

REVIEW

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Microsponges: a breakthrough tool in pharmaceutical research

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Abstract

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

Main body: 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 minimising the negative impact of the drug. The fundamental purpose of microsphere drug administration is to reach the highest possible peak plasma concentration in the blood. The capacity of MDS to self-sterilise is their most prominent attribute.

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.

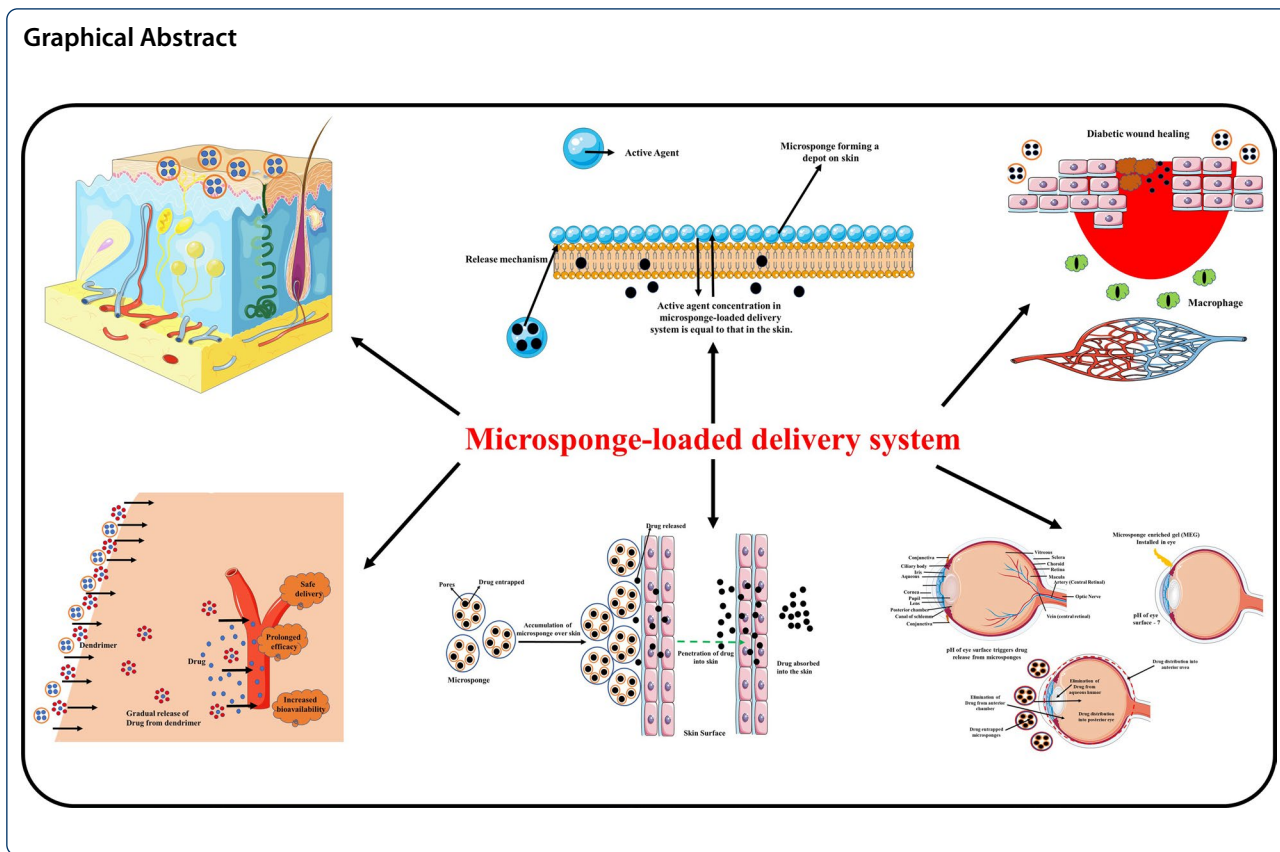
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Graphical Abstract



Background

Drug release techniques are designed particularly for the purpose of delivering drugs to specific places inside the body. This increases the efficiency of drug treatment, and patient compliance has a substantial influence on the health care system [1]. The pharmaceutical industry has learned that delivering APIs to controlled target locations within the body has proven to be a significant issue [2]. Recently, much attention has been dedicated to the creation of novel drug delivery systems based on microsponges, as well as the modification and regulation of drug release performance. By combining a drug with a carrier system, it may be feasible to vary the duration and therapeutic index of the drug [3]. The most consistent and predictable route for active substances to enter the body's local and systemic systems is through the skin, as shown in Fig. 1. The major drawback of the transdermal administration route is that a common route of pharmaceuticals is poorly soluble in water, causing various obstacles during the creation of conventional dosage forms. Another important difficulty with topical pharmaceutical administration is evaporation of the drug, unpleasant fragrance, and visually unattractive carriers, which can result in greasiness and stickiness and may lead to impaired patient compliance [3]. Due to their ineffectiveness,

traditional methods demand a larger amount of drug be incorporated for beneficial therapy. MDS based on polymeric microspheres may be able to achieve this objective [4]. Won created the MDS drug delivery method in 1987; his patents were assigned to Advance Polymer Systems, Inc. Following that, Cardinal Health, Inc. was awarded a licence to use this innovative technology in topical treatments. This corporation launched a huge number of improvements in approach and applied them to over-the-counter items, cosmetics, and pharmaceutically prescribed products [4]. Traditional topical medicines are meant to have an influence on the outer layer of the skin. Following the application of such mixtures, their active moieties are released. They provide a film of concentrated active moiety, which is readily absorbed. This leads to an increased accumulation of medicines in the dermis. MDS can assist to avoid this. Perhaps, the microsponge drug delivery technology can considerably limit drug unwanted effects like itching while yet delivering the medicine efficiently to the skin [5]. Due to their visually unpleasant appearance, as well as their stickiness and greasiness, patients' adherence to ointments is low. On the other hand, the MDS prolongs the time, which drug spends on the surface of the skin. Microsponge delivery technology outperforms other strategies such

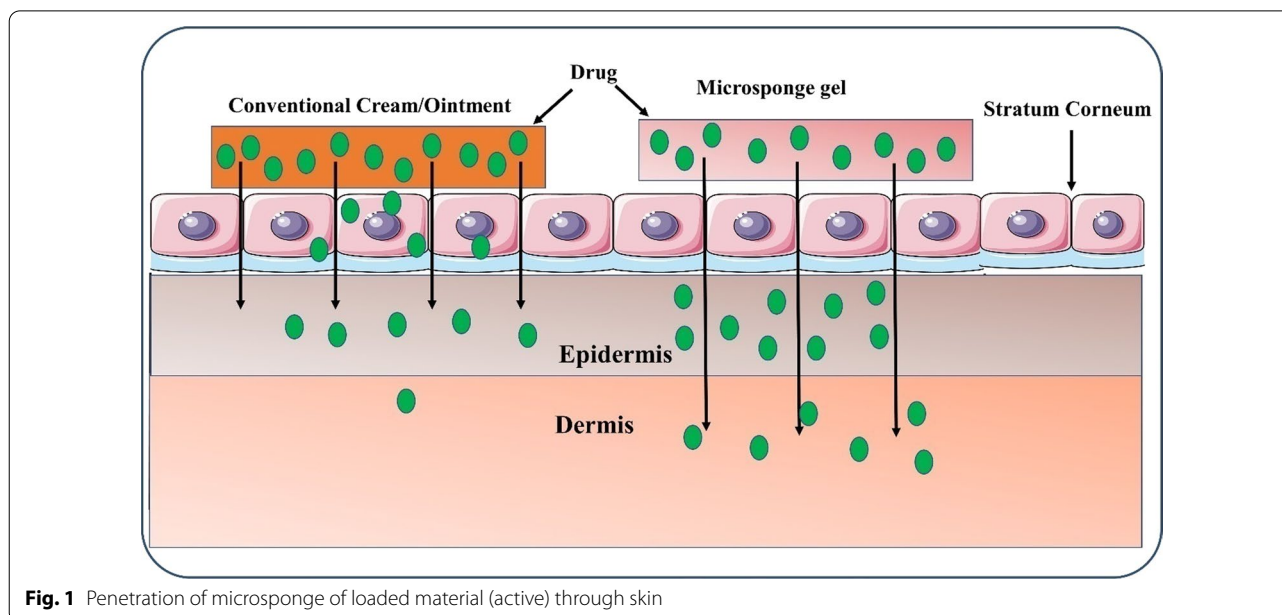


Fig. 1 Penetration of microsponge of loaded material (active) through skin

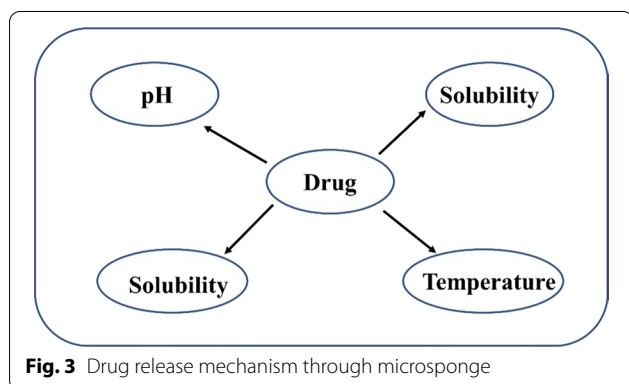
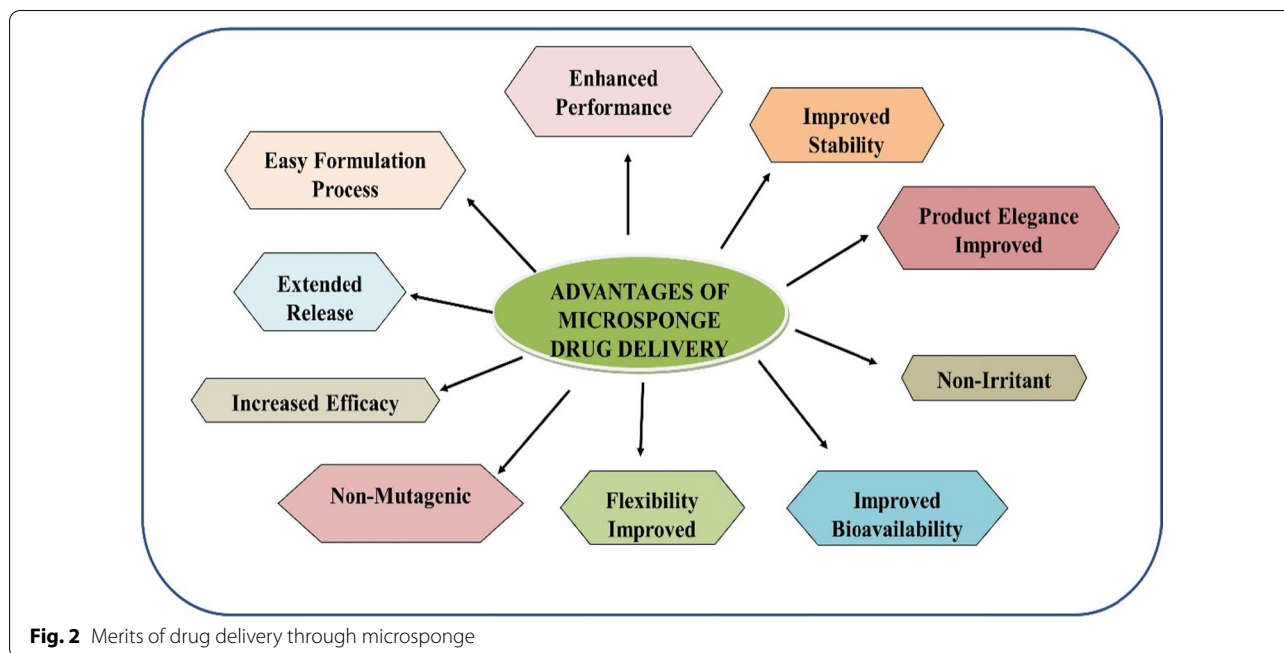
as microencapsulation and liposomes in terms of quality. Liposomes have a limited carrying capacity, are difficult to make, and are chemically and microbially fragile. The rate of release of the pharmaceutical active moiety is routinely regulated in microencapsulation. When the microcapsule wall is ruptured, the pharmaceutically active moiety is released [5]. MDS porous polymeric microspheres are used to extend the life of topical drugs. It is claimed that they release the drug at the smallest practical dose in the most effective manner possible, resulting in greater stability and the capacity to reduce undesirable effects and change the drug release profile. MDS is capable of absorbing secretions, which results in less greasy skin. These are microscopic, inert, and unbreakable spheres that cannot penetrate the skin. They collect to a certain extent in the skin's minute crevices and nooks and release the drug contained within the MDS when the skin needs it. MDS' microspheres size (diameter of 5–300 μm) may vary according to the smoothness of the skin [6, 7]. MDS can assist in avoiding an excessive build-up of components in the skin [7]. Numerous perfumes, essential oils, sunscreens, antifungal, emollient, and anti-infective agents, as well as pharmaceuticals, become trapped in MDS. MDS is stable at pH values ranging from 1 to 11 and temperatures up to 130 $^{\circ}\text{C}$. The vast majority of vehicles and substances are compatible with the components of MDS. Bacteria cannot penetrate a 0.25- μm -diameter MDS pore, which makes MDS compositions self-sterilising [4, 8].

The drug must be totally mixable in the monomer or can be made mixable by adding a small quantity of non-polar solvent. It must be insoluble in water and inert to

monomers. Otherwise, the MDS will deteriorate prior to application, and the vehicle must be stable in proximity to and under specified circumstances of the polymerization catalyst [4, 9]. As shown in Fig. 2, MDS technology possesses various advantages over other drug delivery systems [4, 10, 11].

Main text

A number of polymers were utilised to form the MDS 'cage.' Eudragit RS-100, polylactide-co-glycolic acid, Eudragit RS PO, polydivinylbenzene, Eudragit S-10, polylactic acid, and polyhydroxybutyrate are among the polymers explored for the creation of MDS for utilisation topically or orally. The polymer Eudragit RS-100 was the most commonly examined polymer due to its versatility in allowing the investigator to apply it in a number of ways. By improving the solubility, the polymer Eudragit RS PO also controls drug release. Polymers such as polylactic acid and polylactide-co-glycolic acid were also studied for peptide and protein delivery. MDS generated with these polymers also exhibits the ability to float due to the hydrophobicity of the polymer, by preventing the particles from becoming wet in aquatic circumstances, allowing them to be utilised to make floating MDS. The usage of polymers in the fabrication of MDS reveals that production techniques may be modified to satisfy unique demands. A few MDS formulations further incorporated a plasticizer, such as triethyl citrate, for the active moiety and polymers, which assists in microsponge structural stability [3, 12].



The drug release profile of MDS

These are designed in a way to drug release within the definite period as a result of external stimulus [11, 13]. Figure 3 shows various triggered-based mechanisms employed for drug release in MSD.

pH-stimulated system

By altering the coating on the MDS, pH-dependent drug release is enabled.

Change of temperature

At room temperature, the entrapped drug may be too viscous to move rapidly from the microsp sponge to the

dermis. However, when the temperature of the skin increases, the rate of active flow increases, and hence the rate of release increases as well.

Pressure

Applying pressure while rubbing can result in the release of drugs encapsulated in MDS onto the skin. The amount of gas released is governed by the sponge’s quality. Microsp sponge formulations can be improved by altering the material used and a number of other variables.

Solubility

Water-miscible chemicals (antiperspirants and antiseptics) will release additives in the presence of water. Additionally, the diffusion mechanism may initiate the drug’s release [14].

Engineering of MDS

Apart from the microsp sponge composition, the delivery system’s performance is influenced by the preparation processes used. However, due to their complexity and expense, microsp sponge preparation methods are restricted. Drug release can be performed in two ways: one-step process and two-step process (liquid–liquid polymerization) and quasi-emulsion diffusion method. Both methods are dependent on the physicochemical properties of the active drug that must

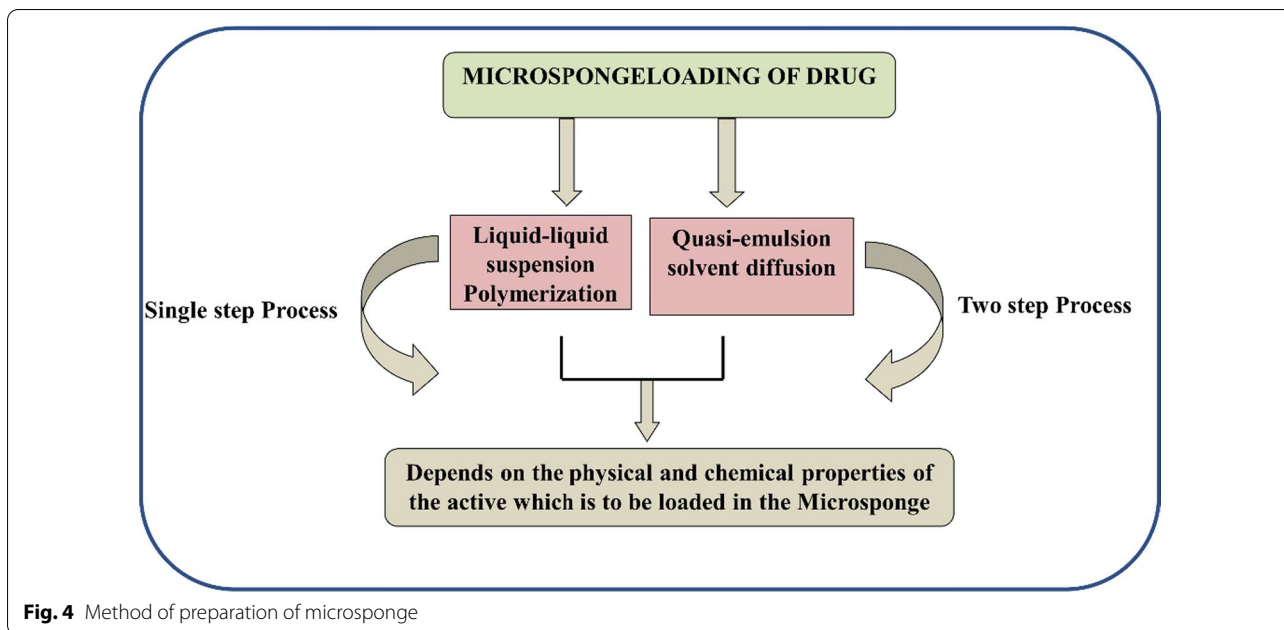


Fig. 4 Method of preparation of microsponge

be entrapped; for example, if the drug is a non-polar and inert material, it will produce a structure that is porosity, as shown in Fig. 4. Porogen drugs that do not inhibit polymerization and do not trigger it, as well as being stable towards free radicals, may be entrapped using a one-step procedure [3, 13].

Liquid-liquid suspension polymerization

Typically, a solution containing monomers and active additives that are water-immiscible is created first. Figure 5 summarises the number of stages involved in liquid-liquid suspension polymerization processes [15]. This water-soluble phase is suspended in water with

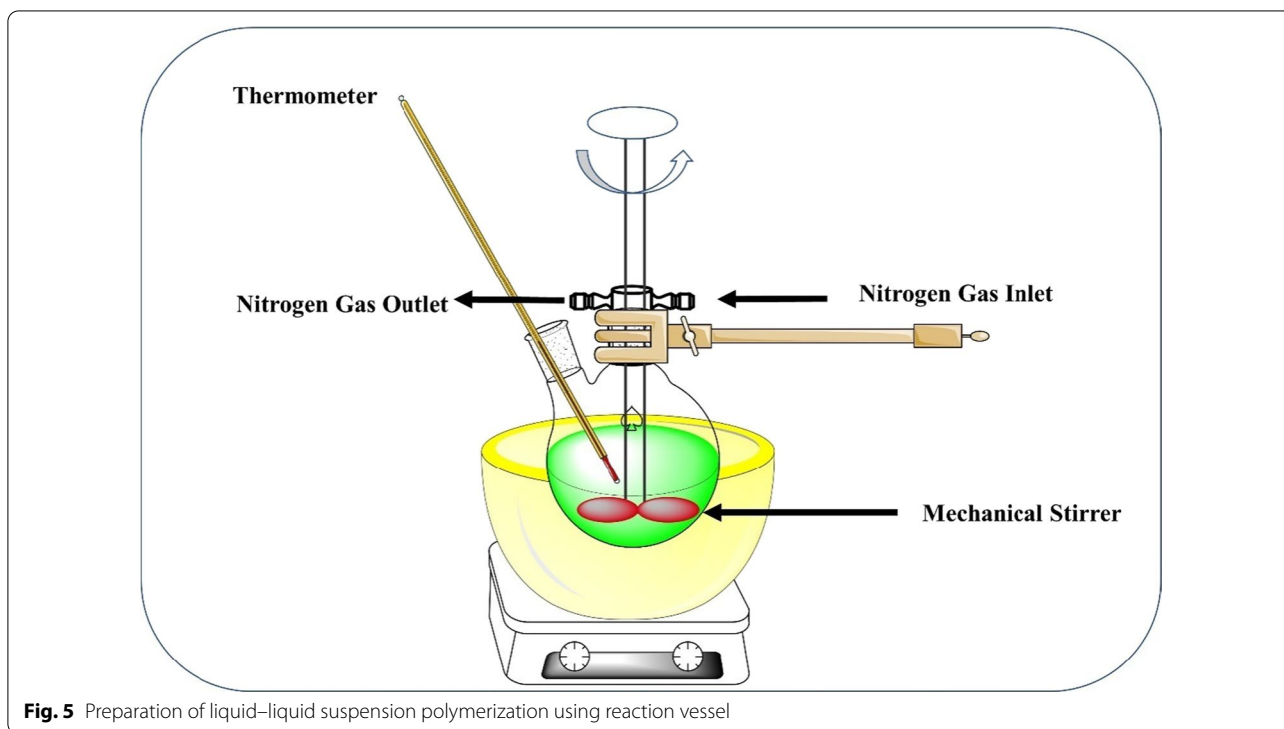


Fig. 5 Preparation of liquid-liquid suspension polymerization using reaction vessel

agitation and often comprises chemicals such as emulsifiers and dispersants. Polymerization is achieved by activating monomers with the assistance of catalysis, temperature elevation, or irradiation after the solution has been formed with separate droplets of the desired size. The polymerization technique results in the formation of 1000 cages of MDS with spherical structures that are linked and resemble a bunch of grapes. After the polymerization is finished, the solid particles will be collected from the resulting suspension. After that, the particles were rinsed and dried before being used again [3, 16].

Quasi-emulsion solvent diffusion

The procedure described here is commonly used to make topical and oral microsponges. The procedure involves the production of two phases, one of which is the inner organic phase, which contains the drug, and the other is the outer aqueous phase, which is then agitated and filtered before being used. The inner phase is then blended drop by drop in the outer phase with the assistance of a mechanical stirrer for 60 min. The quasi-emulsion droplets were formed as a result of continual stirring, and the solid cages of micro sponge were formed as a result of further organic solvent evaporation. After that, the microsponges were filtered and dried in the oven for 12 h. Figure 6 summarises the steps required in micro sponge production utilising the approach quasi-emulsion solvent diffusion [17–19].

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 [3].

Addition of porogen

Porogens such as sodium bicarbonate or hydrogen peroxide were utilised to replace the numerous emulsions in this approach. To do this, the porogen was dissolved in a polymeric solution to create a single-phase system, which was then disseminated in a water phase containing polyvinyl alcohol. After that, an initiator was added to create numerous emulsions, and the organic solvent was evaporated, leaving the particles behind to build MDS [3].

Lyophilisation

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 lyophilisation. This approach produces microsphere holes as a result of the quick solvent removal. Because of the quick elimination of solvent, the lyophilisation

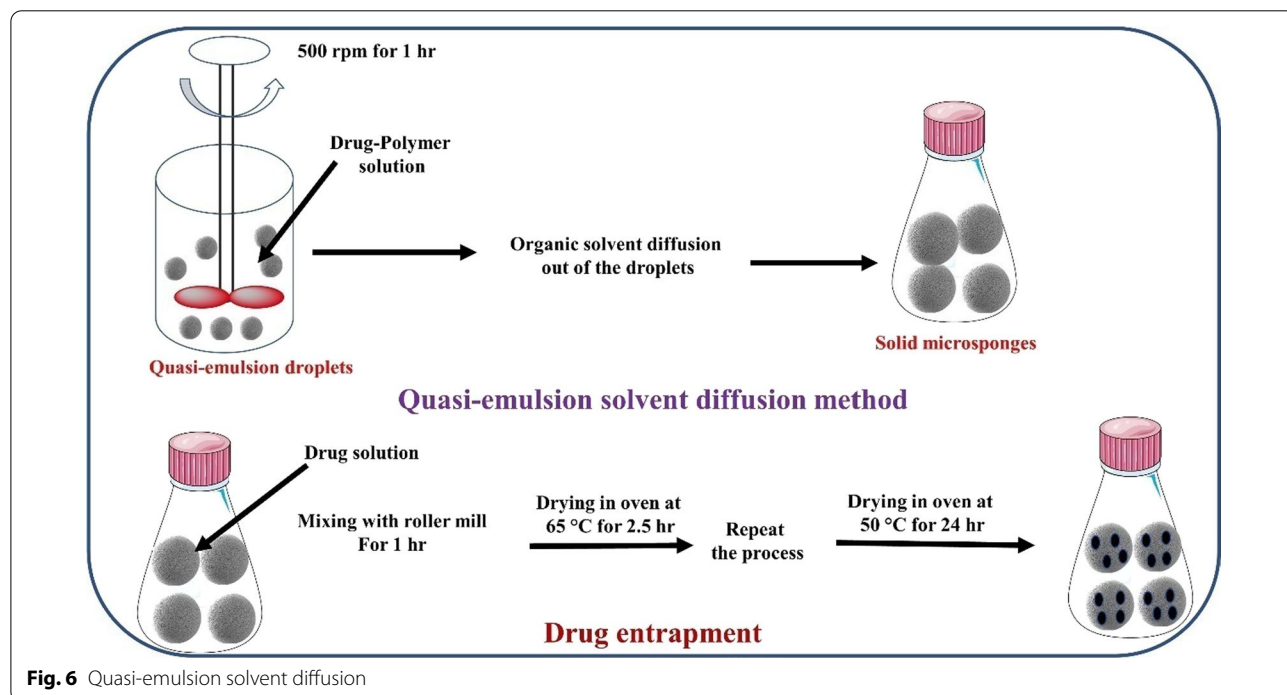


Fig. 6 Quasi-emulsion solvent diffusion

process of producing MDS has the disadvantage of creating shrunken or otherwise fragmented microparticles [3].

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 in Fig. 7. This technique of production is also insufficient in terms of entrapping harmful cross-linking agent residue [3]. Table 1 compares the various strategies utilised in the production of MDS formulations.

Larger particles with a diameter of 30 μm cause grittiness; hence, tiny particles with a diameter of 10–25 μm are preferred for use in topical formulations [6, 8].

Surface morphology and topography

It can be used as a validation parameter to determine this since the produced MDS is coated with Au–Pd in an argon environment [8].

MDS loading efficiency

Equation 1 shows the loading efficiency of MDS [15]:

$$\text{Loading efficiency} = \frac{\text{MDS drug content in actual}}{\text{Theoretical drug content}} \times 100 \tag{1}$$

Equation 1 shows the production yield of MDS:

$$\text{Production yield} = \frac{\text{Practical mass of MDS}}{\text{Theoretical mass of MDS (Polymer + Drug)}} \times 100 \tag{2}$$

Evaluation of MDS

Particle size determination

MDS should not have particles larger than 30 μm, with a typical particle size range of 10–25 μm. Laser light diffractometry or any equivalent technology is used to determine the particle size of loaded or unloaded MDS.

Determination of true density

The real density of MDS can be determined using an ultra-pycnometer under helium atmosphere [20].

Characterisation

The transport of drugs into the vehicle from MDS is also influenced by the pore diameter. The diameter (*D*)

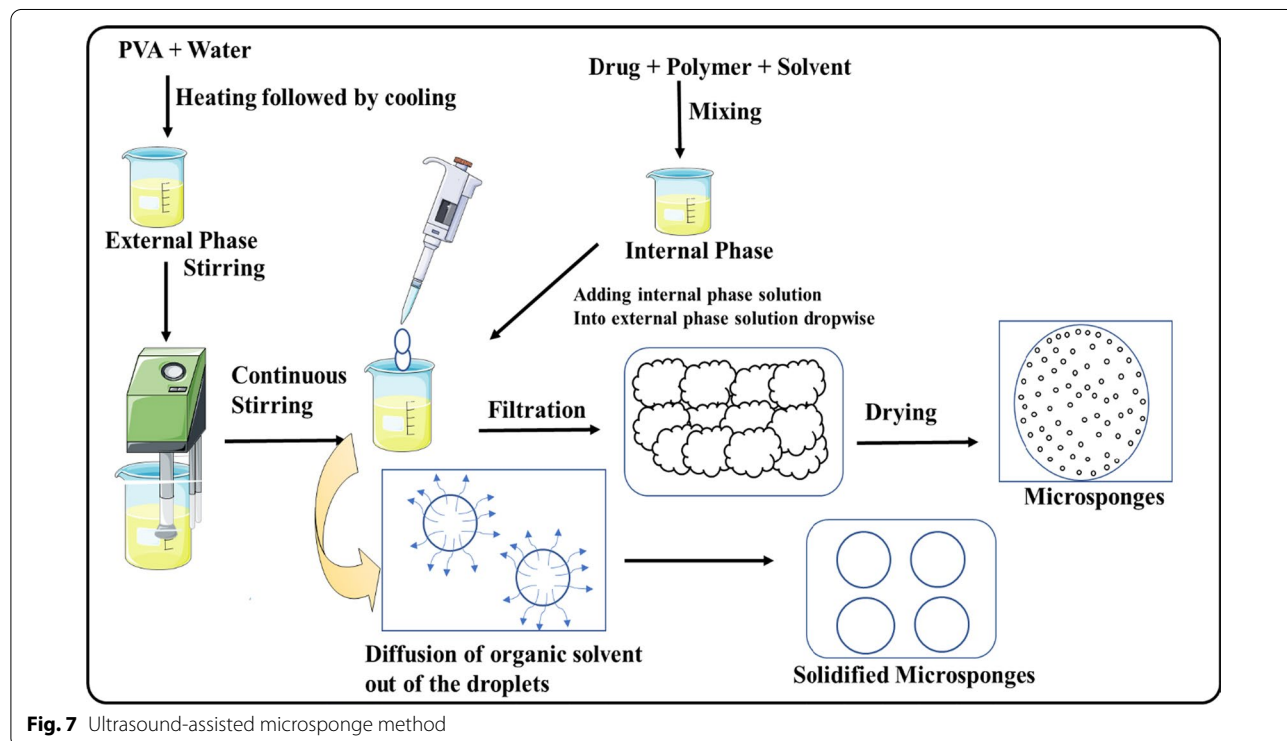


Fig. 7 Ultrasound-assisted microsponge method

Table 1 Comparative evaluation of various methods for the MDS preparation

S. No.	Method of preparation	Pros	Cons	References
1	Liquid-liquid suspension polymerization	It may be adjusted to a single-step or two-step technique for drug loading	(a) Solvent traces and unreacted monomers can be trapped; (b) the structure is non-uniform; (c) the reaction time needed for monomers is considerable; and (d) thermosensitive medicines necessitate two-step methods	[6, 19]
2	Quasi-emulsion solvent diffusion	High drug loading, no monomer entrapment, low solvent traces, MDS size is readily regulated by regulating the stirring rate, and spherical microsponges are obtained	(a) Not appropriate for loading water-soluble medicines, and (b) the monomer reaction takes a long time	[6, 19]
3	Multiple-emulsion solvent diffusion	(a) Water-soluble drugs can be loaded effectively, and (b) proteins and peptides may be entrapped using this approach	Requires the use of water-insoluble surfactants, which can be found in the form of residues in the resultant MDS	[6, 19]
4	Addition of porogen	Extremely porous structure with well-distributed and interconnected pores	Disruption in structure may occur	[6, 19]
5	Lyophilization	Method is simple and quick, and the results are repeatable	To get rid of the organic solvent remnants, vigorous washing is required	[6, 19]
6	Ultrasound-assisted production	No solvent traces, produce rapid and reproducible results	It is possible that an irregular structure may emerge, necessitating the use of cross-linking chemicals, which may be harmful	[6, 19]

of the pore has an impact on the rate of drug release [5, 20]. Equation 3 shows the Washburn equation used to compute the pore diameter of MDS, where D is the pore diameter (μm); γ is the surface tension of mercury (485 dyn/cm); θ is the contact angle (130°); and P is the pressure (psia):

$$D = \frac{-4\gamma \cos \theta}{P} \quad (3)$$

Porosity studies

To examine the size of nanocavities generated in MDS, a porosity analysis can be done. Pore structure, diameter, and volume can be calculated as per Eq. 4. Porosity can be determined as

$$\text{Porosity (\%)} = \frac{\text{Bulk volume} - \text{True volume}}{\text{True volume}} \times 100 \quad (4)$$

Compatibility studies

TLC and FTIR both can be used to explore drug compatibility with reaction mixtures [8].

Resiliency

Resiliency of MDS also represents the viscoelastic nature and may be changed to make beadlets that are softer, as required [15].

In vitro dissolution studies

In vitro dissolution can be carried out with USP XXIII in dissolution assembly containing a 900 ml solution of saline phosphate buffer with a particular pH, heated to 37.5°C , and spun at a set rotation rate per minute [21].

Stability studies

The investigations of stability are carried out in accordance with the International Council of Harmonization (ICH) criteria [21].

Polymer/monomer composition

The entrapped drug partition coefficient between the microsphere and the vehicle should be determined [6].

Studies on drug release and drug deposition

Typically, a Franz static diffusion cell is used to release the medicine from semi-solid dosage forms. In this procedure, the epidermal side of the skin is exposed to adequate temperature, while the dermal side, or skin inner side, is exposed to the receptor solution. The receptor compartment contains 20 mL of buffer media, which should be agitated at 600 rounds per minute and kept at $32 \pm 0.5^\circ\text{C}$. The skin was soaked with the diffusion

medium for 1 h before the test sample was applied. A particular amount of the sample is put in the donor compartment. Diffusion cells are used to assess the amount of drug that is deposited on the skin, and they are subsequently deconstructed at specified time intervals. The skin is then gently removed, and the drug-affected area of the skin is cleansed with distilled water [5].

Formulation considerations

1. MDS drug distribution system actions may then be used in a variety of goods such as lotions, creams, soaps, and powders. Certain thoughts are considered while developing the vehicle in order to attain the desired product features. The active substances' solubility in the vehicle should be kept to a minimum. If this is not the case, the vehicle will minimise the MDS activity [22].
2. In order to minimise cosmetic issues, no more than 10–12% w/w MDS should be used in the car. Polymer designs and payloads for active MDS should be tuned for the needed release rate for the specified period. Some considerations should be made while developing vehicles for a specific application in order to attain the required product attributes.
3. To avoid cosmetic issues, the powder load in the car should be sufficient (not more than 10–12%) [23]. The active agent's solubility in the vehicle should be limited; otherwise, the skin will degrade the polymer before it is delivered to it. For the release of the active agent throughout the specified duration, polymer design, as well as loading levels, must be suitably determined.

Safety considerations

Microsphere systems are built up of commonly used polymers with extremely low levels of remarkable monomers; also, cross-linking physiologically disables them, since the body is unable to biodegrade them and replicate them in other substances [24].

These microspheres are incredibly huge and pass through the stratum corneum due to their size. They linger under the skin's surface, gradually releasing their substance over time. This release pattern reduces the excessive build-up of active substances in the epidermis, perhaps improving topical drug safety [25].

Applications of MDS

Microsphere technology in cosmetics

Microsphere 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 mouthwashes 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 [26].

MDS-based delivery systems for drug triggering

Because of the increased effectiveness of drugs when formulated as microsponge, improved safety, and better visual look of formulations used for topical treatments, over-the-counter drugs, and personal care items, microsponge delivery systems are being considered. This delivery method is designed to allow the active moiety to be released at a slower pace over time, perhaps reducing adverse effects while maintaining therapeutic efficacy. They can be used for a variety of purposes. It is mostly utilised for topical preparations, but it has also been employed recently for drug delivery via the oral route. It gives a formulator a variety of possibilities for making medicine or cosmetic product. They are made in such a way that they distribute active moiety efficiently with the least amount of dosage, as well as improve product stability, reduce adverse effects, and change drug release. Treatments including different moisturisers, sunscreens, and specific rejuvenate items are included in the microsponge delivery system that combines over-the-counter products [15, 27]. The microsponge system is used for topical administration in three ways in products that are in development or on the market:

- 1) The active moieties are released for a prolonged period of time by the MDS reservoir.
- 2) As a container for undesired things, such as excess skin oils, to be absorbed.
- 3) MDS are closed containers that keep the components away from the skin while they work on the surface [15].

MDS are porous sponges that are used for topical treatment and, more recently, oral delivery of active ingredients. MDS is designed to administer a medicine efficiently with the smallest amount possible, as well as to increase product stability, reduce adverse effects, and change the release of a drug [28]. Table 2 summarises the available marketable items.

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 (Fig. 8 and Table 3). 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 [30, 31]

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 microsponge. The pH of the microsponge oral drug administration is regulated by it. Figure 9 shows that when the microsponge is removed from the mouth; the medicine is not delivered to the mouth and is protected by gastric juice (pH 1–3) owing to enteric coating. The coating dissolves in the gut owing to the action of colonic enzymes (glycosidases), and the medicine begins to distribute after 6 h. When MDS move through the descending colon of the big intestine, they transport the most drugs.

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 microsponge 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 localised drug action at the targeted spot [19, 32]. Table 4 shows a list of drug candidates investigated using microsponge delivery for oral drug administration.

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 (Fig. 10). 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

Table 2 List of the microsp sponge-based drug delivery system marketed products

S. No.	Marketed product name	Ingredients	Manufacturer	Applications	References
1	Ultra guard	Dimethicone	Scott Paper Company	This formulation can prevent rashes on the skin caused by diaper use; it is also hypoallergenic and contains skin protectants	[5, 8, 29]
2	Salicylic peel 30	30% Salicylic acid	Biomedic	Removing dead skin cells without causing injury to healthy skin	[5, 8, 29]
3	NeoBenz [®] Micro	Benzoyl peroxide/methyl methacrylate/glycol	Intendis Inc. Morristown NJ07962 USA	It has antibacterial effects and is also a keratolytic agent	[5, 8, 29]
4	Retin-A-micro	0.1% and 0.04% Tretinoin, methyl methacrylate/glycol dimethacrylate, base is of aqueous gel	Biomedic Sothys	Fine lines and wrinkles on the skin can be minimised, skin discoloration due to ageing can be decreased, and skin smoothness can be improved	[5, 8, 29]
5	Salicylic Peel 20	Salicylic acid 20%	Biophora	Improvement may be noted in the fine lines; acne and pigmentation are reduced	[5, 8, 29]
6	Line eliminator DUAL RETINOL FACIAL TREATMENT	Vitamin A	Biophopra	Improvement in pigmentation and acne, as well as a reduction in fine wrinkles	[5, 8, 29]
7	Dermalogica oil control lotion	Niacinamide, yeast extract, caffeine, zinc gluconate, biotin, enantia chlorantha bark extract, and salicylic acid	John and Ginger dermalogica skin care products	To reduce the greasy sheen on the skin's surface	[5, 8, 29]
8	Carac cream	0.5% Fluorouracil, 0.35% methyl methacrylate/glycol dimethacrylate cross-polymer and dimethicone	Avon	Reduces the appearance of fine lines, wrinkles, and age-related discoloration of the skin	[5, 8, 29]
9	EpiQuin Micro	Hydroquinone and retinol	SkinMedica Inc.	To minimise skin irritation, MDS gently distribute the medicine to the skin with continued exposure	[5, 8, 29]
10	Retinol 15-night cream	Pure retinol and vitamin A	Sothys	Continuous use of Retinol 15-night cream results in visible improvements in wrinkles and fine lines reduction, apparent improvement in skin discoloration caused by ageing, and increased skin smoothness	[5, 8, 29]
11	Lactrex [™] 12% moisturising cream	12% Lactic acid, ammonium lactate, water, and glycerine	SDR Pharmaceuticals Inc., Andover, NJ, USA, 07,821	This microsp sponge preparation is easy to apply and delivers long-lasting skin moisturisation. The water and glycerine incorporated in the preparation serve to make the skin softer and to offer moisturisation to dry, flaky, and cracked skin	[5, 8, 29]

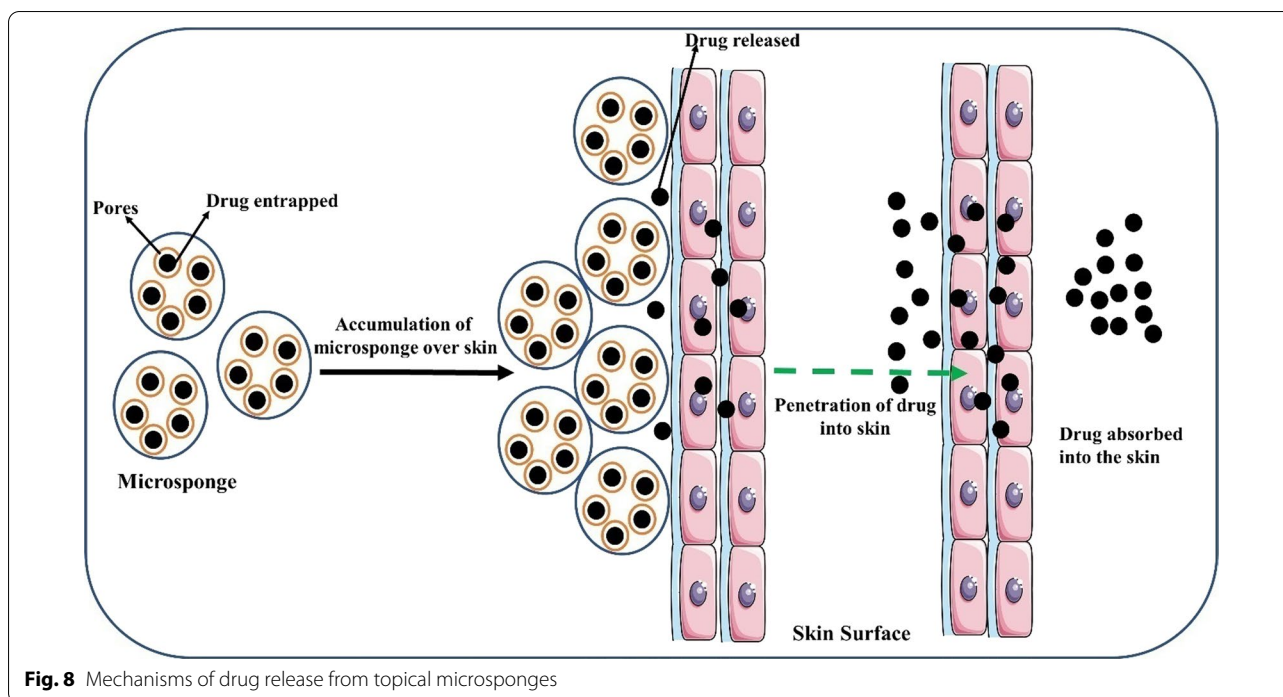


Fig. 8 Mechanisms of drug release from topical microsponges

Table 3 Some examples of MDS currently marketed as cosmetic products

S. No.	Name of the product	Active moiety	Indications	Manufactures	References
1	Retin-A-micro	Tretinoin	Acne vulgaris	Ortho-McNeil Pharmaceutical, Inc. USA	[30, 31]
2	Carac cream	Fluorouracil	Actinic keratoses	Dermik Laboratories, Inc. USA	[30, 31]
3	Line eliminator dual retinol facial treatment	Retinol	Anti-wrinkle	Avon Products, Inc. UK	[30, 31]
4	Retinol night cream	Retinol	Anti-wrinkle	Biomedical IMPORIUM, South Africa	[30, 31]
5	Lactrex™ 12% moisturising cream	Lactic acid	Moisturiser	SDR Pharmaceuticals Pvt. Ltd., India	[30, 31]
6	EpiQuin micro	Hydroquinone and retinol	Hyperpigmentation	SkinMedica, Inc. USA	[30, 31]
7	Oil-free matte block SPF20	Zinc gluconate	Sunscreen	Dermalogica, LLC, USA	[30, 31]
8	Ultra guard	Dimethicone	Protective for babies	Scott Paper Company, USA	[30, 31]
9	Micro-peel plus/acne peel	Salicylic acid	Acne vulgaris	Biomedical IMPORIUM, South Africa	[30, 31]
10	Retinol cream	Retinol	Skin supplement	Biomedical IMPORIUM, South Africa	[30, 31]
11	Glycolic acid moisturiser w/ SPF 15	Glycolic acid	Anti-wrinkle and soothing agent	AMCOL Health and Beauty Solutions, Inc. USA	[30, 31]

in the blood crosses the blood–retina barrier and reaches the eye’s posterior chamber [6].

MDS in cosmetics and dermatology

Won’s initial patents for micro sponge technology were issued to Advanced Polymer Systems, Inc. in 1987. Micro sponge technology was used in cosmetics,

over-the-counter (OTC), and prescription medicinal goods by this firm. MDS ensures drug localisation 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

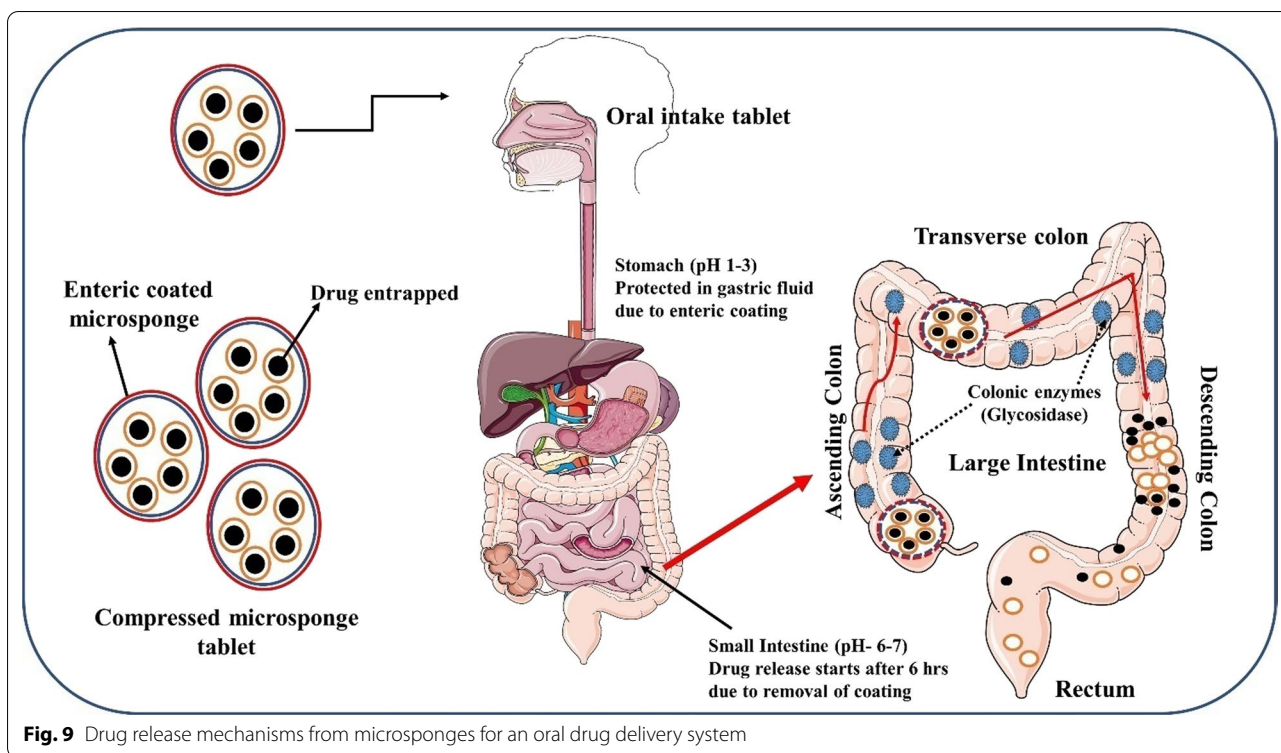


Fig. 9 Drug release mechanisms from microsponges for an oral drug delivery system

Table 4 Drug candidates explored using microsponge delivery systems for dermatological and cosmetic applications

S. No.	Drug candidates	Formulation type	Cosmetic and dermatological applications	References
1	Fluocinolone acetonide	Gel	Skin inflammation	[31, 32]
2	Mupirocin	Emulgel	In both primary and secondary skin infections	[31, 32]
3	Fluconazole	Gel	Antifungal	[31]
4	Silver sulfadiazine	Gel	Burn wounds with a partial thickness	[31, 32]
5	Oxybenzone	Gel	Sunscreen	[31, 33]
6	Terbinafine	Gel	Fungicidal (hair and skin infection)	[31–33]
7	Paeonol	Cream	Anti-inflammatory and anti-melanin activity	[31]

than dermatological products due to minimal regulatory restrictions. Table 5 and Fig. 11 list some examples of microsponge-based cosmetic products now available on the market [31].

Furthermore, skin targeting with microsponge drug delivery devices is possible, preventing excessive drug absorption into the percutaneous blood circulation. Table 6 and Fig. 12 show microsponge-based formulations for dermatological applications that have been produced using a variety of medicines [51].

MDS used for bone and tissue engineering

When polymethyl methacrylate powder was mixed with liquid methyl methacrylate monomer and tricalcium

phosphate grains and calcium-deficient hydroxyapatite powders in water, the mixture formed bone-like compounds that looked like real bone. The final composites looked like they had holes in them and were like microsponges. The basic fibroblast growth factor (bFGF), which was incorporated into a collagen sponge sheet, was released into the mouse sub-cutis as the sponge matrix degraded. The bFGF had local angiogenic activity in a dose-dependent way. Microsponges of collagen with bFGF were injected into the hind limb of a mouse that had been deprived of blood. This caused a significant increase in blood flow, which could not have been achieved by giving the bFGF bolus. These findings show how important and useful type I collagen is as a source of bFGF [63,

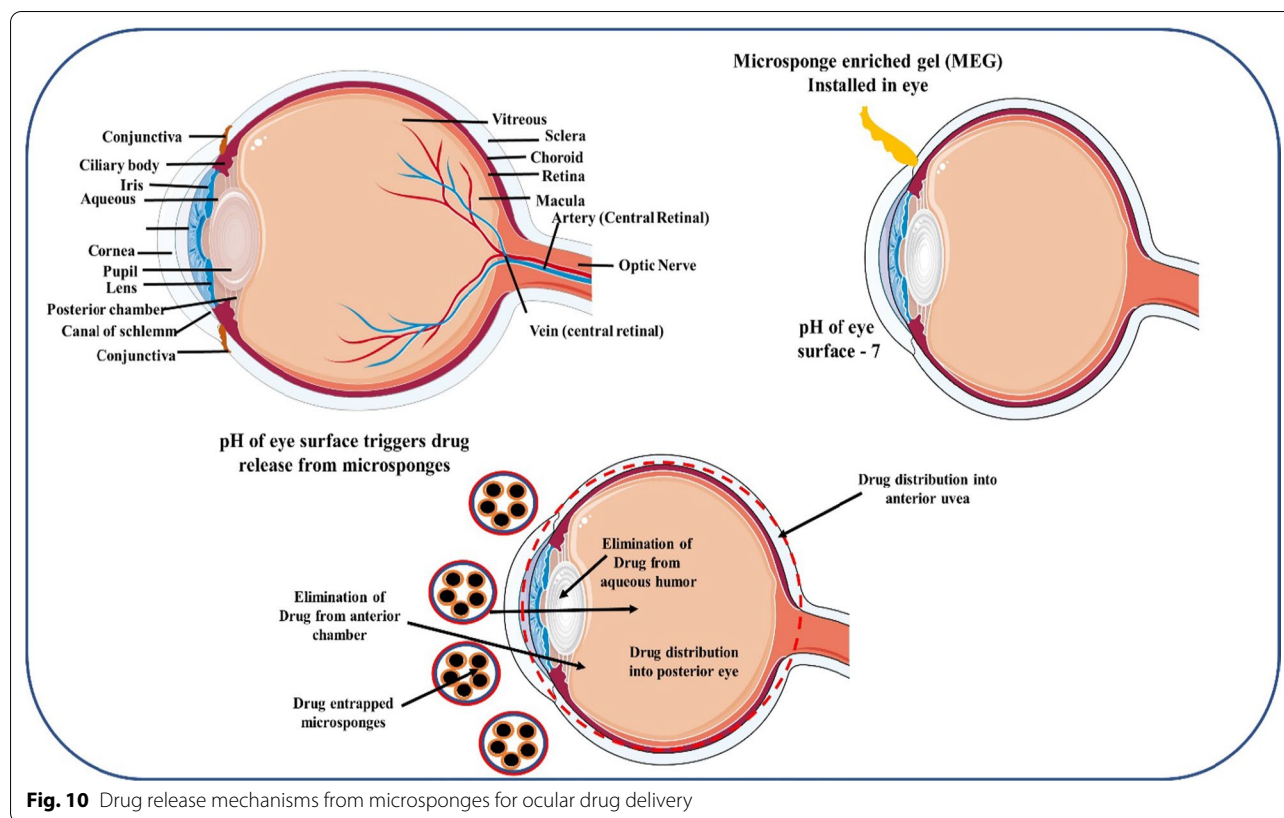


Fig. 10 Drug release mechanisms from microsponges for ocular drug delivery

[64]. A biodegradable graft material with the collagen microsponge was made for cardiovascular tissue grafting because it would allow the tissue to grow back from scratch [65]. Using biodegradable polymer and collagen microsponge, an engineered patch is made that could be used to help repair the cardiovascular system. This patch could also be used as a new surgical material [65].

MDS in arthritis

The use of a microsponge to dispense diclofenac has been studied in the treatment of arthritis (Fig. 13). Diclofenac is the most often prescribed nonsteroidal 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. Osmani et al. used a quasi-emulsion solvent diffusion technique to manufacture MDS gels containing diclofenac diethylamine to achieve a prolonged release for arthritis therapy. They compared their findings to the commercial Voltaren Emulgel 1.16 per cent w/w. The gel only released 81.11 per cent of the medicine in 4 h, but the microsponge-based gel released the drug over 8 h [62]. Hadi et al. 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 per cent to 12 h [66].

Skin protection using MDS

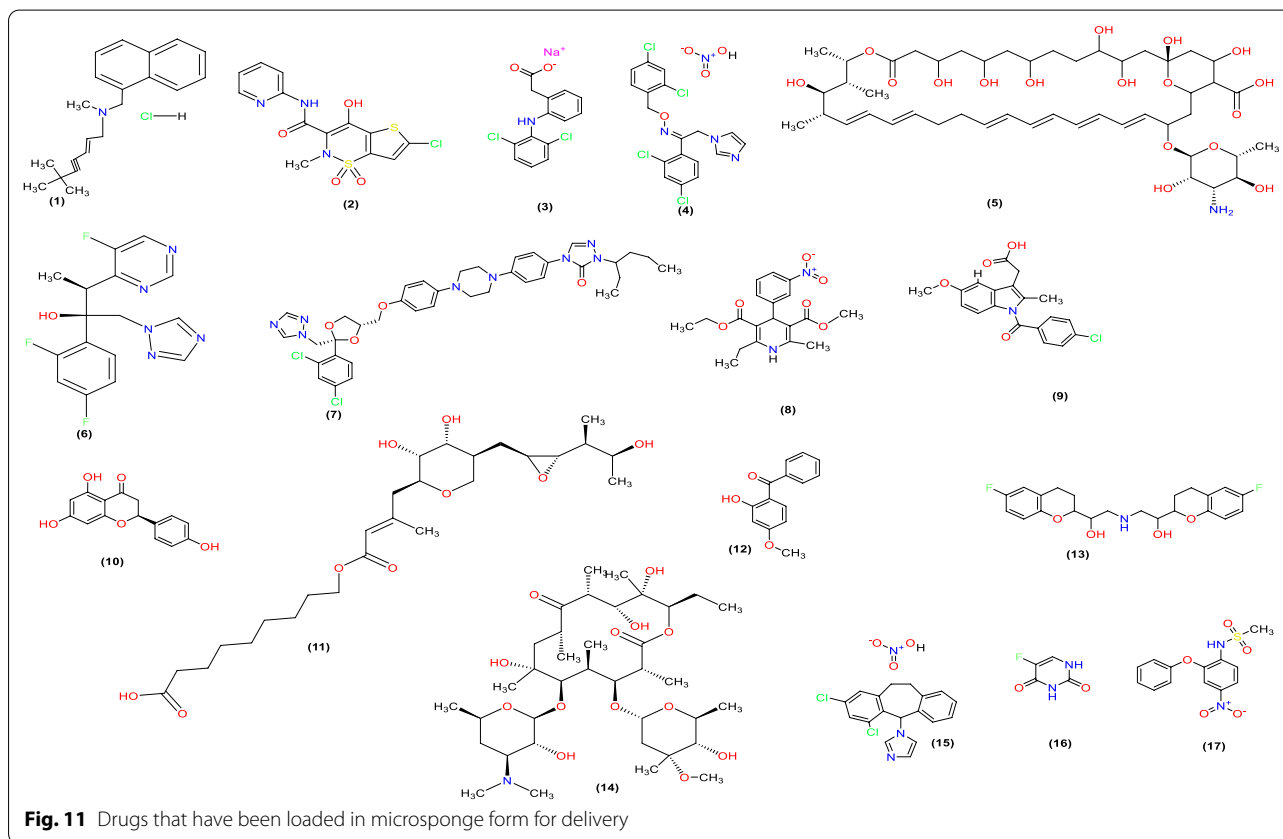
UV radiation may cause sunburns and malignancies like basal carcinoma and malignant melanoma; hence, sunscreens are used to protect against it. To improve the impact, MDS can be employed. MDS was developed by Pawar et al. to deliver oxybenzone, a broad-spectrum sunscreen chemical, to the skin. To make it, they employed a quasi-emulsion solvent diffusion method. When applied as a lotion or cream, oxybenzone produces skin irritation, dermatitis, and systemic absorption. They employed 32 factorial designs to maximise the influence of ethyl cellulose and dichloromethane and then dispersed it in hydrogel for future research. The entrapment efficiency of the revised formulation was determined to be 96.9% 0.52 per cent. The gel released in a controlled manner and did not irritate the rats' skin. The highest recovery was seen during the creep recovery test, suggesting significant elasticity. In comparison with the one on the market, the formulation had a better sun protection factor, as well as less irritation and toxicity. The microsponge gel had an SPF of 25, but the marketed lotion had an SPF of 20, which might be due to the

Table 5 List of research work that was conducted on MDS for topical administration of drugs

S. No.	Drug	Method of preparation	Observation	References
1	Terbinafine hydrochloride (1)	Quasi-emulsion solvent diffusion	Controlled drug release is noticed with less adverse effects, and the requirement for fungal treatment gel administration is also minimised	[33]
2	Lornoxicam (2)	Quasi-emulsion solvent diffusion	The anti-inflammatory impact of drug-loaded gel MDS was compared to oral conventional formulations using an in vivo approach, and it was discovered that the microspoonge-loaded drug was more effective as an anti-inflammatory medicine. Rheumatoid arthritis, osteoarthritis, and active lumbar sciatica therapy all benefit from this treatment	[34, 35]
3	Diclofenac sodium (3)	Double emulsification technique	The improved MDS gel was comparable to commercially available gel and did not cause significant skin responses. The improved formulation is more beneficial for regulated release of diclofenac sodium into the skin	[36]
4	Oxiconazole nitrate (4)	Quasi-emulsion solvent diffusion	The oxiconazole nitrate MDS gel that was prepared demonstrated potential controlled drug release and is more helpful than traditional formulation treatment	[37]
5	Nystatin (5)	Quasi-emulsion solvent diffusion	In this study, the formulations of traditional Nystatin gel and nystatin-loaded microspoonge gel were compared, and it was discovered that the microspoonge gel demonstrated much more drug release than the traditional nystatin gel	[38]
6	Voriconazole (6)	Quasi-emulsion solvent diffusion	The drug release from a voriconazole-loaded microspoonge gel was prolonged, indicating that it might be a potential alternative to conventional therapy in the treatment of fungal infections	[39]
7	Itraconazole (7)	Quasi-emulsion solvent diffusion	When itraconazole was designed as a microspoonge drug delivery system, it was shown to release in a controlled manner	[40]
8	Nitrendipine (8)	Quasi-emulsion solvent diffusion	A drug that is poorly water soluble was given a sustained release profile	[41]
9	Indomethacin (9)	Quasi-emulsion solvent diffusion	Indomethacin-loaded MDS outperformed traditional indomethacin formulations as an analgesic and anti-inflammatory drug	[42]
10	Naringenin (10)	Quasi-emulsion solvent diffusion	When compared to a simple naringenin gel, a naringenin-loaded microspoonge gel demonstrated threefold better drug deposition into the skin. It is a drug that is used to treat atopic dermatitis	[43]
11	Mupirocin (11)	Emulsion solvent diffusion	The Draize patch test revealed that the optimised microspoonge formulation of mupirocin was stable and non-irritating to the skin. In a rat surgical wound model infected with <i>S. aureus</i> , a microspoonge-based emulgel exhibited long-term effectiveness	[44]
12	Oxybenzone (12)	Quasi-emulsion solvent diffusion	The oxybenzone-loaded microspoonge demonstrated considerable and enhanced oxybenzone topically retention over a prolonged period of time. When compared to the marketed formulation, this MDS preparation also boosts the factor for UV protection, according to this study. It also reduces the drug's toxicity and irritating impact	[45]
13	Nebivolol (13)	Oil-in-oil emulsion solvent diffusion	Because the combination of nebigolol microspoonge and gel resulted in rapid wound healing, it is also seen as a significant step forward in the treatment of diabetic wounds	[46]
14	Erythromycin (14)	Quasi-emulsion solvent diffusion	Erythromycin is quickly inactivated in the gastrointestinal environment, causing gastric disturbances such as diarrhoea, nausea, vomiting, and abdominal discomfort. This can be avoided by encapsulating the drug in a microspoonge and administering it via a topical route, which provided an 8-h prolonged release	[47]

Table 5 (continued)

S. No.	Drug	Method of preparation	Observation	References
15	Eberconazole nitrate (15)	Quasi-emulsion solvent diffusion	The drug-loaded microsponge gel released the drug in a regulated manner, with no discomfort to the rat skin. When compared to the marketed cream of eberconazole nitrate, an in vitro skin deposition investigation revealed a fourfold increase in drug retention in the stratum corneum layer of skin	[48]
16	5-Fluorouracil (16)	Quasi-emulsion solvent diffusion	The in vivo local bioavailability investigation revealed that the formulation optimised as a microsponge gel of 5-fluorouracil increased drug deposition by 5.5 times. When compared to a commercially available 5-fluorouracil formulation, there was a considerable reduction in skin irritation	[49]
17	Nimesulide (17)	Quasi-emulsion solvent diffusion	When compared to the conventional preparation of nimesulide gel, prepared microsponge formulations of nimesulide demonstrated more controlled release of pharmacological activity. The outcomes of the therapy of paw oedema inflammation in rats using MDS gel loaded with nimesulide were also significantly improved	[50]



microsponge gel's slower drug release, which resulted in prolonged oxybenzone retention [45].

MDS in acne

Acne is a common skin problem that is frequently accompanied by skin inflammation. Benzoyl peroxide is

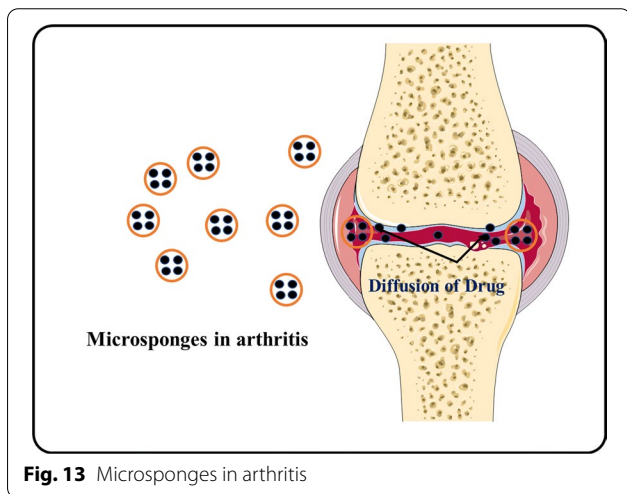
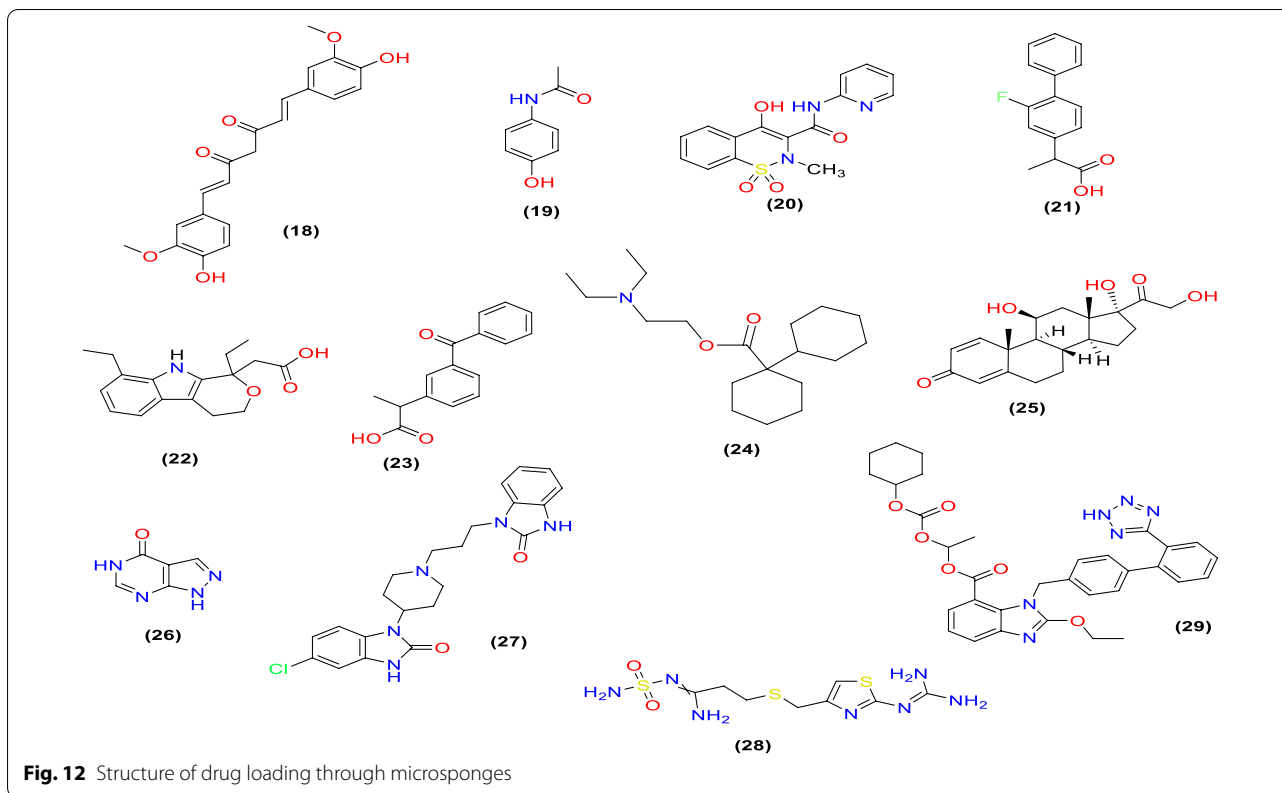
the most common drug used to treat it. Jelvehgari and his colleagues used ethyl cellulose MDS on the skin to inhibit the release of benzoyl peroxide. Drug release was greater for the first hour and then stayed consistent for the next 7 hours, according to research. This might be owing to the existence of a nonencapsulated drug, which once

Table 6 Microsponge-based formulations for dermatological applications

S. No.	Drug	Method of preparation	Observation	Reference
1	Curcumin (18)	Quasi-emulsion solvent diffusion	It was observed that the prepared MDS loaded in gelatine capsule shell released 93.2% curcumin, but the capsule packed with pure curcumin released just 11.7% throughout the course of an 8-h period. As a result, the manufactured curcumin microsponge was shown to be a more competent drug delivery system capable of giving an extended-release rate of drug in oral treatment, and therefore it was discovered to have greater promise than the traditional curcumin formulation	[52]
2	Paracetamol (19)	Quasi-emulsion solvent diffusion	This study demonstrated the potential of MDS to load pharmaceuticals that are required to be used in high quantities, indicating that drugs loaded with MDS had a higher loading efficiency than drugs loaded with alternative microparticle delivery methods	[53]
3	Piroxicam (20)	Quasi-emulsion solvent diffusion	It was discovered that MDS with a porous structure and a spherical form could be made. Physical parameters of the prepared tablets were found to be acceptable. When compared to piroxicam pure table, there was a significant improvement in dissolving rate	[54]
4	Flurbiprofen (21)	Quasi-emulsion solvent diffusion	This research discovered that when MDS are compressed, they generate a mechanically robust core tablet with a long-term drug release profile. They also created a colon-specific tablet utilising the pore-plugged approach, and the tablets created using this technology had zero-order release kinetics	[55]
5	Etodolac (22)	Quasi-emulsion solvent diffusion	Etodolac microsponge was created, and the entrapment altered the drug's release rate, resulting in a reduction in the severity of adverse effects	[56]
6	Ketoprofen (23)	Quasi-emulsion solvent diffusion	When compared to commercially available ketoprofen tablets, the ketoprofen-loaded MDS exhibited improved bioavailability; nonetheless, these microsponge tablets demonstrated delayed drug release and absorption. As a result, the microsponge tablet improves the lag time for drug emergence in plasma and also maintains drug concentration for a longer period of time	[57]
7	Dicyclomine (24)	Quasi-emulsion solvent diffusion	This study found that as the amount of emulsifying agent is raised, the size of microsponge particles increases as well. In addition, when raising the drug/polymer ratio, a decrease in manufacturing yield and smaller particle size is seen, while drug content is enhanced. It has also been discovered that increasing the polymer content leads to better drug release control	[58]
8	Prednisolone (25)	Quasi-emulsion solvent diffusion	Prednisolone-loaded MDS outperformed traditional dosage forms in terms of targeting the medicine to the colon. This stops the medicine from being released in the upper region of the GIT and only delivers it to the colon and the area around it	[59]
9	Allopurinol (26)	Quasi-emulsion solvent diffusion	With the requisite per cent entrapment efficiency and per cent buoyancy, the produced microsponge formulation of allopurinol displayed a sustained drug release profile for up to 12 h. A one-month stability study was conducted under accelerated conditions, and no significant changes in formulation were observed	[60]
10	Domperidone (27)	Quasi-emulsion solvent diffusion	In comparison with the usual marketed formulation Domstal [®] , MDS put in capsules exhibited prolonged drug release of 76.38 per cent at the end of 8 h. As a result, it was determined that the newly created domperidone microsponge formulation would be a potential alternative to traditional gastroparesis and emesis therapy	[61]
11	Famotidine (28)	Quasi-emulsion solvent diffusion	Famotidine-loaded MDS demonstrated a drug release profile that was consistent across time	[62]

released became constant, suggesting that the entrapped drug had been freed [67]. Osmani et al. produced a cream using miconazole nitrate MDS, an anti-acne agent, to achieve prolonged release. The Eudragit RS-100 MDS were created using a quasi-emulsion solvent diffusion

method. MDS was made and incorporated into a cream. Drug-loaded MDS released 78.28% of the drug for up to 8 h, whereas traditional creams were exhausted after 4 h, releasing only 83.09 per cent of the drug [62].



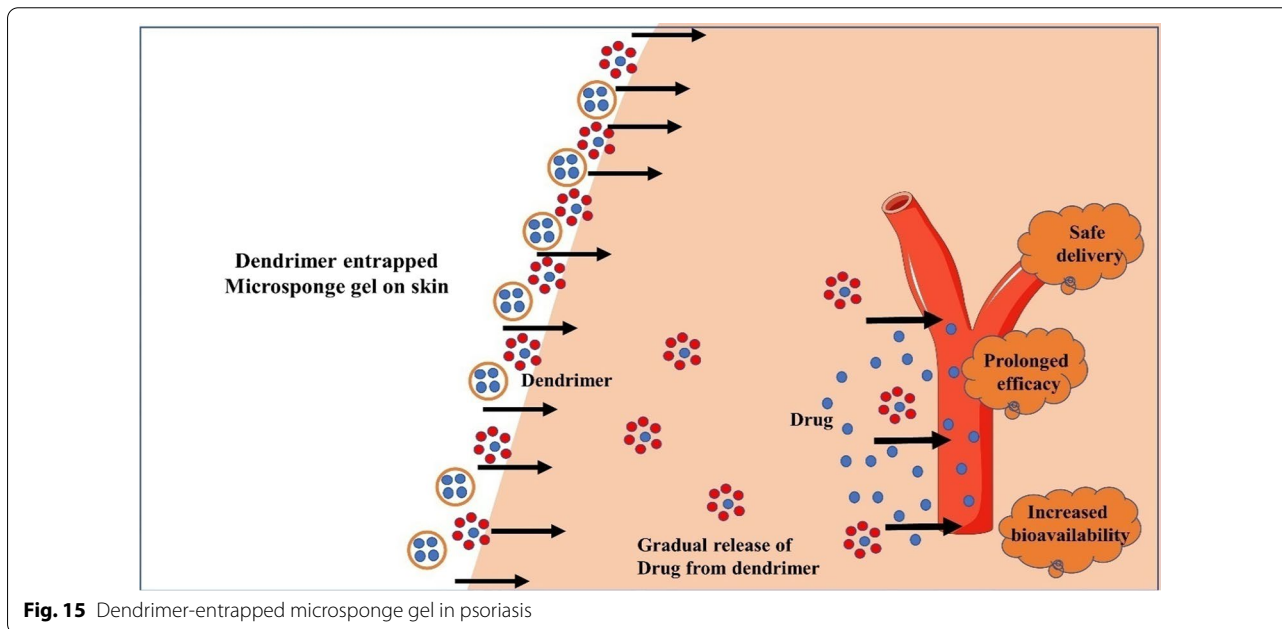
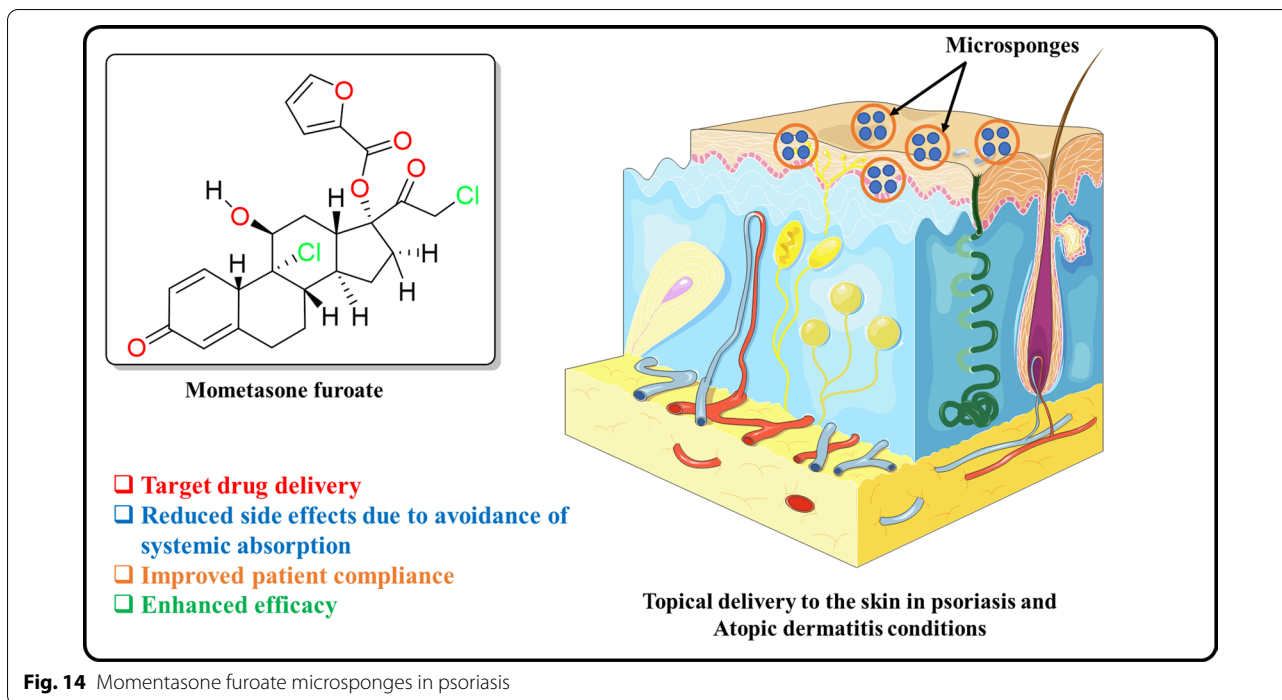
MDS in psoriasis

Psoriasis is a chronic inflammatory disorder that affects the skin. It has a negative impact on the quality of life of sick person. MDS has also been studied as a treatment for psoriasis. To make MDS for the drug mometasone furoate, an emulsion solvent diffusion method is employed (Fig. 14). Mometasone furoate is used to treat inflammatory and pruritic diseases like psoriasis. MDS was created

using the emulsion solvent diffusion process. The release profiles demonstrated a biphasic release with an initial burst effect. 29–36% of the medicine was released in the first hour, and 78–95% of the drug was released after 8 h [44]. Due to the continuous release of drug, a microsponge gel containing clobetasol propionate was used for psoriasis therapy to reduce the number of applications necessary. They discovered that drug release might last up to 12 h, versus 2.5 h in the usual form [44]. Dithranol microsponge gel is encapsulated in a dendrimer for efficient topical therapy and useful in psoriasis (Fig. 15) [68].

MDS in skin infections

MDS is also used to treat eczema and atopic dermatitis in the form of gels or lotions. Mupirocin is a topical antibiotic that is used to treat both primary and secondary skin infections. Mupirocin MDS was developed by Amrutiya et al. for long-term usage against skin infections. They used an emulsion solvent diffusion approach to generate mupirocin MDS, which they then put into an emulgel foundation. Researchers were able to demonstrate controlled drug release using a cellulose dialysis membrane. Figure 16 shows that a considerable proportion of the medicine persisted in the skin for up to 24 h after release and drug deposition investigations on the rat belly skin. The increased formulations were shown to be stable and



non-irritating in a Draize patch test. The drug release from the ointment lasted up to 4 h, whereas the release from the microsponge gel lasted up to 10 h [44].

Diabetic wound healing using MDS

Pandit *et al.* made nebivolol-loaded MDS and encapsulated them in gel to keep the wound moist during the

last stages of healing. Taking nebivolol, which is an anti-hypertensive drug, dilates the blood vessels. In diabetic wounds, the nitric oxide route reduces diabetic neuropathy and improves the function of the endothelial cells in the wound. It was confirmed from in vitro test that after 8 hours, about 80% of the drug was released. Due to the microsponge gel, the release of the drug has been slowed

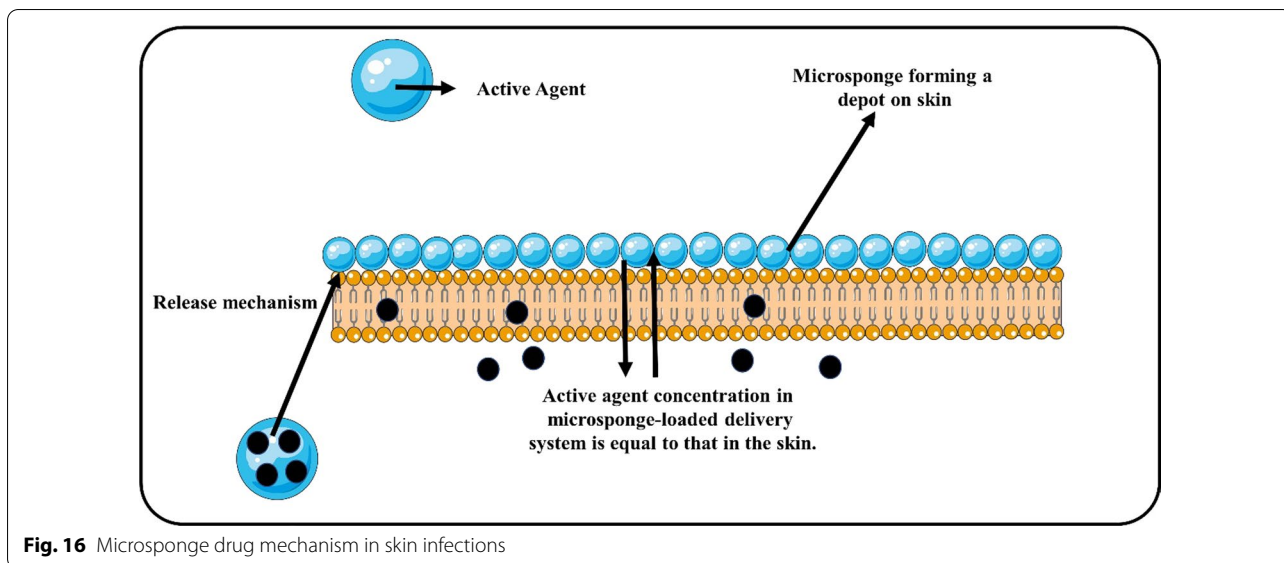


Fig. 16 Microsponge drug mechanism in skin infections

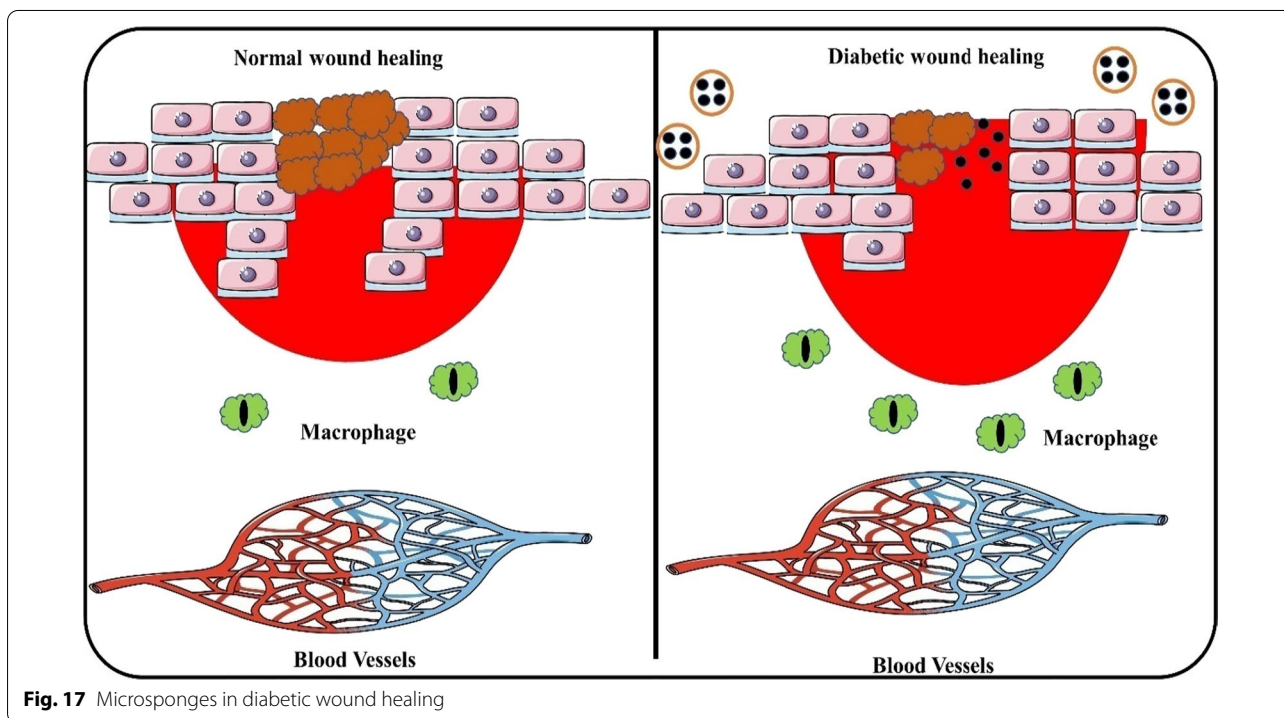


Fig. 17 Microsponges in diabetic wound healing

down. Because of the porous nature of the formulation, diabetic rats show quick wound healing (Fig. 17) [46].

MDS as antifungal

To make MDS of terbinafine hydrochloride, an antifungal drug, Thavva et al. employed a quasi-emulsion solvent diffusion technique. In vitro, the drug-loaded micro-sponge-based gel was compared to a drug-loaded plain

gel. The drug-loaded plain gel released 96.65 per cent of the drug for up to 6 h, but the microsponge-loaded gel released the drug optimally for up to 10 h. Terbinafine hydrochloride-loaded microsponge gels had a longer drug release than conventional gels [33]. Dombé et al. created oxiconazole nitrate MDS using a quasi-emulsion solvent diffusion method, which they then incorporated into the gel. The antifungal oxiconazole nitrate

has limited aqueous solubility, as well as side effects and unpleasant responses. The MDS produced were distinct and spherical in shape, with a high production yield of 61.44–80.45%, showing that this method of preparation was a good strategy for microsphere manufacturing. The highest drug release was found to be 87.77 per cent during an 8-h period. On a microsphere gel, the drug was released in a regulated manner for 12 h [37, 51].

MDS in melanoma

Grimes PE created hydroquinone MDS with 4 per cent hydroquinone and 0.15 per cent retinol for the treatment of melanoma and post-inflammatory hyperpigmentation (PIH). MDS that releases hydroquinone was created to give long-term drug delivery with little skin irritation. It was decided to conduct an open-label experiment. Improvements in sickness symptoms and pigmentation intensity were statistically significant as compared to baseline at weeks 4, 8, and 12 ($p < 0.001$). The lesion area and colorimetry measurements both improved significantly with each visit ($p < 0.001$). The formulation was well tolerated, with only one patient dropping out owing to a non-life-threatening allergic reaction [69].

MDS in colon cancer

MDS can be used to decrease the toxicity and long-term release of oral drugs. Gupta and his team came up with Eudragit RS100-based 5-Fluorouracil MDS to treat colon cancer. There are a lot of different types of solid tumours that 5-FU can be used to treat. 5-FU can be more effective

if it has a higher relative concentration in tumours. As a result, the toxicity level goes down. Oil-in-oil emulsion solvent diffusion was used to make MDS. Pure 5-FU was found to be released in about 20 min, but the MDS makes the release time last for about 5 h. It has been found that when it comes to the viability of cells, MDS-loaded 5-FU is better than 5-FU on its own. In the study, it was found that 5-FU MDS can be used instead of oral 5-FU to treat cancer (Fig. 18) [70].

Other applications

MDS has emerged as a novel drug delivery technology that may be utilised to deliver siRNA and fibroblast growth factor in addition to topical and oral administration. Because a single RNAi microsphere may transfer more than half a million copies of siRNA to a cell, this method of siRNA administration can be used and extended in the field of modern therapeutics and pharmacological research. Researchers employed a new approach that combines femtosecond X-ray single-shot diffraction with an X-ray free-electron laser and coherent diffraction imaging with synchrotron X-rays to explore the nanostructure formation involved in RNA interference microsphere. Figure 19 depicts the mechanistic transfer of siRNA from a microsphere [6, 71].

Recent advances in the MDS

Advanced formulations are being developed by several researchers and pharmaceutical businesses. They are as follows, with a higher level of stability than MDS.

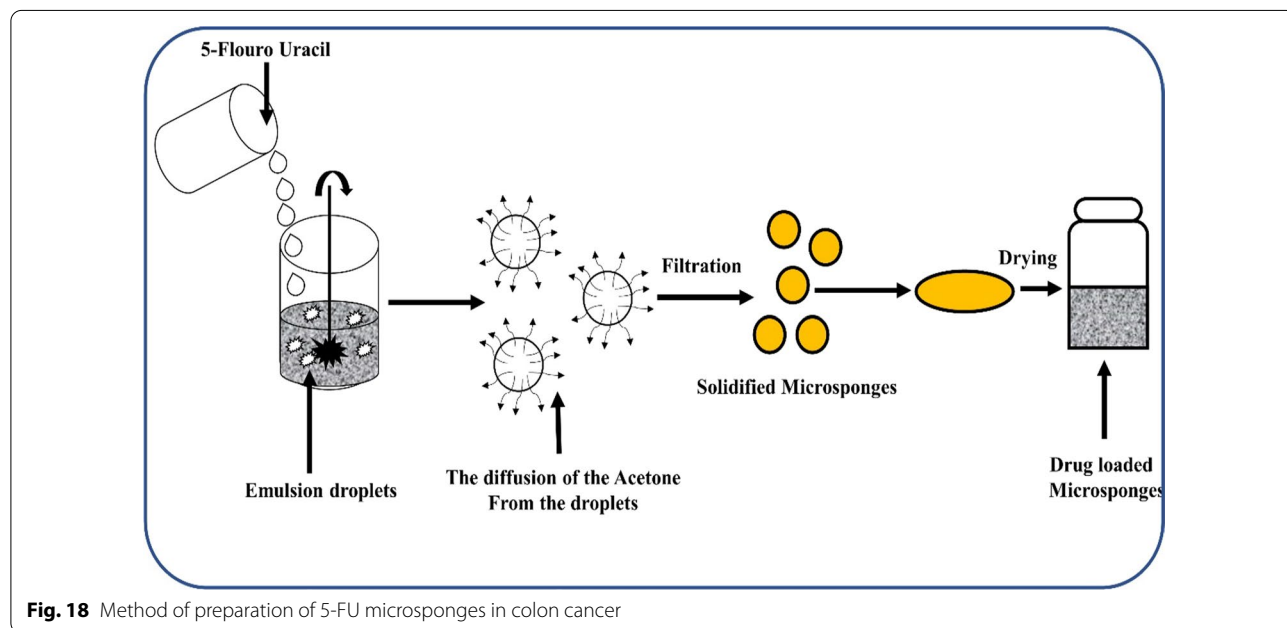
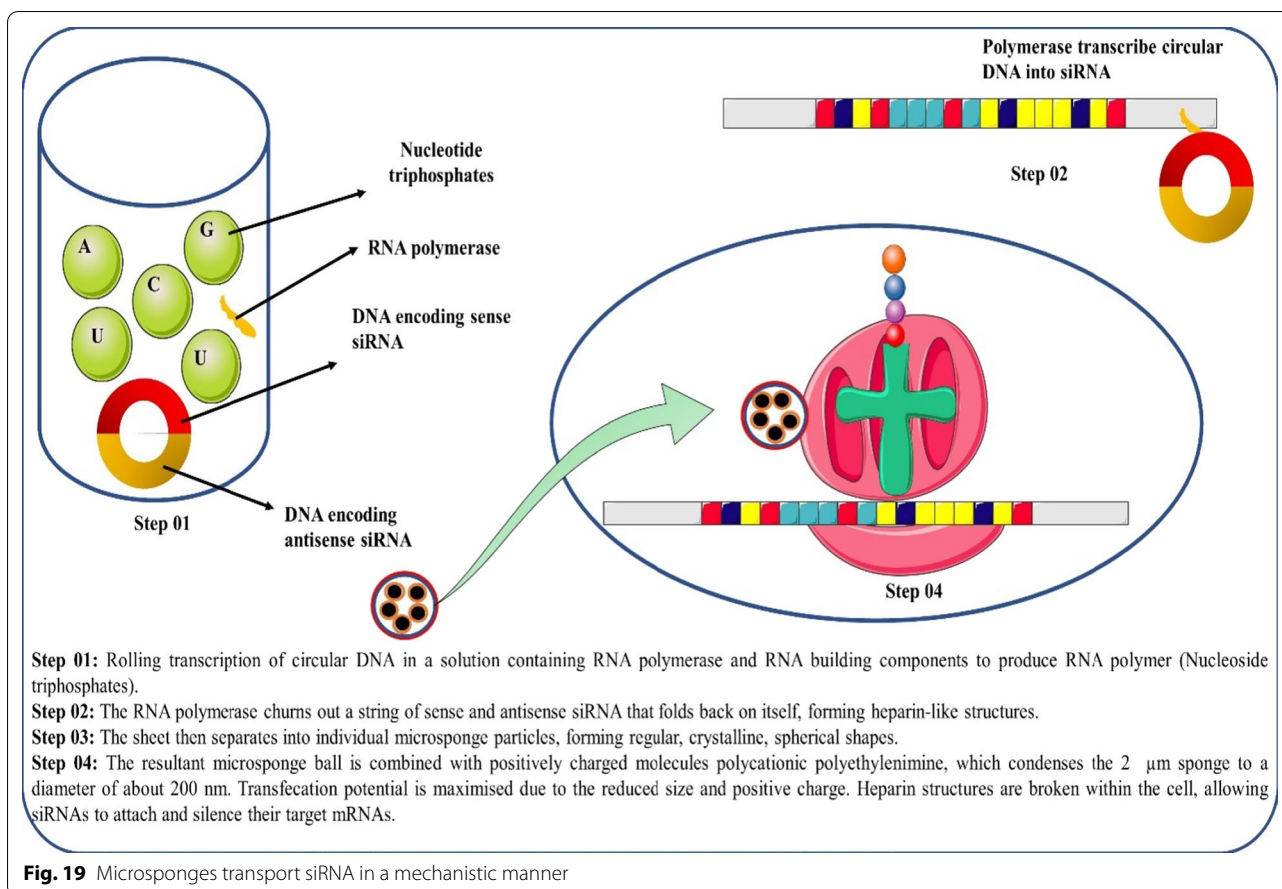


Fig. 18 Method of preparation of 5-FU microspheres in colon cancer



- 1) *Nanosponges* These have been shown to be excellent carriers for gas transport. When cytotoxic is combined with nanosponges as carrier systems, the efficacy of the drug is increased, by allowing it to be utilised to target cancer cells. Cross-linking the β -CD molecule with biphenyl carbonate produces β -CD nanosponges. They can be utilised to make both hydrophilic and hydrophobic medicines. Flurbiprofen, dexamethasone, itraconazole, and other drugs were examined using this sophisticated approach [72].
- 2) *Nanoferrosponges* Nanoferrosponges are self-promising carriers with increased penetration towards a particular location due to an external magnetic reaction that allows carriers to penetrate deeper tissue before magnetic material is excluded, leaving a porous system behind.
- 3) *Porous microbeads* Porous microbeads were created as a result of better microsphere properties. Polymerization and cross-linking processes are utilised to create solid porous microbeads. The monomer used in the high internal phase emulsion approach has an exterior oil phase, an internal aqueous phase, and a

cross-linker. Topical, oral, and buccal drug delivery systems all use microbeads. Due to increased RNA stability and effective siRNA encapsulation, this technique provides a novel therapeutic pathway for siRNA administration [73].

Future perspectives of microsponge drug delivery

Because of its diverse uses in pharmaceuticals and its peculiar porosity system properties, the microsponge drug delivery system will have a very bright future in the next years. One of the primary problems for this drug delivery system in the future will be the oral delivery of peptides, which can be accomplished by using core delivery of drug-loaded MDS and varying and applying the number of polymer ratios. As a result, the microsponge drug delivery system is a very promising subject in the future that should be investigated for its potential benefits [17].

In the near future, MDS devices might be investigated for tissue engineering. Tissue engineering has a lot of promise for improving patients' quality of life. A good example is vascular tissue engineering. The traditional

strategy is to employ an extended type of polytetrafluoroethylene, which is used therapeutically to recreate bigger diameter arteries; however, this method is not suitable for tiny arteries since they are seen as foreign material by the body, causing thrombosis. As a result, a bypass mechanism is necessary. A unique intended vascular graft with tiny calibre made of polyglycolic acid and polylactic acid was constructed utilising a scaffold design process and provided with microsp sponge to shape a vascular patch, which was subsequently tested on dogs. And the results revealed that the dogs healed completely without any complications and that there was no need to employ an anti-thrombotic drug with the graft because it is comprised of the biodegradable polymer [5, 6]. The true difficulty of drug delivery via microsp sponge system in the near future is achieving core/shell delivery of active loaded MDS for oral administration of peptides by changing the polymer ratio [73].

MDS is a novel drug delivery system with unique properties such as enhanced product performance and elegance, extended release, and improved drug release profile, reduced irritation, improved physical, chemical, and thermal stability, which makes it flexible to develop novel product forms. Biodegradable polymers can also be employed for tissue engineering and regulated oral drug administration. It offers a wide range of benefits when it comes to formulation. Alternative drug delivery methods, such as parenteral and pulmonary, must also be developed for MDS. These carrier systems were used in cosmetics because of their elegance. These advancements allowed researchers to use them in a variety of ways. These formulation innovations also open up new avenues for drug delivery. As a result, microsp sponge-based drug delivery technology is expected to become a viable drug delivery matrix material in the future for a variety of therapeutic applications [74, 75].

Conclusions

Microsp sponge technology and the adaptability it provides have a lot of promise in the market because of the desire for novel and highly efficient pharmaceutical and cosmetic goods. MDS is a promising technology for the highly regulated release of an active chemical loaded in MDS, which also leads to a decrease in pharmacological side effects while maintaining therapeutic efficacy. It also exhibited considerable improvements in formulation stability, as well as increased formulation elegance and flexibility. Based on a number of studies, they are also thought to be non-toxic, non-allergic, and non-mutagenic in nature. This drug delivery mechanism is now employed mostly in over-the-counter (OTC) skincare products, prescription medicines, cosmetics, and sunscreens. As a result of its diverse possibilities in drug administration, it

is a very promising technology that is likely to be thoroughly examined in the next years through a variety of research projects.

Abbreviations

5-FU: 5-Fluorouracil; MDS: Microsponges delivery system; OTC: Over-the-counter; RNA: Ribonucleic acid; API: Active pharmaceutical ingredient; XRD: X-ray diffraction method; DSC: Differential scanning calorimetry; PIH: Post-inflammatory hyperpigmentation.

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Author contributions

VT and AT contributed to conceptualization; BP, VT and AT helped in writing—original draft preparation; AT and MK performed writing—review and editing. All authors have read and approved the final manuscript.

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Availability of data and materials

Data and material will be available on request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

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