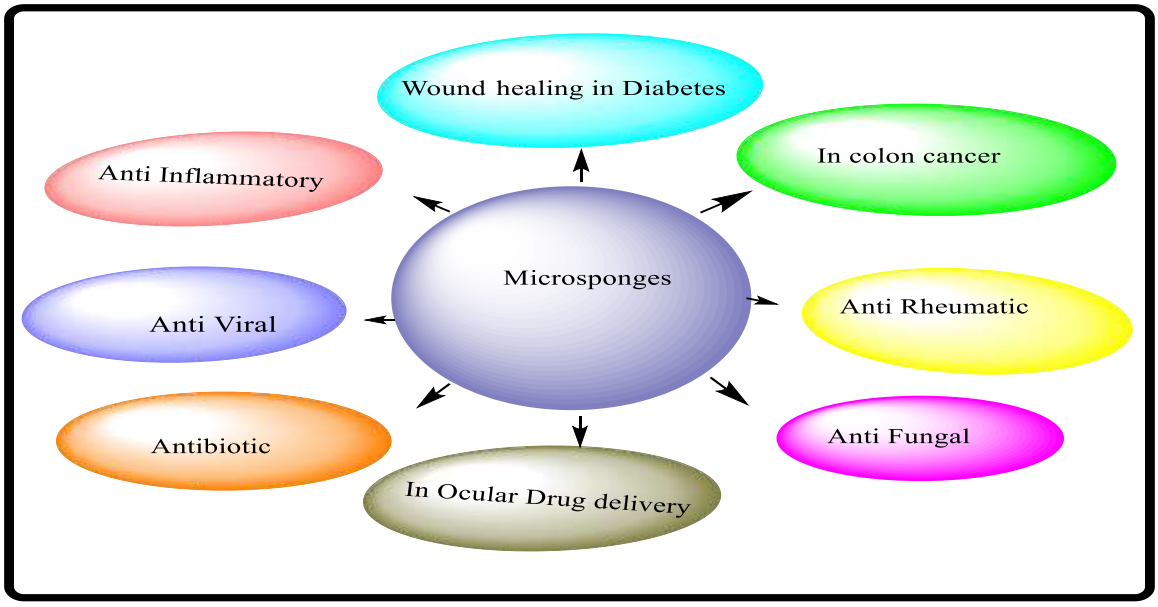

Fig 3: Applications of Microsponge medication system

Polymers for preparation of Microsponges [35-45].

Microsponges are a type of polymeric material that are widely used in pharmaceuticals and cosmetics for controlled release of active ingredients. The following are some commonly used polymers for preparing microsponges be in view figure 6.

1. **Polyvinyl alcohol (PVA):** Due to its biocompatibility, non-toxicity, and effective film-forming capabilities, PVA is a water-soluble polymer that has been utilized to create microsponges. PVA-based microsponges are said to have superior swelling capabilities and persistent drug release behaviour [35].
2. **Polyacrylates**: Due to their excellent water-absorption capabilities and biocompatibility, polyacrylates are frequently utilized in the creation of microsponges. Microsponges have been created using a variety of polyacrylates, including poly (ethyl acrylate), poly (methyl acrylate), and poly (butyl acrylate) [36].
3. **Chitosan:** A biopolymer made from chitin, chitosan is frequently utilized in drug administration since it is biocompatible and biodegradable. According to reports, chitosan-based microsponges display prolonged medication release and can be utilized to treat a variety of illnesses, including cancer as well as diabetes [37].
4. **Polycaprolactone (PCL):** Due to its outstanding mechanical qualities and biocompatibility, PCL, a biodegradable polymer, has been used to create microsponges. According to reports, PCL-based microsponges demonstrate persistent drug release behaviour and can be used to treat a variety of diseases, namely osteomyelitis [38].
5. **Polyethylene Glycol:** Microsponges made of polyethylene glycol (PEG) have been developed as prospective medication delivery systems. PEG is a biocompatible and biodegradable polymer that may be synthesized using a variety of techniques, including solvent evaporation and emulsion polymerization, which can be cross-linked using various cross-linking agents, such as hexamethylene diisocyanate [39].
6. **Polystyrene (PS):** PS microsponges have undergone extensive research in preparation for use in the cosmetics sector. PS is a hydrophobic polymer that can be cross-linked using a number of different cross-linking agents, such as divinylbenzene, and it may be created using a number of different techniques, including emulsion polymerization as well as suspension polymerization [40].
7. **Polyacrylamide (PAAm):** Microsponges made of PAAm have been created as a possible medication delivery mechanism. The preparation of PAAm, a water-soluble polymer that may be cross-linked using a variety of agents, including N,N'-methylenebisacrylamide, by emulsion polymerization and inverse suspension polymerization methods.[41].
8. **Eudragit:** The synthetic polymer family known as Eudragit is frequently employed in pharmaceutical formulations because of its high biocompatibility, bio adhesion, and controlled drug release characteristics. Microsponges made of eudragit have undergone substantial research as medication delivery devices. For making microsponges, different varieties of Eudragit polymers, such as EudragitRS100, EudragitS100, EudragitL100, Eudragit RSPO, and EudragitRL100, have been used [42–45].

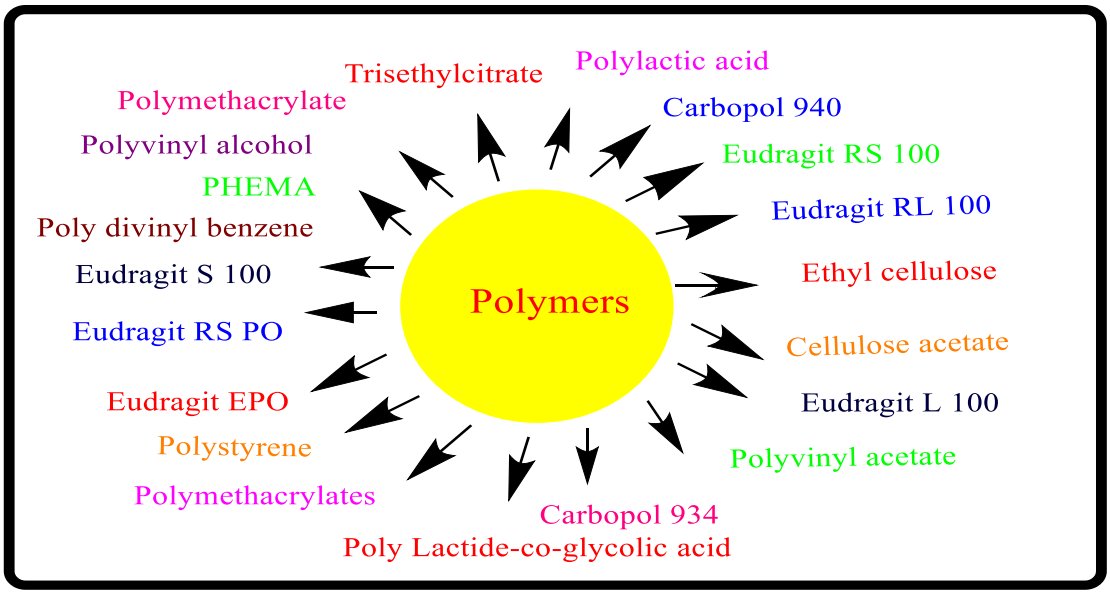

Fig 6: Polymers for preparation of Microsponges

Method of preparation of Microsponges

A. Liquid – Liquid suspension polymerization technique [46 -50]

Cross-linked polymeric particles having a sponge-like morphology are called microsponges, and they are made using the liquid-liquid polymerization process. In this method, a water-in-oil emulsion is created, with

the oil phase containing the surfactant and the initiator, and the aqueous phase containing the monomers and crosslinking agents. Then polymerization begins, leading to the production of microsponges be seen in figure 7 Liquid – Liquid suspension polymerization technique.

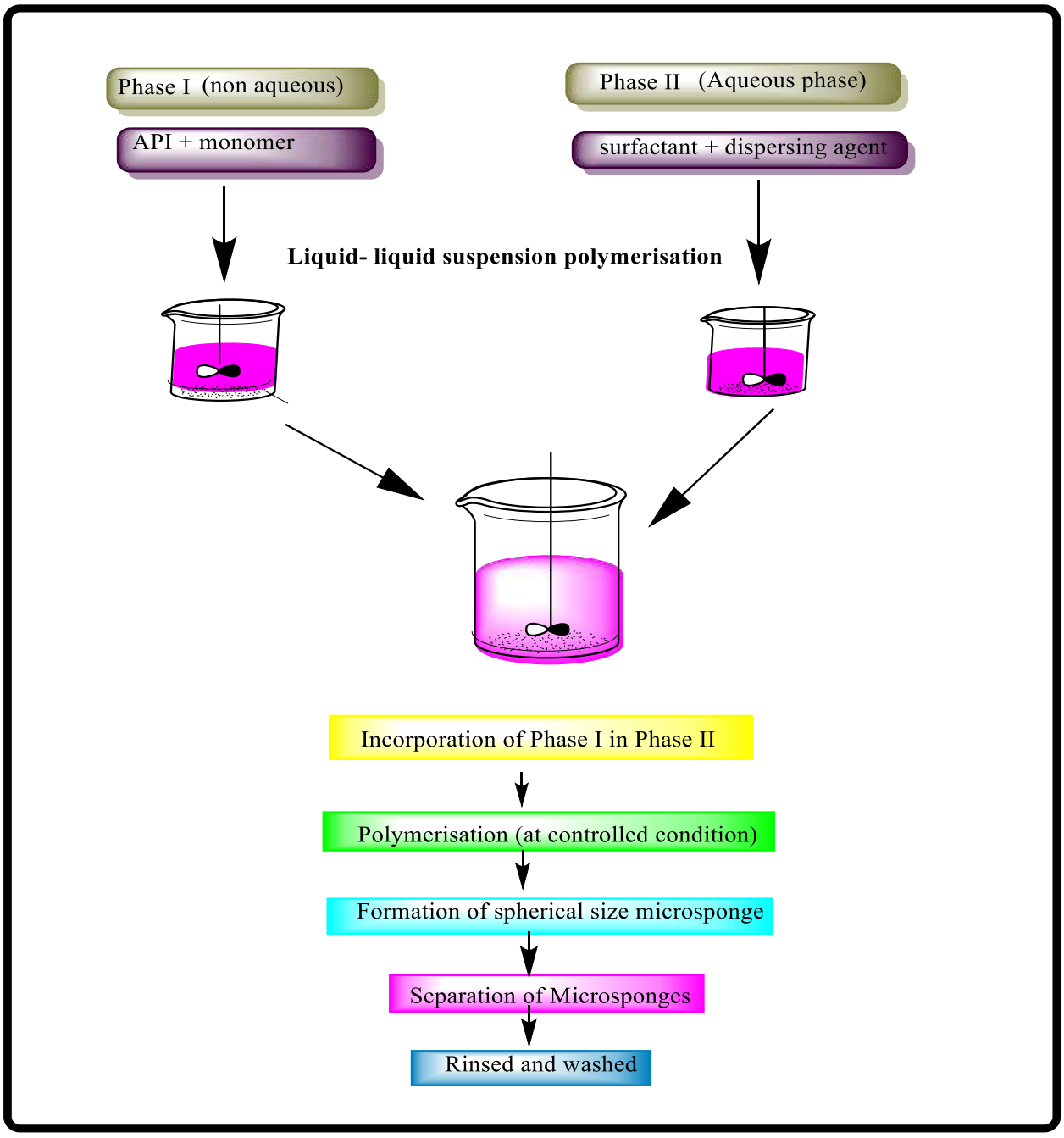

Fig 7: Liquid-liquid suspension polymerization technique

B. Quasi-emulsion solvent diffusion technique [51-55]

The process of making microsponges using the quasi-emulsion solvent diffusion method is quite popular. This method involves combining the drug and polymer in a volatile solvent, followed by the controlled diffusion of the resulting quasi-emulsion into a nonpolar solvent. The generated microsponges have a size range of 5-300 µm, are crosslinked, porous, and spherical particles. The quasi-emulsion solvent diffusion approach for making microsponges is described in the following figure No 8.

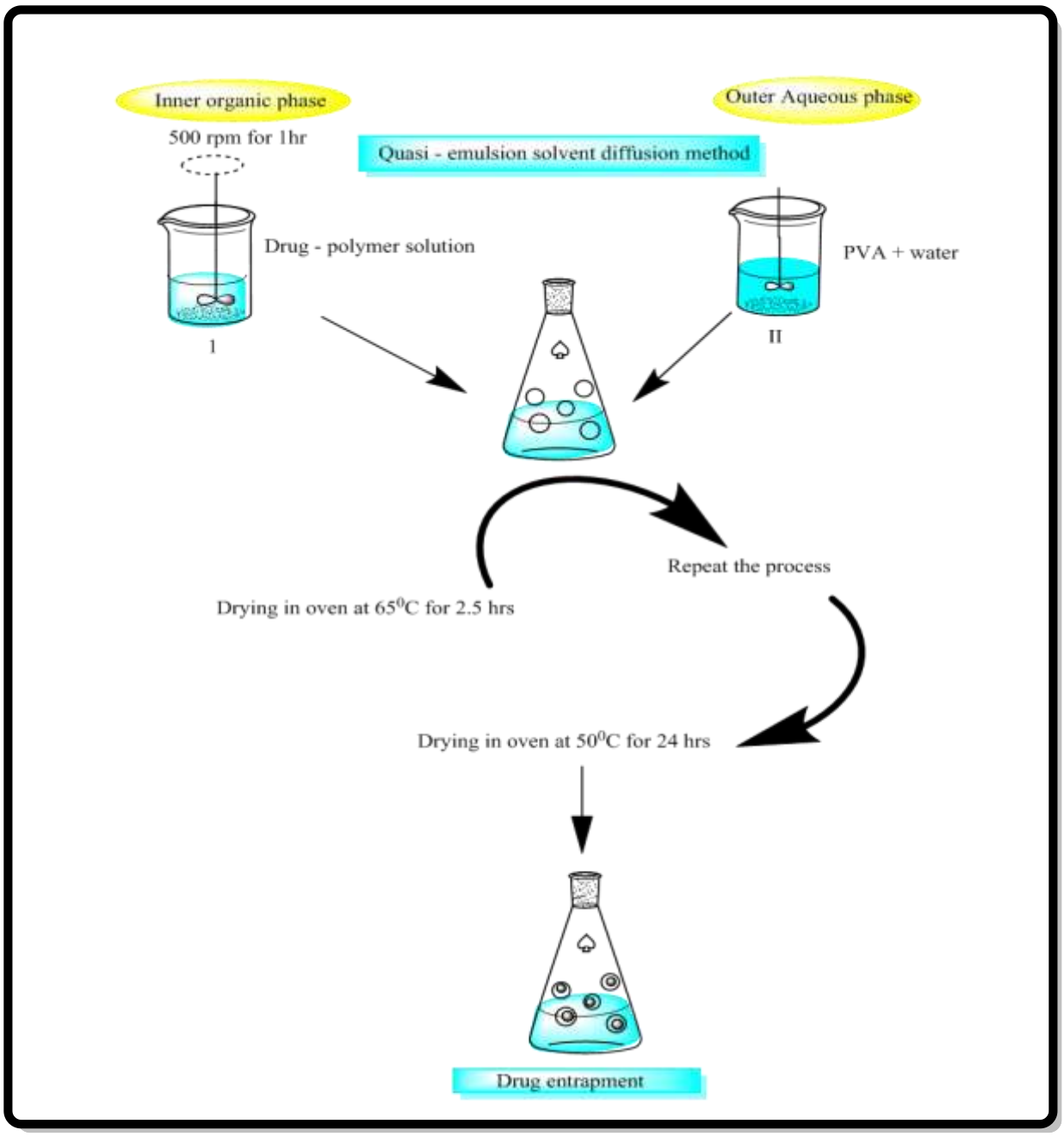

Fig.8 : Quasi-emulsion solvent diffusion technique

C. Multiple-emulsion (W/O/W emulsion) Solvent Diffusion [56- 59]

The production of biodegradable porous microspheres used cutting-edge design techniques. In this method, an internal aqueous phase containing an emulsifier such span, polyethyleneimine, and stearyl amine was combined with an organic polymeric solution. This non-emulsion was then re-dispersed in an external PVA-containing aqueous phase to produce a double emulsion as shown in figure 9.This method has the advantage of being able to entrap both water-soluble and water-insoluble medications. It can also be utilised to entrap proteins and other thermolabile substances. Several authors also referred to xanthan gum as an emulsifier in order to stabilise the interior without emulsion.

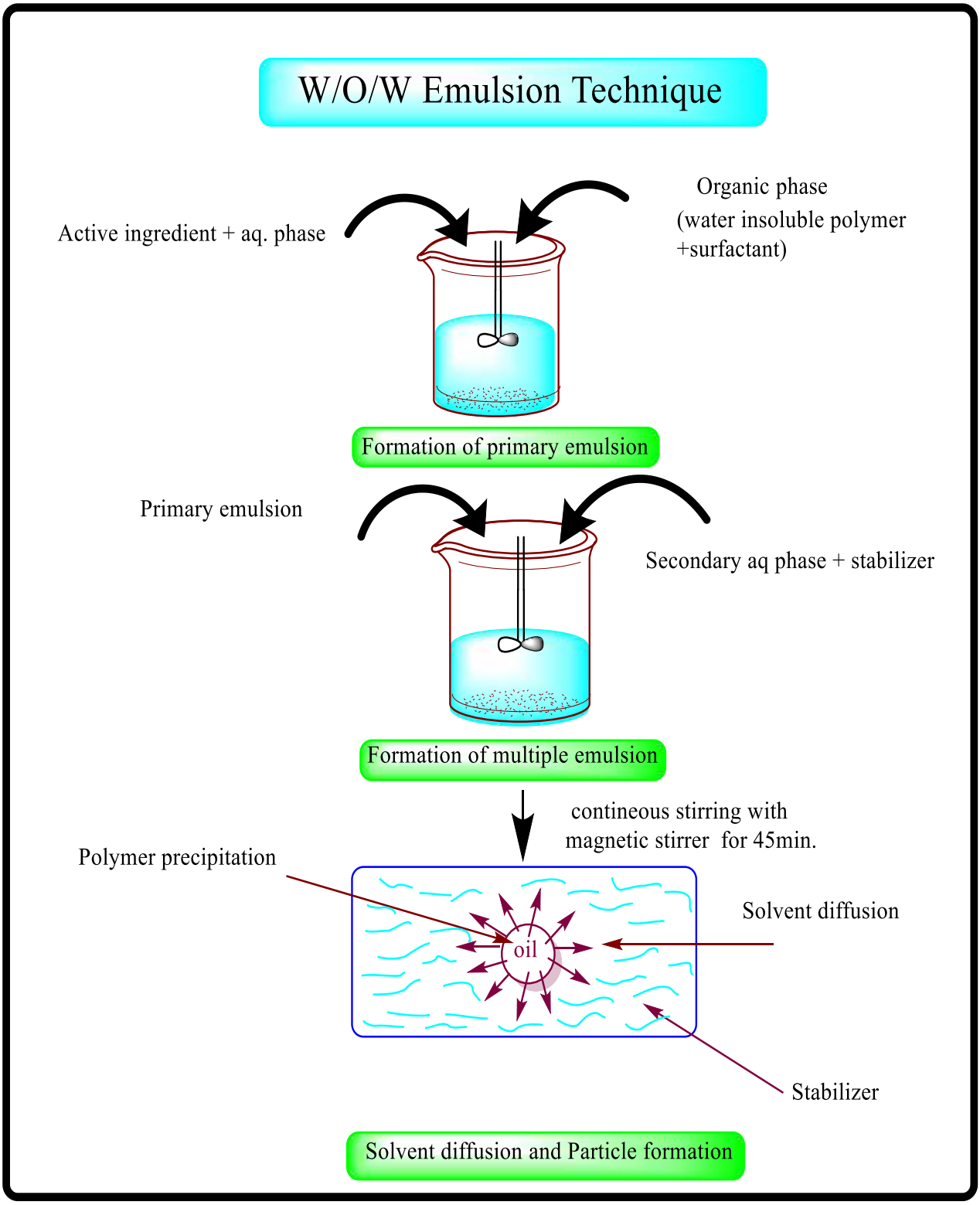

Fig.9: Multiple-emulsion (W/O/W emulsion) Solvent Diffusion

D. Addition of Porogen [60-64]

In this procedure, a porogen such as sodium bicarbonate or hydrogen peroxide replaced multiple emulsions inside. To do this, a single-phase system made up of the porogen was first produced in the polymeric solution and then redispersed in an aqueous phase that included PVA. The organic solvent was then allowed to evaporate, leaving behind the microparticles required to produce the microsponges, and an initiator was added to the multiple emulsion. With sizes ranging from 5 to 20 µm, pores that were linked and regularly spaced were produced by adding hydrogen peroxide be visible in figure 10.

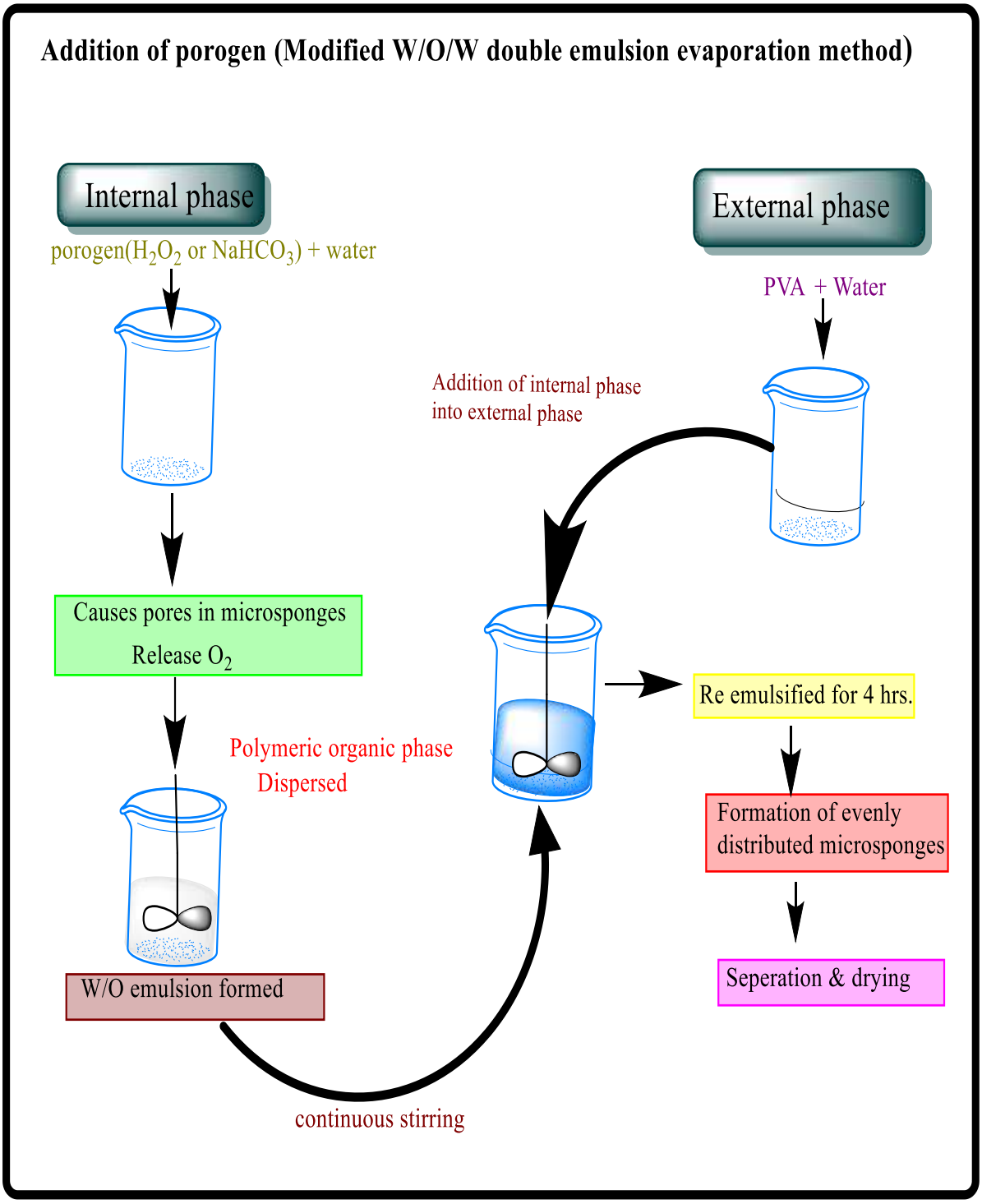

Fig10. Addition of Porogen

E. Oil in Oil Emulsion Solvent Diffusion technique [65-69]

As previously mentioned, the technique used polylactide glycolic acid as the polymer, fixed oil (corn or mineral) and dichloromethane with span 85 as the exterior phase solvent and internal phase solvent, respectively. The internal phase was continually mixed into the dispersion medium and added dropwise to produce the microsponges as shown in figure 11. This method was utilised to produce hydroxyzine HCl-loaded Eudragit RS-100 microsponges with liquid paraffin serving as the continuous medium and acetone serving as the dispersing solvent. The physicochemical characteristics of the drug and the polymer employed to make the microsponges determine the choice of the organic solvent and exterior phase.

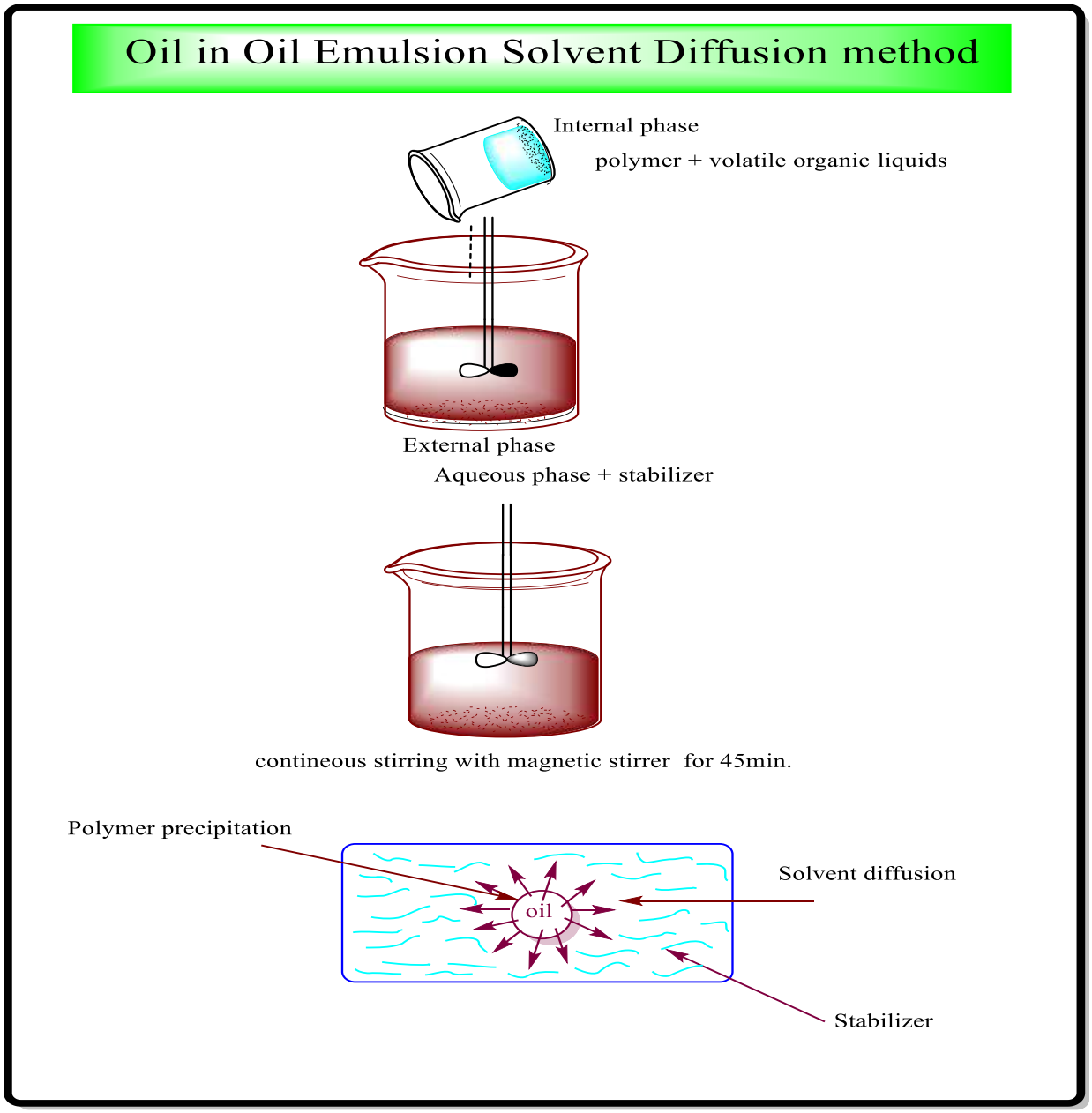

Fig.11 Oil in Oil Emulsion Solvent Diffusion

F. Lyophilization [70-74]

For drying of microsponges lyophilization technique is used. The process involves the removal of water by sublimation of ice crystals formed in the microsponge matrix. The microsponges are first frozen and then placed in a vacuum chamber where they are exposed to a low-pressure environment. The vacuum causes the ice to sublimate, leaving behind a dry microsponge.

The lyophilization technique has several advantages including preservation of the microsponge structure and morphology, the ability to achieve high drug-loading capacity, and improved stability of the microsponge during storage. However, this technique also has some limitations including longer processing times, the need for specialized equipment, and the potential for loss of drug activity due to the high temperatures and vacuum conditions used during the process.

This technique is commonly used in the pharmaceutical industry for the preparation of various dosage forms, including injectables, oral tablets, and capsules.

H. Ultrasound-Assisted Production [75-78]

Microsponges are prepared using a relatively recent technique called ultrasound-assisted manufacturing. In this method, the microsponges are created by applying ultrasonic radiation to a mixture of medication and

polymer solution. The process uses high-frequency ultrasonic waves to create cavitation bubbles, which put mechanical stress on the polymer solution and induce microsponges to grow be visible in figure 12.
Reduced solvent use, quicker processing times, greater drug loading, and improved encapsulation efficiency are just a few benefits of the ultrasound-assisted production method. This method can also be simply expanded for industrial production.

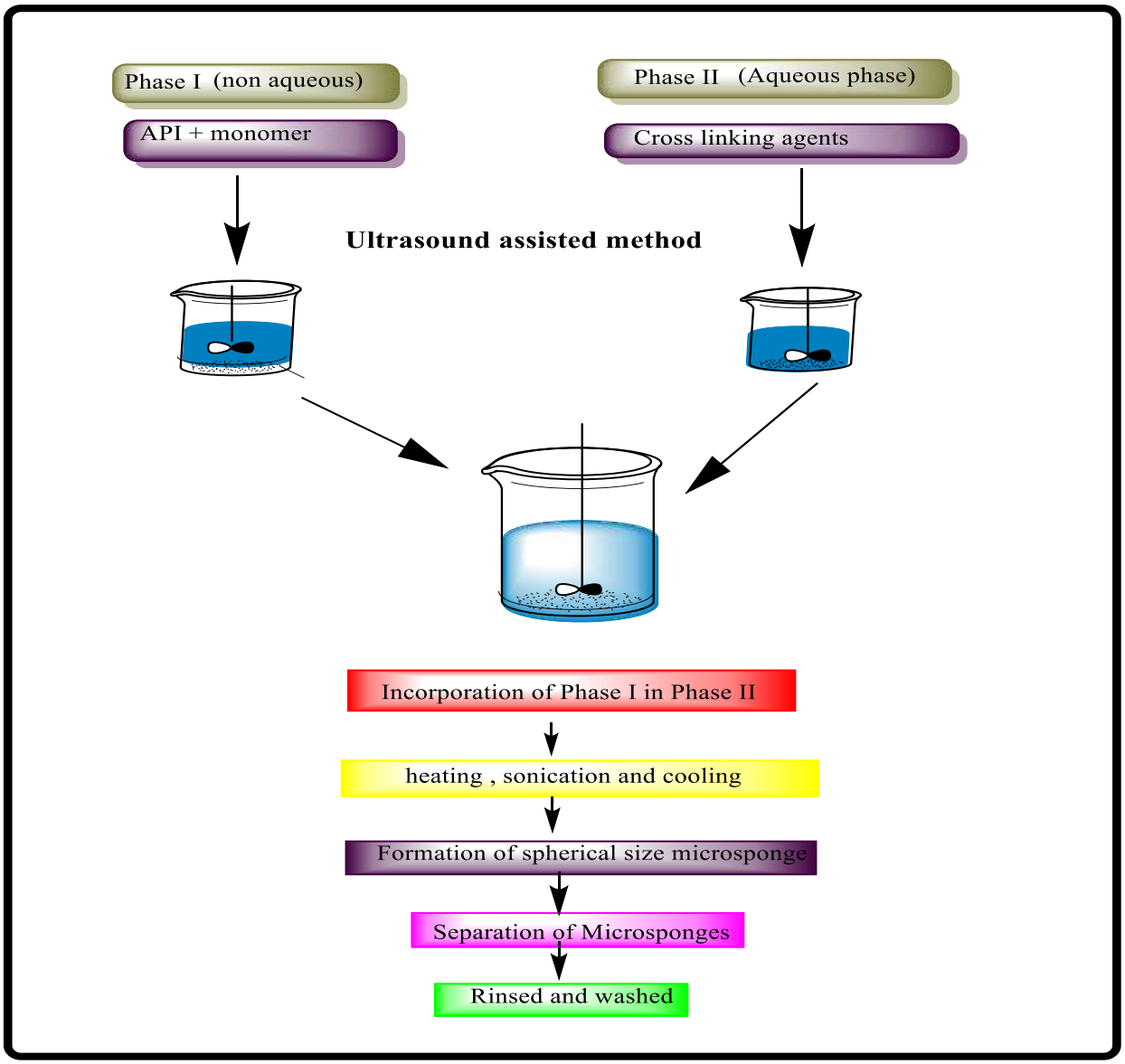

Fig.12 Ultrasound-Assisted Production

Drug release mechanism [79-82]
Hypothetical mechanism and Programmable drug release mechanism are the two main type of drug release mechanism be seen in figure 13

Hypothetical mechanism of action
a) The active component is free to move in and out of the microsponges and into the vehicle until the vehicle reaches equilibrium, at which point it becomes saturated. This is possible because the microsponge particles have an open structure (i.e., they do not have a continuous membrane enclosing them).
b) Skin-contacting microsponges are prepared and used.
c) The already-present active substance in the vehicle will be absorbed into the skin.
d) As a result, the active ingredient will begin to flow from the microsponge particle into the vehicle and then onto the skin. This process will continue until the vehicle is either dry or absorbed.

e) The active component will continue to be released gradually to the skin even after that, providing sustained release over time, thanks to the microsponge particles remaining on the stratum corneum's surface.

Programmable drug release mechanism

In order to build microsponge delivery systems that release functional chemicals over time in response to one or more external stimuli, these programmable parameters can be efficiently regulated. The following are the key release mechanisms of this system:

1) Sustained or Timed Release: For polymer microsponges, pore diameter, volume, and resiliency are assessed to provide the necessary sustained release effects. In the development of sustained-release microsponges, various physical and chemical parameters of the entrained active ingredients, such as volatility, viscosity, and solubility, will be investigated. 2) Release on Command: Microsponges can be designed to release the given amounts of active ingredients over time in response to external stimuli.

a) Pressure Release: When pressed or squeezed, the Microsponge System releases the active ingredient, increasing the amount of entrapped active ingredient on the skin. The stability of the microsponges and the release of the sponge can both affect how much material is discharged. According to a study, the increase in the drug's diffusion coefficient under higher pressure settings caused an increase in the rate of ciprofloxacin release from Eudragit RL100 microsponges (79).

b) Temperature Release: Depending on the temperature, the active substances in the microsponges can release. Because they are so thick, active substances that persist a little at room temperature may not be able to pass instantly from the microsponge to the skin. The flow rate increases and the release also improves when the skin's warmth rises. A study found that as the temperature rose from 25°C to 37°C, the rate at which tetracycline was released from chitosan microsponges increased (80).

c) pH Release: By altering the microsponge's coating, it is possible to facilitate the release of the pH-based active ingredient. A study found that as the pH of the release medium dropped from 7.4 to 1.2, the rate of diltiazem hydrochloride release from sodium alginate microsponges increased [81].

d) Solubility: When water is present, a microsponges filled with water-soluble chemicals like antiseptics and deodorants release their contents. Diffusion, which takes into account the material's distribution coefficient between the microsponge and the external system, can also activate the discharge. According to a study felodipine, which has a lower solubility, nifedipine released from chitosan microsponges more quickly [82].

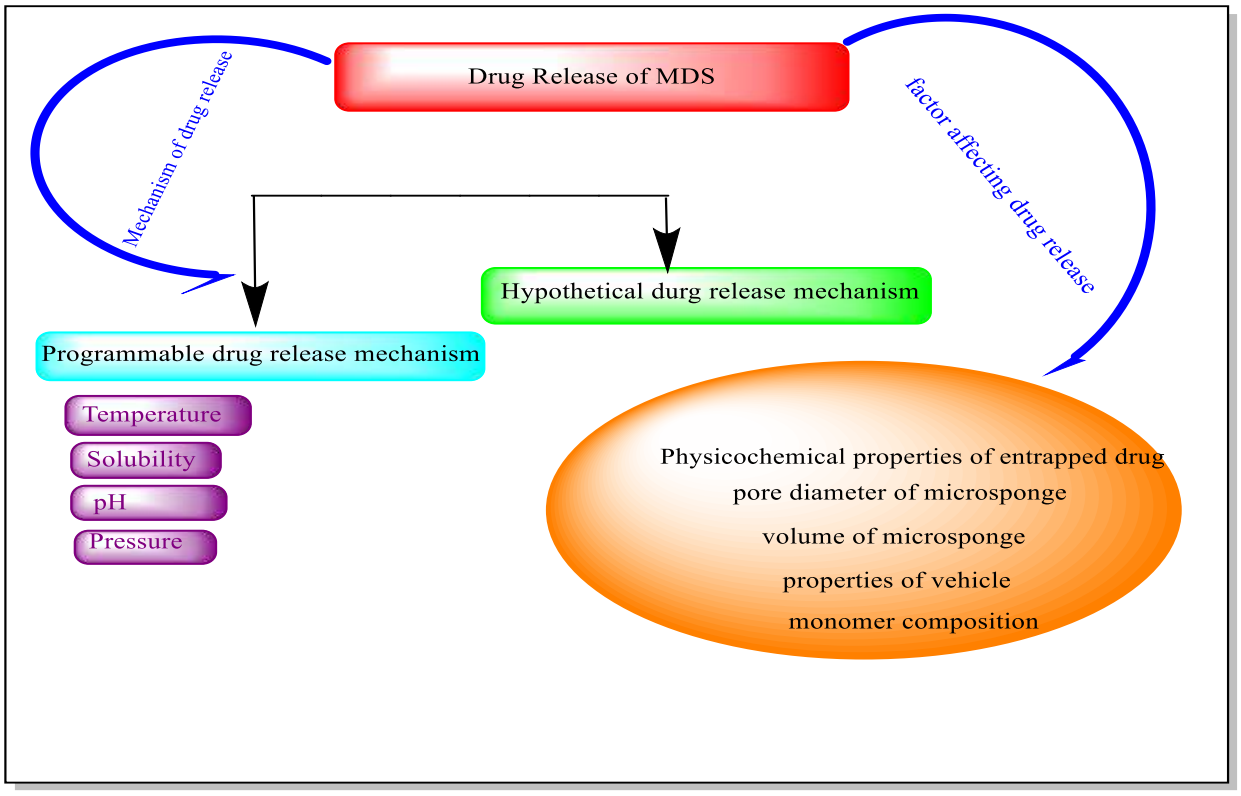

Fig13. Drug release mechanism from Microsponges

Previous research work done on microsponges: [83-108]

A. Anti inflammatory activity

1. Rajurkar et al. created an anti-inflammatory topical gel of naproxen with Eudragit RS 100 as the polymer by using the quasi-emulsion solvent diffusion process. The purpose of this work was to create microporous particles with encapsulation of naproxen in order to regulate the drug's skin release. Numerous physical characteristics of the microsponge were researched to optimise the best formulation. By using FT-IR, the drug's compatibility with the excipients was investigated. The microsponges' surface shape, loading efficiency, and production yield were measured. It was demonstrated that the drug:polymer ratio and stirring rate affected the microsponge drug release behaviour and particle size. An increase in the drug:polymer ratio in different formulations showed regulated drug release from microsponge [83].
2. Using PVA as an emulsion stabiliser and Eudragit RS 100 Mahajan et al. formulated Microsponge of indomethacin using the Quasi emulsion solvent diffusion approach. Evaluation of prepared microparticles were done by FTIR, Differential scanning colorimetry, X- ray diffraction and scanning electron microscopy. The release of drug from the formulation was noted by dissolution study in phosphate buffer at pH 6.8 and hence revealed that above formulation is best than the conventional dosage form. [84].
3. Kshirasagar et.al, developed Diclofenac Diethylamine microsponge based gel by using carpool as a polymer. characterization of micro sponges as well as gel was done. For quantitative drug estimation from the commercial gel and optimised microsponge gel, this approach worked well. Using WinNonlin software version 8.1, the primary goal of the experiment is to analyse the pharmacokinetic profile of diclofenac diethylamine in marketed gel and microsponges gel [85].
4. Bhatia et.al, 2018 prepared microsponge of curcumin by quasi-emulsion solvent diffusion technique using ethylcellulose and PVA as carriers. These are characterized by FTIR, SEM, DSC and it was observed that the release rate 93.2% compared with conventional that was 11.7% in 8h [86].
5. Bhavsar et al., 2019 designed microballones of ibuprofen using the quasi- emulsion solvent diffusion approach and ethyl cellulose polymer, extending the drug's release in the upper GIT by nearly 12 hours. Four batches were made, and F2 was deemed the most optimal formulation since it had the highest yield and entrapment efficiency [87].

For Skin Infection

6. Kumar et al. (2013) developed Microsponge of Mupirocin as an antiboitic using Eudragit RS 100 and PVA as an emulsion stabiliser. According to the results, a higher drug: polymer ratio resulted in a slower rate of Mupirocin release from microsponges [88]
7. Using dichloromethane and diethyl cellulose as polymers and a quasi-emulsion solvent diffusion technique, Pawar et al. (2015) created an Oxybenzone microsponges loaded topical gel. Hydrogel was filled with the optimised formulation. The findings showed that the product's improved sun protection factor outperformed commercial formulations with lower levels of toxicity and irritation [89].

Anti fungal

8. Killedar et al., 2019 created a microsponge containing amphotericin B using a quasi-emsolvent diffusion technique using an extended release polymer called Eudragit RS 100. Aspargillus fungates and Candida albicans responded better to treatment with the Amphotricine B gel Microsponges than with the conventional dosage form, according to research [90].
9. Bansode et al., 2019 used the Quasi-emulsion solvent diffusion technique to manufacture a microsponge containing Nystatin using ethyl cellulose as a stabiliser and PVA as an emulsifier. The P6-coded microsponge formulation showed a greater loading efficiency and manufacturing yield, according to physical analysis. F3 optimized gel formulation discharged 81.03% of the medication after 12 hours compared with conventional dosage form that is 12.34% in 8 hrs. [91].
10. Syed et al., 2020 used eudragit RL100 to create a quasi-emulsion solvent diffusion method to create microsponges of fluconazole. The gel was created, tested for a number of factors, and put through in vitro release tests. The Eudragit RL 100 microspheres that had been loaded with fluconazole shown an excellent release profile and were stable in the tested conditions [92].

Anti viral activity

11. Utilising PVA as an emulsifier and ethyl cellulose as a stabiliser, Chandramouli et al. (2012) created an acyclovir microsponge entrapped gel utilising the emulsion solvent diffusion method. The initial formulation displayed a viscosity of 206.72 psi, a spreadability of 11.75 g cm/s, and a drug content of 92.37%. These investigations revealed pertinent drug release [93].

12. Patil, N.S. et al. 2018, prepared microsponges of Ritonavir utilising Quasi emulsion solvent diffusion and nine distinct polymer ratios. The generated microsponges' particle size, production yield, entrapment effectiveness, and drug content were all examined. Microsponges were discovered to be spherical in shape and to have pores by scanning electron microscopic pictures. The pH, viscosity, spreadability, and diffusion study of the microsponge were next assessed after they had been added to the 1% carbopol gel. As a result, the Ritonavir gel formulation based on microsponges would be a promising substitute for traditional therapy for the safer and more effective treatment of a variety of skin conditions [94].

Ocular drug delivery

13. Using ethyl cellulose, triethyl citrate, and PVA by Quasi emulsion solvent diffusion approach, Obiedallah et al. (2018) created a Microsponge entrapped gel of acetazolamide that was incorporated into a 25% pluronic acid F127 gel. Drug to polymer ratio (2:1) in Formulation S2 demonstrated good entrapment effectiveness of 82% [95].
14. A microsponge containing diclofenac sodium was developed in 2021 by RAJASHRI B. et al. using the Eudragit RS100 polymer and a quasi solvent diffusion process. Diclofenac loaded microsponges were introduced into the ocular in situ gel to provide controlled release by the microsponge and an improved residence time by the gelling mechanism. Optimized formulation, with a polymer to drug ratio of 1:7, showed 87.94% in vitro release after 6 hours, as well as an adequate manufacturing yield (68.13%), entrapment efficiency (62.86%), drug content (80.73%), and necessary particle size (7.52µm).
15. Archna et al. 2021 used Eudragit RS100 and ethyl cellulose to manufacture atenolol microsponges utilising an oil-in-oil emulsion solvent diffusion technique. With a medication concentration of 93.89%, F8 has the highest among the 10 formulations [97].
16. Neamam et al. produced microsponges of ketorolac trimethamine by using a double emulsion process with PLGA as a polymer and PVA as a stabiliser. Several formulations were developed; among them, evaluated microsponges (F14) had maximum entrapment efficiency (74%) and percentage yield (83%) [98].

Anti Rheumatic activity

17. Osmani et al. (2015) employed the quasi-emulsion solvent diffusion approach to generate microsponges of diclofenac diethylamine using ERS-100 and other polymers. These were characterised by SEM, DSC, FT-IR, XRD, and particle size analysis, and their morphology was checked. The results of the SEM analysis showed that the spherical microsponges had a mean particle size of 7.21 µm and a porous surface. Formulation F2 demonstrated extended release at a 1:2 ratio up to 81.11% [99].
18. Using Carbopol 934, PEG, and triethanolamine, Sharma et al. produced microsponges of Aceclofenac using the Quasi-emulsion solvent diffusion method. In 8 hours, the improved gel displayed a controlled release of 71.33%. [100].
19. Yeteng et al. used a quasi-emulsion solvent diffusion technique to make lornoxicam microsponges utilising four different surfactant systems: polyvinyl alcohol (PVA), Tween80, Gelucire 48/16, and Gelucire 50/13. Within 4 hours, the transdermal gel combination that was optimised led to a 72% reduction in inflammation [101].
20. Using ethyl cellulose and PVA as carriers, Shelke et al. created a microsponge of a herbal medicine using the quasi-emulsion solvent diffusion approach. Paw edoema and joint thickness significantly decreased with formulation codes M1 and M4, respectively [102].

Diabetic wound healing using MDS

21. Using the polyethylene glycol (PEG) 8000 as a solvent, Biswal et al. created microsponges of gliclazide and compared them to solid dispersion in PEG 6000. The production of microcrystals, higher wettability, and enhanced dispersibility in systems containing PEG 8000 may be the causes of the increased Gliclazide dissolution rate [103].
22. Patel et al. synthesised Nebivolol-loaded microsponges and encapsulated them in gel using the quasi-emulsion approach to preserve the wound's hydration throughout the last stages of healing. It was confirmed by an in vitro experiment that around 80% of the medicine had been released after 8 hours [104].
23. Shuhaib et al. created mefenamic acid microsponges using a quasi-emulsion approach with ethyl cellulose and PVA. Out of nine formulations, the second one has good permeability [105].

MDS in colon cancer

24. Flurbiprofen microsponges were developed by Orlu M et al. using Eudragit RS 100 and the quasi-emulsion solvent diffusion process. An entrapment strategy was also employed by a commercial Microsponge® 5640 device to trap FLB. In systems meant for colon-specific drug administration, the use of Microsponge® 5640 and microsponges created utilising the quasi-emulsion solvent diffusion technique was found to be successful [106].
25. Using Eudragit L100 and ethanol, Sareen et al. produced curcumin microsponges using the quasi-emulsion solvent diffusion method. Formulation F7 demonstrated entrapment efficiency of 78.13% and drug release of 84.12% [107].

Janakidevi et al, prepared microsponges of 5- amino salicylic acid by Quasi emulsion diffusion technique using Eudragit RS 100, Eudragit S 100 and Eudragit L 100. Out of nine formulations ES1, EL1 and ESR1 were selected. Out of these three ES1 showed the best release rate [108].

Literature review table [109- 124]

S NO	MDS	Drug	Polymer	Formulation	% of drug release	Application	Marketed formulation	References
1	Colon targeted	Mesalamine	EudragitRS100 Eudragit L100 Eudragit S100	Tablet	ES100 showed best release upto 95.7%	Inflammatory bowel disease	Pentasa	110
2	Topical drug delivery	Oxiconazole	Eudragit S100 Eudragit L100	Gel	F3 with ES100 showed 87.77% drug release	Antifungal	Zordem E	111
3	Colon targeted	Curcumin	Eudragit L100	Tablet	F7 showed maximum drug release i.e.84.12%	Ulcerative colitis	Curcumin Boost	112
4	Targeted drug delivery	Fluconazole	Eudragit L100	Capsule	F4 showed maximum drug release upto 81.36%	Anti fungal	Diflucan	113
5	Topical drug delivery	Ketoconazole	Eudragit S100 Eudragit L100	Gel	F5 with ES100 showed maximum drug release upto 92.12% for 8 hours	Anti fungal	Nizral	114
6	Controlled oral drug delivery system	Clindamycin	Eudragit EPO100	Oral disintigrating tablet	Showed drug release within 1-2 minutes	Improved pediatric & geriatric patient compliance by taste masking	Cliford-150	115
7	Transderm al drug delivery system	Meloxicam	Eudragit S100 Eudragit L100 Eudragit E 100	gel	Inhanced dissolution rate	Oesteoarthritis	Wellcam 15	116
8	Colon specific	N aproxen	Eudragit RS100	Tablet	F1 showed drug release upto 94.45%	Anti inflammatory	Realdom- 500	117
9	Colon targeted drug delivery system	Prednisolone	Eudragit ES 100	Tablet	F9 showed effective & maximum drug release i.e 87.5%	Anti inflammatory	Prediom	118
10	Topical drug delivery system	Luliconazole	Ethylcellulose Eudragit RSPO	gel	F1 showed max. drug release upto 97.26 %	Antifungal	Lulifin Lupizol	119
11	Topical drug delivery system	5-Flouourecil	Eudragit RL30 D	Cream	5.5 fold increase in skin deposition	Skin cancer	FLONIDA	120
12	Herbal microspon ge sunscreen gel	Polyherbal extracts	Ethylcellulose	Gel	Showed excellent drug release	Anti inflammatory	_	121
13	Microspon ges drug delivery system	Candesartan cilexetil	ERS 100, ERL 100, ES 100	microsges	Improved solubility and dissolution rate.	Antihypertensive	ATACAND	122

					Formulation3 with ERS 100 showed max drug release.			
14	Topical drug delivery system	Econazole nitrate	ERS 100, Ethylcellulose, Carbopol	Hydrogel	extended drug release	Antifungal	Oricon	123
15	Colon specific drug delivery system	Metoprolol succinate	Ethyl cellulose	Microsponges	Microflora activated sustained release colonic system	Antihypertensive	Metoprolol Succinate	124
16	Colon targeted drug delivery system	Amifostine	Eudargit L 100 E55	Microcapsules	microcapsules provided effective radioprotection compared to the bulk drug	Anti cancer	Migon Plus,Migrabeta Plus, Amiget	125
17	Topical drug delivery	Tazarotene	Ethyle cellulose	gel	Out of T7&T8, T8 showed drug release upto 12 hrs.	Psoriasis	Tazorac	126

Table I: Literature review of microsponges

Comparison of Microsponges with other controlled drug delivery system

Because of their large drug loading capacity, regulated drug release, greater stabilities, and compatibility with a variety of medications (such as ketoprofen, benzyl peroxide, retinol, fluconazole, and ibuprofen), microsponges are preferable to other innovative drug delivery systems, as noted in table II. [125-131].

Properties	**Liposomes**	**Microcapsules**	**Nanoparticles**	**Microsponges**
Drug release rate	Unregulated drug release	Unregulated drug release	uncontrolled drug release	controlled drug release
Stability study At high temperature 130^0C At high pH(1-11)c	unstable	Unstable	Unstable	Stable
Entrapment efficiency	Low	Low	Moderate	High
Large scale production	Not possible	Not possible	Not possible	Possible
Drug payload	Less	Limited	Limited	Maximum
Cost	Expensive	Expensive	More expensive	Less expensive

Table II: Comparison of Microsponges with other novel drug delivery system

Recent patents related to microsponges drug delivery system

S. No.	**Patent No**	**Title**	**Discription**	**Inventor**	**Current Assignee**	**Year**	**References**
1	US20230249149A1	Porous polysiloxane microspheres	In this invention microsphere are formed by double emulsion tech. these are used as filler & sensor application	Dakota Even	Honeywell Fedelal manufacturing and tech LLC	**2022**	132
2	US20210346279A1	Compositions comprising tapinarof for the treatment of pruritis	This invention includes composition for topical use in prutitis.	Marcel Zighelboim	Sol gel technology Ltd.	2021	133
3	US9752122B2	Edible and animal product free micro-carriers for engineered meat	This invention model comprises porous microcarrier used to grow cell and incorporated in final engineered product	Francoise Suzanne Merge	Modern Meadow Inc	2017	134
4	US20220380723A1	Methods to produce defined, spherical, bio-degradable macroporous hydrogel for cellular agriculture	This invention is used in perfused bioreactor to culture adult stem cell	Patrick Nonnemacher	Innocent Meat GmbH	2022	135
5	US20210236416A1	Treatment of skin disorder with topical roflumilast combination composition	This invention shows its response in skin disorder like acne, rosacea	Moshe Arkin	Sol. Gel technologies ltd.	2021	136

6	US20210236432A1	Composition comprising roflumilast for treating hidradenitis suppurativa and prurigo nodularis	This model used for treatment & prevention of skin disorder like acne and rosacea	Moshe Arkin	Sol. Gel technologies ltd.	2021	137
7	US20200114007A1	Enhancement of the efficacy of therapeutic protein	Administration of atleast one mammalian protein to a mammal for enhancing absorption, distribution and release.	Jeanetta Du plessis	North west university	2020	138
8	US20210137735A1	Apparatus and method of treating blepharitis, meibomian gland dysfunction and dry eye disease	This invention include small handheld electromechanical devices perform a microblephar exfoliation of eye lid margin using disposable microsponges	Bryan Minelli	Danelli ocular creation LLC	2019	139
9	CN115670944A	Microsponge with anti ageing effect	This invention relates to cosmetic fields. It show anti ageing effect with good safety and good storage stability & higher permeability.	Jiang Shanshan, Li Yan	Shandong Furida Biological Co. Ltd.	2022	140
10	ES2942164T3	Biodegradable mesh implants for soft tissue repair, in particular hernia repair	This invention deals with biodegradable mesh implants for use in soft tissue repair	Hans Ulrich Bear	Hans Ulrich Bear	2019	141
11	KR101900387B1	Microsponges having controlled solubility & improved dissolution property	The present invention relates to microsponges having improved solubility & remelting properties	Ahn Jong-won, Seungmin choi	Blisspack Co. Ltd	2018	142
12	EP3083729B1	Surfactant responsive emulsion polymerization microgel	This invention improves rheological property & improve stability.	Shui- Jen Raymond Hsu	Lubrizol Advanced material. Inc	2017	143
13	WO2022125520A1	Insect cell membrane microparticles for detoxification of insect pollinators	This invention describes methods for detoxifying insect pollinators of one or more pesticide	James webb	James webb	2022	144
14	ES237708T3	Topical anti acne preparation containing retinoid, antibiotics & keratolytic	This invention comprises of topical anti acne preparation containg retinoid& peroxide of benzoyl in microsponge.	Fernando Ahumada Ayala	Laboratrios Dermatologicos Darier SA de	2019	145

Table III: Recent patents related to microsponges drug delivery system

Current Statues

Current developments in MDS Innovative formulations are being developed by numerous scientists. They are more stable than MDS and are as follows [146].

Nanosponges: These have proven to be superior gas transport carriers. By enabling the medicine which can be used to target cancer cells, cytotoxic is more effective when paired with nanosponges as carrier systems. Both hydrophilic and hydrophobic drugs can be made using them. Using this sophisticated method, medicines such as flurbiprofen, dexamethasone, itraconazole, and others were investigated.

Self-promising nanoferrosponges exhibit enhanced penetration into a particular region due to an external magnetic response that permits carriers to reach a deeper level before magnetic material is eliminated, resulting in the formation of a porous system.

Porous microbeads: Due to improved microsphere characteristics, porous microbeads were developed. The processes of polymerization and cross-linking are used to create solid porous microbeads. An exterior oil phase, an inner aqueous phase, and a cross-linker make up the monomer in the high internal phase emulsion technique. Microbeads are used in **medication delivery systems for topical, oral, and buccal usage. [147].**

Future Prospects

One of the latest cutting-edge drug delivery technologies that was initially designed for topical drug delivery is the microsponges. They can also be employed for regulated oral medication administration employing biodegradable polymers and tissue engineering. It offers a variety of benefits for formulating. It is possible to turn liquids into powders that flow freely. Without the use of preservatives, formulations can be created with otherwise incompatible constituents and long-lasting stability. So, with relation to formulations like the transdermal delivery system, microsponges will be the perfect drug delivery system. One of the cutting-edge drug delivery technologies that were initially created for topical drug delivery is the microsponges. They can

also be employed for regulated oral medication administration employing biodegradable polymers and tissue engineering. It offers a variety of formulation options.

Conclusion

Microsponges are superior to other novel formulations and other conventional dosage forms when it comes to topical drug administration and colon medicine targeting. More research is being done to balance the cost and effectiveness of therapy because it is a highly competitive technology. Consequently, it is a rather new field that has to be investigated as they contains exclusive properties like reduced irritation, extended release, self sterilization due to their small size and good compatibility with the most of ingredients. Numerous studies have already discussed the possibility of Microspheres for directing the drug molecule to the ascending colon and stomach, among other GIT sections. Due to sponge-like structure, it improves compressibility and creates mechanically robust tablets. Their compressed tablets can be utilised for chronic conditions and have been effectively examined for colon targeting. As a result, the technology of microsponge is projected to develop into an important drug delivery matrix substance for a variety of therapeutic applications in the future.

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