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REVIEW

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Microsponges: a promising frontier for prolonged release-current perspectives and patents

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Abstract

Background Microsponges are one of the advanced drug delivery systems that facilitates precise and controlled release of active ingredients that are suitable for topical and oral use. These porous microspheres are typically sized between 5 and 300 µm, offer benefits including controlled release, stability, and minimized side effects. Manufacturing techniques like quasi-emulsion solvent diffusion and liquid–liquid suspension polymerization are usually employed to prepare microsponges, although various challenges arise from the use of potentially hazardous organic solvents.

Main body Microsponges possess distinct traits such as extended drug release, formulation flexibility, and high drug loading capacity. Entrapment of drugs requires considerations of solubility, stability, and miscibility, while evaluation methods encompass production yield and particle size analysis. Their applications range from dermatological to biopharmaceutical delivery, with diverse products utilizing this technology. Ongoing innovations about microsponges are evident in patents concerning medical dressings and hyaluronic acid delivery systems.

Conclusion Microsponges present a promising avenue in drug delivery, despite many challenges. Current review addresses on limitations and diverse products highlighting commercial viability. Patent activity signifies continued interest, suggesting significant potential for enhancing patient care.

Keywords Microsponges, Oral administration, Controlled release, Quasi-emulsion solvent diffusion, Topical delivery, Target release

1 Background

Innovative drug delivery technology is rapidly evolving and microsponges are at the forefront in innovative pharmaceutical technology. The technology associated with microsponge drug delivery holds immense potential in realizing the objective of precise and regulated drug administration at specific sites. As a result, researchers have given it a lot of attention [1]. Microsponges are non-collapsible, strongly cross-linked, porous microspheres made of polymeric materials with size ranging between 5 and 300 µm diameter. They possess the ability to load a wide range of active ingredients such as essential oils, antimicrobial agents, fragrances, sunscreens, anti-inflammatory compounds, and antifungal agents. Lately, the use of them for oral administration was also been studied [2, 3, 5]. When used as topical drug carriers, microsponges offer a steady and extended rate of drug release, minimizing discomforts and side effects without compromising the therapeutic efficacy [4]. The purpose of microsponges is to effectively administer a pharmaceutically active substance at the lowest possible dose as well as to improve the formulation stability, elegance, and flexibility, reduce side effects and alter the

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drug release profile in controlled or sustained manner [6]. There are several ways to produce the topical drug formulations using microsponge delivery mechanism, including lotion, gel, or cream. When the microsponge formulation is applied topically, the microsponge delivery system (MDS) releases its active ingredients in response to different stimuli, viz., friction, pH, and temperature at certain timings [7]. Excessive accumulation of drug in the dermis and epidermis may be avoided using microsponge system. As a result, it can considerably decrease irritability without compromising in producing therapeutic activity [6, 8]. Because of their sponge-like structure, microsponges offer special features like easy dissolving and quick compressing of materials. They provide better patient compliance, stable, nontoxic, non-allergic, and non-mutagenic while they offer very few adverse effects unlike other drug delivery systems [2]. Dermal delivery of drug is a broad area of use for microsponges but they are also used for oral administration, advances in bone and tissue engineering, illness detection, and RNAi (ribonucleic acid interference) silencing. The rapid progression of drug delivery technology is further propelled by the emergence of innovative categories of pharmaceuticals and biopharmaceuticals, encompassing proteins, peptides, and nucleic acid-based therapeutics. Consequently, microsponge drug delivery systems represent a burgeoning field that demands thorough exploration [9]. Like enhancement of solubility, precision in targeted organ action, augmented drug stability, targeted medication administration, controlled dispensation of drugs, controlled Release of drugs, dermal drug delivery, oral administration of drugs, advancements in engineering of bone tissue, advances in cardiovascular engineering, rebuilding the vascular walls [10]. Figure 1 shows the structure of microsponges.

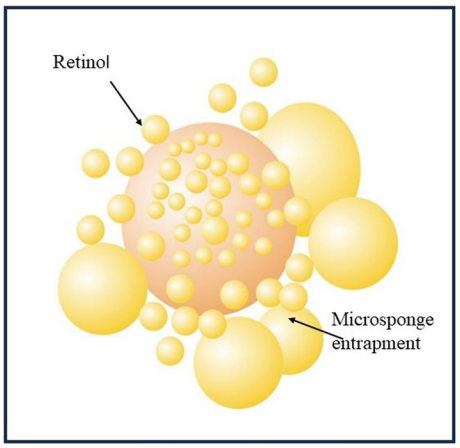

Fig. 1 Structure of microsponge

2 Main text

2.1 Characteristics of microsponges [1, 11]

1. Majority of components and vehicles can be used to formulate microsponges.
2. Microsponges exhibit complete miscibility with a small quantity of nonpolar solvent.
3. Microsponge formulations remain stable over the pH range between 1 and 11.
4. Microsponges are stable at temperatures as high as 130° C.
5. Microsponges demonstrate stability when exposed to the catalyst and within the environment of polymerization.
6. Microsponges are self-sterilizing as they possess pores of 0.25 µm, which do not allow bacteria to permeate into them.
7. Microsponge compositions can be economical and free flowing.
8. Up to 50–60% of microsponge formulations exhibit substantial entrapment.
9. They are flexible to formulate.
10. It offers prolonged release of drug for up to 12 h.

2.2 Advantages of microsponge delivery system [9, 10]

1. Microsponges can absorb oil at a ratio of up to six times their weight without experiencing desiccation.
2. They offer prolonged drug release for up to 12 h.
3. Enhance the robustness at chemical, physical, and thermal levels.
4. Adaptability to create innovative product shapes.
5. They regulate the drug release.
6. Exhibit, improved patient compliance with less irritability and improved tolerance.
7. Can exhibit site specific and targeted activity.
8. MDS have stability over a pH range 1–11.
9. They are free from harmful effects, non-irritating, non-mutagenic, and non-allergic.
10. Exhibits increased drug stability and high drug loading capacity.
11. Compared to other technologies such as liposomes and microencapsulation, MDS is easy to prepare, has a larger payload, and a wider spectrum of chemical stability.
12. MDS allows the incorporation of immiscible products and increases drug's bioavailability.
13. Compatible with all vehicles and other excipients and the solution is easy to navigate and reasonably priced.

2.2.1 Advantages over conventional formulations

Conventional topical formulations are formulated with the aim of targeting outer layers of the skin. Upon application, these formulations gradually release their active constituents that form a concentrated coating that absorbs fast. As a result, dermis and epidermis experience an accumulation or excessive buildup of drug, while the microsponges possess the capability to mitigate this issue by releasing the active ingredient to the skin in a gradual manner. Consequently, the microsponge system has the potential to significantly diminish side effects such as irritation, while maintaining its efficacy. Examples of such formulations include MDS of benzoyl peroxide, which has minimum irritation and good efficacy [12].

2.2.2 Advantages over ointments

Patient compliance is decreased by the ointment's greasy texture. Ointments are not particularly successful as drug delivery vehicles since these compounds require high concentrations of active ingredients to work, which might lead to irritation and sensitization. Bad odors, uncontrollable evaporation of active ingredients and possible drug-vehicle incompatibilities are disadvantages of topical preparations. However, the microsponge system in the epidermis or under the skin's surface prolongs the activity without any irritation or other issues faced by normal ointments [13].

2.2.3 Advantages over liposomes and microencapsulation

MDS offers benefits in comparison with alternative approaches such as liposomes and microencapsulation. Microcapsules often lack the ability to regulate the rate of active substance leakage. Once the wall ruptures, the active ingredients enclosed within the microcapsules are promptly released. The drawbacks associated with liposomes encompass reduced drug loading, less heat stability, complex formulation processes, limited chemical stability, and susceptibility to microbial instability. Conversely, the microsponge system exhibits robustness, enduring temperatures up to 130 °C, and remains stable within a pH range between 1 and 11, distinguishing it from the aforementioned systems. Additionally, its self-sterilizing nature is attributed to an average pore size of 0.25 µm, preventing the access of pathogens while maintaining compatibility with diverse vehicles and substances. Moreover, it retains its free-flowing characteristic and offers a higher drug load capacity ranging between 50 and 60% [14].

2.3 Limitations [11]

1. The process of microsponge formulation includes addition of organic solvents which are called porogens and are found to be harmful to the environment and public safety as some of them may be very combustible.
2. There are instances where the residual monomer traces found in microsponge formulations are poisonous and dangerous to human health.

2.4 Properties of the actives for entrapment into microsponges [15–17]

1. Drugs used for microsponge formulation should ideally possess minimal solubility; failing which, the vehicle may degrade the microsponge before application.
2. Drug must not react with monomers and must not cause the preparation's viscosity to rise while being formulated.
3. It must maintain stability under conditions of polymerization.
4. Should be miscible with minimum quantity of solvent.
5. Drug ought to keep the microsponge's spherical structure intact.
6. In order to eliminate cosmetic defects, the vehicle must be restricted to containing only 10 to 12% w/w of microsponge.

2.5 Microsponge preparation methods

2.5.1 Quasi-emulsion solvent diffusion technique

Microsponges by quasi-emulsion solvent diffusion method is prepared by dissolving the polymer in suitable solvent usually ethanol which forms an inner phase. Subsequently, the drug will be added into the inner phase and the mixture was permitted to dissolve for a duration of 15 min at 35 °C under ultrasonication. In the next step, the outer phase is prepared by dissolving polyvinyl alcohol (PVA) in distilled water at an ambient temperature. Following this, the inner phase is combined with the outer phase at room temperature and the mixture is subjected to continuous stirring for a duration of two hours at 500 rpm. This results in microsponge formation, later the preparation is filtered to isolate microsponges. Subsequently, the resultant product is cleaned and dried at 40 °C in an oven [18–20].

Figure 2 illustrates the quasi-emulsion solvent diffusion preparation process.

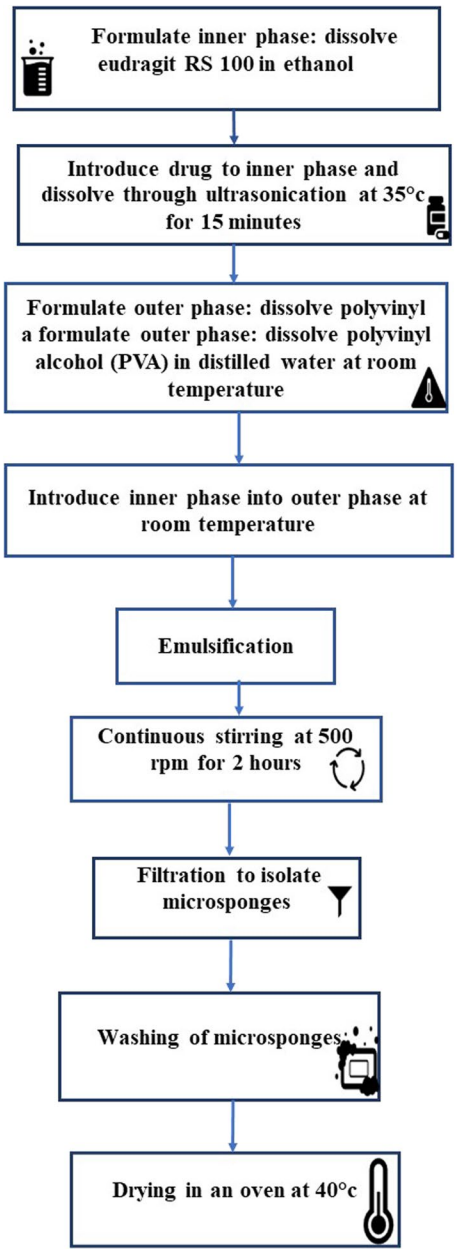

Fig. 2 Quasi-emulsion solvent diffusion preparation method of microsponge

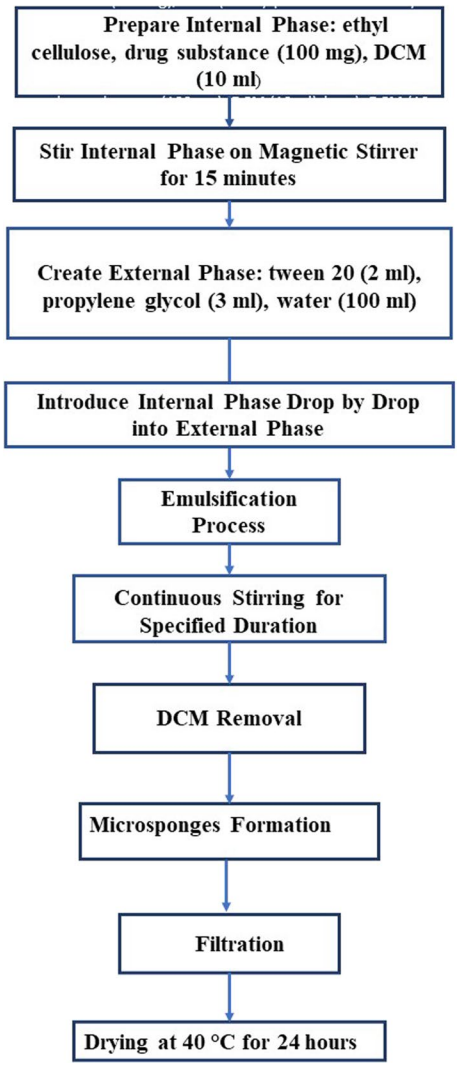

Fig. 3 Quasi-emulsion solvent evaporation preparation method of microsponge

2.5.2 Quasi-emulsion solvent evaporation technique

Quasi-emulsion solvent evaporation technique is one of the very feasible methods to prepare microsponges. Dichloromethane (DCM), ethyl cellulose, and drug were used to create the internal phase and the internal phase is stirred on a magnetic stirrer for 15 min. Subsequently, the internal phase should be cautiously introduced drop by drop into a solution comprising a surfactant and plasticizer in water, which serves as the external phase. Upon the completion of the emulsification process, the mixture is subjected to continuous stirring for about 1 h. This results in the elimination of DCM that leads to the formation of microsponges. The suspension formed is thus filtered to obtain microsponges and is dried for 24 hours at 40 °C [21, 22].

Figure 3 illustrates the preparation process for quasi-emulsion solvent evaporation.

2.5.3 Liquid–liquid suspension polymerization

This technique involves the use of monomers, surfactant, and the active ingredient that are dissolved in a suitable solvent. To create a suspension, the above mixture is added with a suspending agent [23]. Once the suspension containing distinct particles of the desired size is

established, polymerization is triggered either through the addition of a catalyst or by raising the temperature, occasionally supplemented with radiation. The polymerization process yields a reservoir-like configuration featuring surface perforations in specific cases, an inert liquid, which is fully miscible with the monomer but immiscible with water, is employed to establish the pore network throughout the polymerization process. Upon completion of the polymerization, the liquid is extracted, resulting in the formation of microsponges that interpenetrate with previously generated microsponges. These microsponges serve as carriers in topical treatments by including a range of active ingredients, including antifungal agents, rubefacients, anti-acne chemicals, and anti-inflammatory agents. A two-stage process is employed when the medication is vulnerable to the conditions of polymerization. Figure 4 illustrates the preparation of suspension polymerization in a liquid–liquid system using a reaction vessel.

An overview of the many steps involved in creating microsponges is provided below:

Step 1: Selection of monomer and the monomer mixture.
Step 2: Creation of chain monomers after initiating polymerization.
Step 3: Ladders are formed by the cross-linking of chain monomers.
Step 4: Production of spherical particles.
Step 5: Bunches of microspheres are produced when the microspheres agglomerate.
Step 6: Bundles bind together to form microsponges [9, 24].

2.6 Mechanism of drug release

In reaction to one or more external stimuli, microsponges tend to release drug in a predetermined amount. Figure 5 represents the mechanism of drug release via microsponge delivery system.

Solubility The rate at which active agents are discharged from microsponges can be triggered by an aqueous media, such as sweat. The release of the active drug can be influenced by factors such as the solubility of the drug in the external medium, the concentration gradient, or the capacity of the microsponge network to expand [25].

Pressure release When the microsponge system is compressed or squeezed, fluid or the active ingredient is released, resupplying the skin with the amount of entrapped active component. The sponge's release and the microsponges' resilience may also have an impact on the amount released [26, 28].

Temperature change Temperature can be used to trigger the release of drug from microsponges. At ambient temperature, numerous of the encapsulated active ingredients may exhibit excessive viscosity, hindering their direct flow from the microsponges onto the skin.

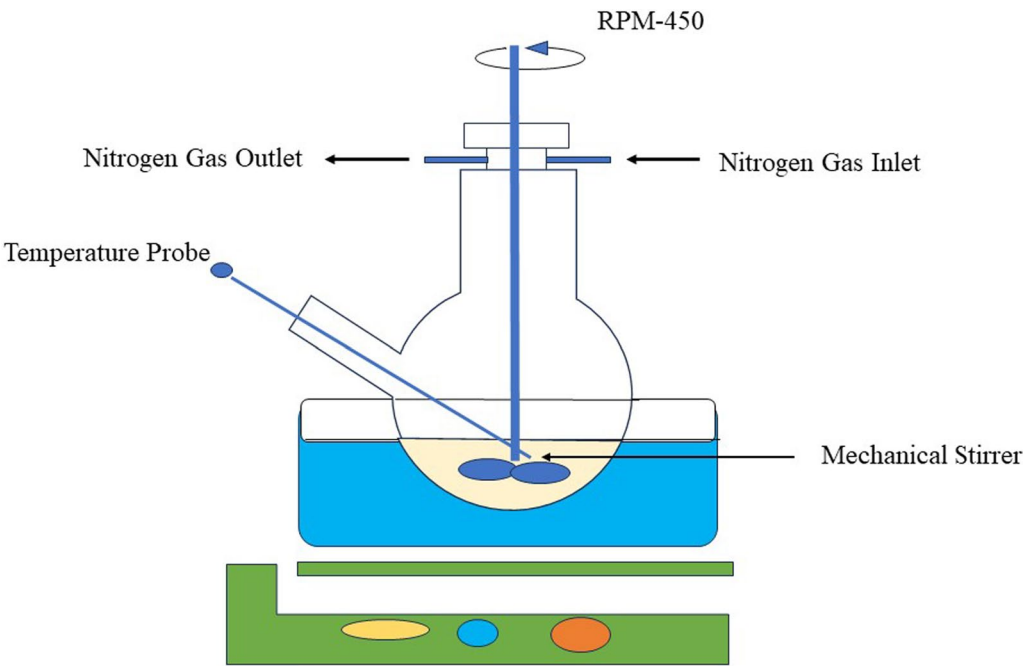

Fig. 4 Preparation of suspension polymerization in a liquid–liquid system using a reaction vessel

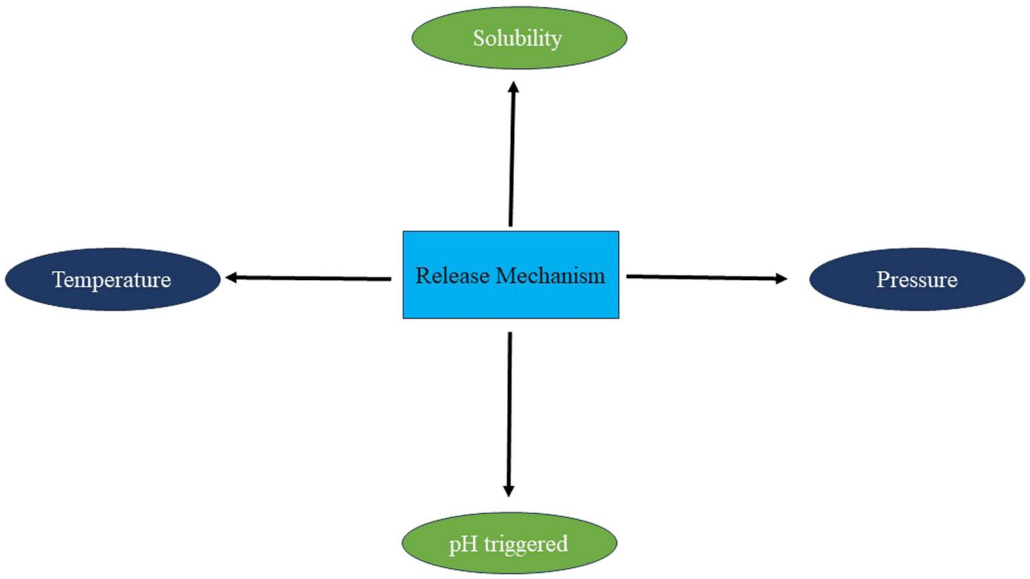

Fig. 5 Mechanism of drug release via microsponge delivery system

Raising the temperature of the skin also raises the flow rate, which raises the release [27].

pH triggered systems By altering the microsponge's covering or coatings, the microsponges can release drug as pH-based released [28].

2.7 Characterization and evaluation of microsponges

2.7.1 Production yield

The practical or production yield of the microsponges can be calculated using the following formula [29, 30].

$$x = \frac{\text{Actual yield}}{\text{Theoretical yield}} \times 100 \quad (1)$$

2.7.2 Particle size analysis

The particle size of the produced microsponges can be analyzed by a particle size analyzer. This instrument enables sample measurement within the range of 0.020 to 2000 mm. The particle size of microsponges can also be determined by an optical microscope [31, 32].

2.7.3 Drug content

To estimate the drug content in microsponges, 100 mg equivalent microsponges are precisely weighed and mixed in 100 milliliters of phosphate buffer solution (PBS) (pH 6.8). The mixture should be filtered through a 0.45-µm membrane filter and the samples are to be analyzed at a suitable wavelength using ultraviolet–visible (UV) spectrophotometer. The drug content can be calculated using the following formula [33].

$$\text{Drug Content}(\%) = \frac{\text{Amount of drug}}{\text{Weighed amount of microsponges}} \times 100 \quad (2)$$

2.7.4 Entrapment efficiency

The solvent extraction method can be used to assess the drug entrapment efficiency. Ten mg of precisely weighed microsponge particles is dissolved in 5 mL of methanol using a magnetic stirrer for a duration of 20 min. 20 mL of freshly prepared phosphate buffer solution (PBS) must be added and heated to a temperature range of 45–50 °C till the formation of a clear solution. Later, methanol is allowed to evaporate, cooled to 25 °C and filtered. Following appropriate dilutions, the drug's concentration is measured using UV spectroscopy. To compute drug encapsulation efficiency (DEE%), the following formula can be used [1, 34].

$$\text{DEE}\% = \frac{\text{Actual drug content of microsponge}}{\text{Theoretical drug content of microsponge}} \times 100 \quad (3)$$

2.7.5 Physical compatibility testing using differential scanning calorimetry (DSC)

This is an essential assessment method for determining any potential physical interactions between the drug and excipients through thermal analysis. Any alteration in the thermogram from that of the pure drug indicates the presence of physical incompatibility. The temperature and enthalpy scale of the DSC are calibrated using indium as the internal standard. Following hermetic

sealing within an aluminum pan, the powder sample of microsponges undergoes a gradual heating process at a rate of 10 °C/min, spanning from 30 to 300 °C, while being subjected to a nitrogen atmosphere flow of 20 ml/min [6, 35].

2.7.6 Scanning electron microscopy (SEM) analysis

The morphology of the microsponges prepared is studied using scanning electron microscopy (SEM) [21, 36].

2.7.7 Chemical compatibility testing using Fourier transform infrared analysis (FTIR)

Using infrared light, the FTIR spectra of the drug-loaded microsponges and the drug alone are examined to search for any chemical interactions. The FTIR analysis is done using a KBr disk standard and scanned within the range of 400 cm^{-1} to 4000 cm^{-1} [5, 21].

2.7.8 X-ray powder diffraction (XRD)

To comprehend the X-ray diffraction (XRD) pattern of both the pure drug and the optimized formulation, the XRD findings for the samples are acquired using an XRD technique fitted with a nickel filter and copper target. The powder sample is applied uniformly and smoothed out onto metal stages with glass bottoms. The XRD pattern of each sample is obtained with a step increment of 0.10 (2θ) and a dwell time of one second between successive measurements, covering a range from 10 to 500 (2θ) [37, 38].

2.7.9 Stability study

In accordance with "International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use" (ICH) recommendations, various conditions must be set to conduct stability experiments on drug-loaded microsponges. The microsponge formulations are stored under conditions of 40 °C ± 2 °C and 75% ± 5% relative humidity for a duration of three months. Three months later, the microsponges are to be subjected to in vitro drug release studies and physical properties evaluation [2, 38].

2.7.10 Polymer/monomer composition

The drug release from microspheres is controlled by polymer composition, drug loading, and microsponge size. Modifying the drug's partition coefficient between the vehicle and the microsponge system allows for direct influence by the polymer composition of the MDS on the rate of entrapped drug release. A valuable approach for investigating drug release from microsponge systems with diverse polymer compositions involves plotting the cumulative percentage of drug release against time [39].

2.7.11 Resiliency

The rheological properties of the formulation can be modified by changing the concentration of cross-linking agent and polymer composition in order to control its flow characteristics and deformation behavior. On the other hand, one should remember that increasing the concentration of cross-linking agents in order to modify viscosity may lead to the reduction or fluctuations in drug release [40, 41].

2.7.12 In vitro drug release

100 mg equivalent weight of microsponges is weighed accurately and the in vitro drug release studies can be done using USP dissolution testing apparatus type II (USP II). An aliquot of microsponge suspension is administered onto a dialysis membrane (pore size 14,000 Da, diameter 17.5 mm, HI-media) to determine the drug release. The dialysis bags must be fastened using paddles and positioned within dissolution vessels filled with buffer solution. Subsequently, the vessels are subjected to stirring at 50 rpm once the temperature is stabilized to 37 ± 1 °C. Evaluation of drug release into the surrounding solution, attributed to membrane diffusion, is conducted by periodically collecting samples from the solution at specified time intervals. UV visible spectrophotometer can be used to quantify the amount of drug released from microsponge formulation [33, 42].

2.8 Different analysis comparing the drugs with various microsponge methods

Listed in Table 1.

2.9 Applications of microsponge systems [10]

Porous polymeric microspheres known as microsponges are primarily utilized in topical applications, although recent advancements have expanded their use to oral administration. They offer a diverse range of possibilities for formulators engaged in the creation of pharmaceutical and cosmetic products. Microsponges are formulated to maximize the efficacy of delivering pharmaceutical active ingredients at minimal doses, concurrently elevating stability, mitigating side effects, and modulating drug release dynamics.

1. Microsponges often demonstrate an erratic release profile of active pharmacological ingredients (API). The emergence of the enclosed API within the microsponges is promptly observed upon rupture of the capsule membrane.
2. There exists a payload efficiency ranging between 50 and 60%.

Table 1 Different analysis comparing the numbers of drugs with microsponge methods [43–60]

Drug	Observation	Method of Preparation	References
Honey	The study demonstrated that the optimal honey-loaded microsponge formulation possessed favorable antimicrobial and antioxidant properties, suggesting its potential in biomedical applications, including wound healing and tissue regeneration, and warranting further exploration in cosmetics and dermatology	Quasi-emulsion solvent diffusion	[43]
Nebivolol	The swift wound healing observed with the combination of nebivolol microsponge and gel represents a significant advancement in diabetic wound therapy	Oil-in-oil emulsion solvent diffusion	[3]
Diclofenac sodium	The enhanced MDS gel, compared to its commercial counterparts, exhibited minimal skin reactions, favoring regulated diclofenac sodium release into the skin	Double emulsification technique	[4]
Mupirocin	The optimized mupirocin microsponge formulation proved skin-stable and non-irritating in the Draize patch test, whereas a microsponge-based emulgel demonstrated prolonged efficacy in a rat model of S. aureus-infected surgical wounds	Emulsion solvent diffusion	[44]
Oxybenzone	The oxybenzone-loaded microsponge showed significant and improved topical retention of oxybenzone over an extended duration, enhancing the UV protection factor and reducing drug toxicity and irritation compared to marketed formulations	Quasi-emulsion solvent diffusion	[45]
Naringenin	In contrast to the basic naringenin gel, the naringenin-loaded microsponge gel exhibited a threefold increase in drug deposition into the skin, offering potential for atopic dermatitis treatment	Quasi-emulsion solvent diffusion	[46]
Erythromycin	Encapsulating erythromycin in a microsponge and administering it topically ensures sustained release for 8 h, thereby preventing gastrointestinal inactivation and associated disturbances	Quasi-emulsion solvent diffusion	[47]
Nystatin	The study compared traditional nystatin gel with nystatin-loaded microsponge gel, revealing significantly greater drug release in the microsponge formulation	Quasi-emulsion solvent diffusion	[37]
Terbinafine hydrochloride	Controlled drug release has been observed to reduce the occurrence of adverse effects, consequently minimizing the need for frequent administration of antifungal gel treatments	Quasi-emulsion solvent diffusion	[48]
Voriconazole	The voriconazole-loaded microsponge gel exhibited extended drug release, suggesting its promise as an alternative therapy for fungal infections, potentially surpassing conventional treatments	Quasi-emulsion solvent diffusion	[30]
5-Fluorouracil	In vivo assessment showed that the microsponge gel formulation of 5-fluorouracil increased drug deposition by 5.5 times compared to the commercial formulation, significantly reducing skin irritation	Quasi-emulsion solvent diffusion	[49]
Indomethacin	Indomethacin-loaded MDS showed enhanced effectiveness as an analgesic and anti-inflammatory medication compared with conventional indomethacin formulations	Quasi-emulsion solvent diffusion	[19]
Eberconazole nitrate	The microsponge gel, carrying the drug, released it in a regulated manner without skin discomfort in rats, and an in vitro study indicated a fourfold increase in drug retention in the stratum corneum layer compared to the commercial eberconazole nitrate cream	Quasi-emulsion solvent diffusion	[50]
Ketoprofen	In comparison with commercial ketoprofen tablets, ketoprofen-loaded MDS showed enhanced bioavailability but exhibited delayed drug release and absorption, thereby improving lag time for drug appearance in plasma and prolonging drug concentration	Quasi-emulsion solvent diffusion	[51]
Paracetamol	The study showed MDS's capacity of MDS to efficiently load high quantities of pharmaceuticals, exhibiting superior loading efficiency compared to alternative microparticle delivery methods	Quasi-emulsion solvent diffusion	[52]
Flurbiprofen	This study found that compression of MDS produces a durable core tablet with prolonged drug release, and employing a pore-plugged approach enables the creation of colon-specific tablets exhibiting zero-order release kinetics	Quasi-emulsion solvent diffusion	[53]
Dicyclomine	Increasing the amount of emulsifying agent correlated with larger microsponge particles, while increasing the drug/polymer ratio led to decreased manufacturing yield, smaller particle size with enhanced drug content, and augmenting polymer content improved drug release control	Quasi-emulsion solvent diffusion	[9]

Table 1 (continued)

Drug	Observation	Method of Preparation	References
Allopurinol	The allopurinol microsponge formulation displayed sustained drug release for 12 h with the requisite entrapment efficiency and buoyancy, and a one-month stability study under accelerated conditions revealed no significant formulation alterations	Quasi-emulsion solvent diffusion	[54]
Famotidine	The famotidine-loaded MDS exhibited a consistent drug -release profile over time	Quasi-emulsion solvent diffusion	[55]
Nitrendipine	Medication characterized by poor water solubility demonstrated a sustained release pattern	Quasi-emulsion solvent diffusion	[56]
Oxiconazole nitrate	The prepared oxiconazole nitrate MDS gel showcased controlled drug release potential, surpassing traditional treatments	Quasi-emulsion solvent diffusion	[6]
Itraconazole	The use of itraconazole in a microsponge drug delivery system has demonstrated controlled release characteristics	Quasi-emulsion solvent diffusion	[7]
Lornoxicam	In vivo comparison showed the superior anti-inflammatory efficacy of microsponge-loaded gel MDS over oral formulations. The beneficial effects extend to rheumatoid arthritis, osteoarthritis, and active lumbar sciatica therapy	Quasi-emulsion solvent diffusion	[57]
Curcumin	Curcumin-loaded microsponge gelatin capsules released 93.2% of curcumin compared with 11.7% from pure curcumin capsules over 8 h, demonstrating superior extended-release capability and greater promise for oral treatment	Quasi-emulsion solvent diffusion	[2]
Etodolac	The creation of the etodolac microsponge altered its release rate, leading to decreased severity of adverse effects	Quasi-emulsion solvent diffusion	[58]
Domperidone	MDS capsules showed a prolonged drug release of 76.38% over 8 h compared to the usual Domstal® formulation, indicating its potential as an alternative therapy for gastroparesis and emesis	Quasi-emulsion solvent diffusion	[59]
Piroxicam	It was found that MDS with a porous, spherical structure could be manufactured, with acceptable physical parameters in the prepared tablets, resulting in a significant enhancement in dissolution rate compared to pure piroxicam tablets	Quasi-emulsion solvent diffusion	[60]

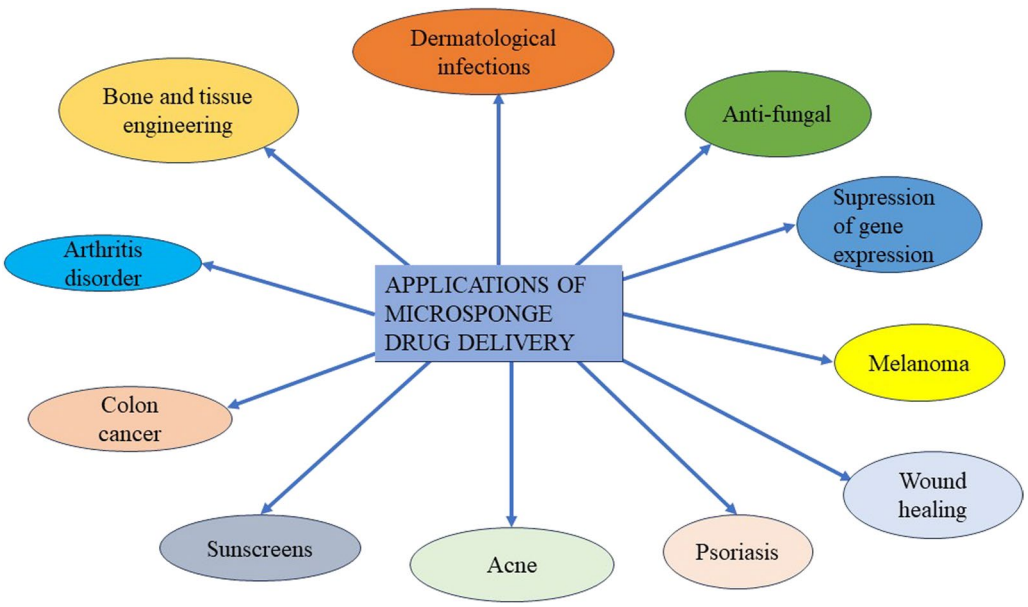

Fig. 6 Summarized uses of microsponges in various formulations

3. Microsponges, being minute spheres, exhibit the capability to absorb skin secretions.
4. User-friendly and economically viable.

2.9.1 Pharmaceutical applications [61]

Summarized uses of microsponges in various formulations are listed in Fig. 6.

2.9.2 Microsponge for topical delivery

Microsponge systems are fabricated using polymers that demonstrate biologically inert properties. Numerous safety evaluations have confirmed that these polymers exhibit characteristics such as non-toxicity, non-mutagenicity, non-irritation, and non-biodegradability. Because of this, the body is unable to break them down or transform them into other chemicals. These systems, albeit minuscule in size, are too big to fit through the stratum corneum when they are added to topical medicines [17]. Figure 7 shows the mechanism of drug release from dermal microsponges.

Fluocinolone acetonide (FA), a corticosteroid agent, is predominantly employed in dermatology to alleviate skin irritations and improve inflammatory conditions [62]. Acne and athletes' foot are treated with benzoyl peroxide (BPO). Common adverse effects include skin irritation, which can be lessened while lowering percutaneous absorption by carefully releasing BPO from the microsponge into the skin [63–65].

A research on development of the mupirocin topical microsponges using emulsion solvent diffusion technique has proved to enhance drug deposition in the skin and achieve sustained release. The impact of formulation and procedural parameters including agitation speed and volume of the internal phase, on the physical attributes of microsponges, are explored using an optimized drug/polymer ratio and a 32-factorial design. The enhanced microsponges are integrated into a base prepared with emulgel. Various aspects were examined, including the in vivo antibacterial effectiveness of formulations containing microcin, in vitro drug release, and ex vivo drug deposition. The medication and polymer molecules did not interact with the spherical, porous prepared

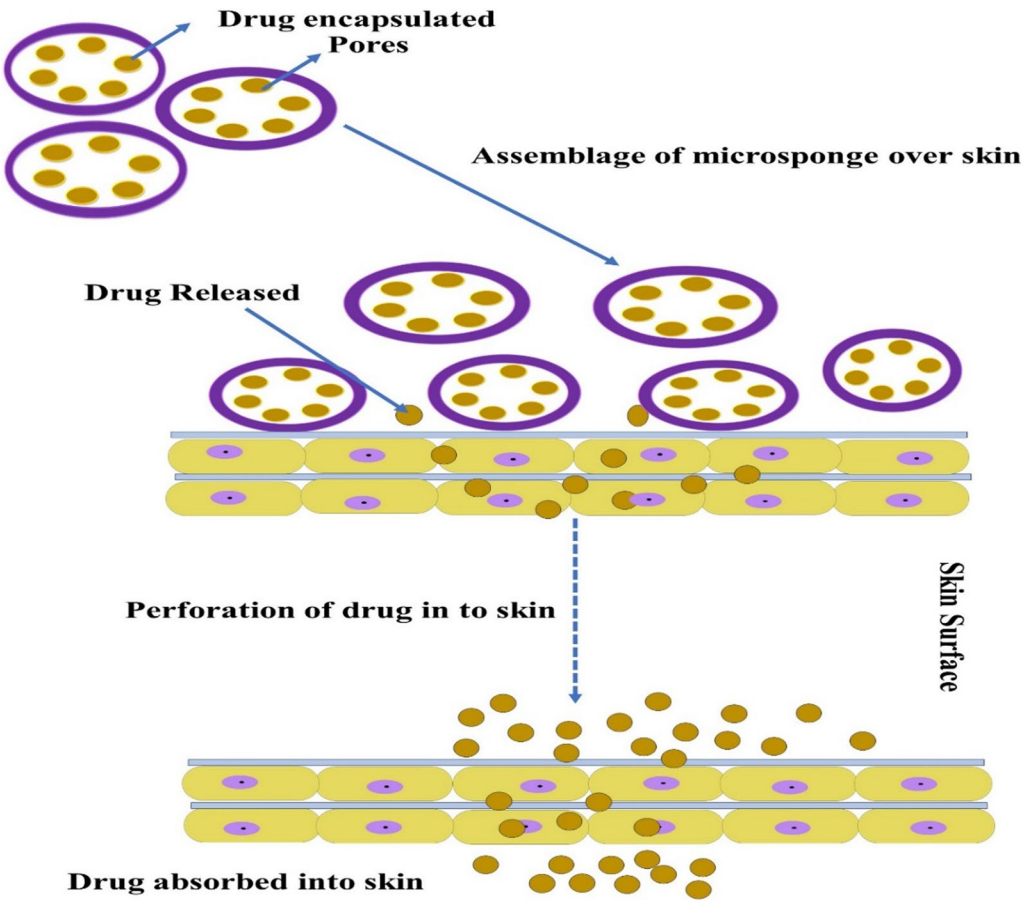

Fig. 7 Mechanisms of drug release from dermal microsponge

microsponges. Preferred physical characteristics were demonstrated by emulgels incorporating microsponges. Drug release assessments conducted with cellulose-based dialysis membranes and drug deposition tests on rat abdominal skin have demonstrated a notable retention of active ingredients within the skin from formulations based on microsponges for up to 24 h. The refined formulations were confirmed to demonstrate stability and skin compatibility test through the Draize patch test. In a murine surgical wound model infected with S. aureus, emulgel formulations containing microsponges demonstrated extended effectiveness. The utilization of mupirocin in topical emulgel formulations showed improved retention and stability on the skin, suggesting the delivery system's enhanced efficacy in treating various skin infections, including primary and secondary conditions such as impetigo, atopic dermatitis, and eczema [66].

*Strong chemotherapeutic medication 5-fluorouracil (5-FU) is used to treat actinic keratosis, a condition caused by chronic sun exposure that results in rigid skin and precancerous cells [67].

2.9.3 Microsponge for oral delivery

Microsponges help to maintain the drugs in a protected environment and release the drug under regulated circumstances to the lower gastrointestinal tract [25]. Through the pores of the microsponge system, weakly water-soluble drugs are captured. It has been shown that when drugs are taken orally, the microsponge system can quicken their rate of solubilization. The medicine is effectively reduced to minute particles due to the extremely small pores, which enhances their surface area and accelerates the solubilization process. An additional benefit is that the microsponge system increases the amount of medication absorbed since it takes a lot longer to transit through the small and large intestine [68]. Figure 8 shows the mechanism of drug release from oral microsponge.

A research showed that ketoprofen microsponges were prepared using quasi-emulsion solvent diffusion method and converted into table dosage forms by direct compression technique. This article proved that the plastic deformation of the microsponge structure enhanced compressibility during the physical combination of the medication and polymer, resulting in the production of mechanically robust tablets [69].

Another research used flurbiprofen (FLB) as drug and prepared microsponges using quasi-emulsion solvent diffusion method. Furthermore, FLB was encapsulated within a commercially available Microsponge® 5640 device utilizing an entrapment technique. The development of colon-specific formulations involved techniques such as compression coating, pore filling, and tabulation of microsponges with a blend of pectin and hydroxy propyl methyl cellulose (HPMC). The sponge-like structure of microsponges, allowed for the plastic deformation of the tablet, results in mechanically robust medication distribution tailored to the colon. In vitro analysis demonstrated a modified release pattern of the medication at the eighth hour, aligning with the time of arrival at the proximal colon, particularly in the presence of enzymes within compression-coated tablet formulations designed for colon-specific delivery. Nevertheless, during the eighth hour, the inclusion of enzymes resulted in a notable augmentation in the release of medication from colon-targeted formulations prepared using pore-plugging microsponges [39].

2.9.4 Microsponges for bone and tissue engineering as substitute for bone

The microsponges were formulated by combining two aqueous dispersions comprising tricalcium phosphate granules, powdered calcium hydroxyapatite, and prepolymerized polymethyl methacrylate powders with liquid methyl methacrylate monomer. The completed composites seemed porous and worked as microsponges. Utilizing the biodegradable properties of the sponge matrix, a collagen sponge sheet encapsulating basic fibroblast growth factor (bFGF) was administered subcutaneously in mice, demonstrating locally angiogenic activity that varied in accordance with dosage form. The bolus injection of bFGF would never have been able to achieve the substantial increase in blood flow that the collagen microsponges containing bFGF produced in the ischemic hind leg of the mouse. Type I collagen acted as a depot for bFGF, which highlights its significance and its therapeutic use [70–72].

2.9.5 Microsponges in oral care cosmetics

By maintaining the release of volatile compounds, microsponge technology offers an exciting prospective application in oral cosmetics, where it can extend the "fresh feel." Tooth pastes and mouth washes can readily absorb microsponges of these volatile substances [73].

2.9.6 Microsponges for biopharmaceutical delivery

Biopharmaceutical delivery and tissue engineering both made use of the microsponge delivery technique. The benefits of synthetic poly(lactic-*co*-glycolic acid) (PLGA-A biodegradable copolymer used in biomedical applications such as drug delivery and tissue engineering) knitted mesh and natural type I collagen were combined to create hybrid 3D scaffolds. For tissue development and cell seeding, collagen microsponges were used, and a mechanically robust PLGA mesh was used as a skeleton. There were three sets of scaffolds: Collagen microsponge could be made in three different ways: sandwich-style (on

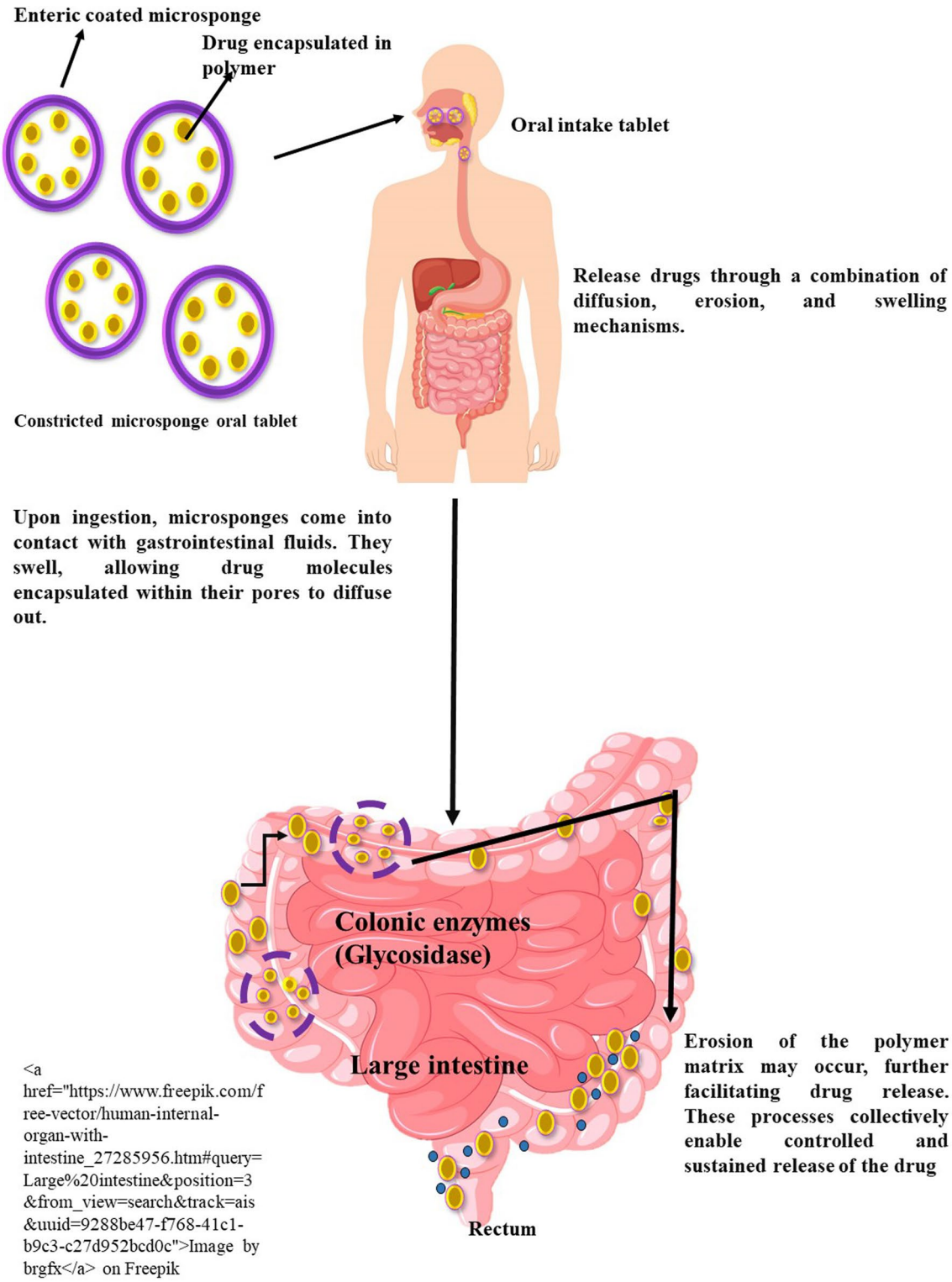

Fig. 8 Mechanisms facilitating the release of drugs from microsponge carriers within an oral drug delivery framework

both sides), semi-thickly (on one side), and thinly (in the crevices between the PLGA mesh) [23].

2.9.7 Vascular wall reconstruction with microsponge technology

A composite construct was created by integrating a collagen microsponge with a biodegradable polymeric scaffold composed of knitted mesh externally reinforced with woven polylactic acid and polyglycolic acid, resulting in the development of a tissue-engineered patch. Tissue-engineered patches devoid of pre-seeding with cells were implanted into the descending aorta of swine (n = 5), the main pulmonary artery of pigs (n = 8), or the right ventricular outflow tract of canines (n = 4). Assessments of the histology and biochemistry were carried after one, two, and six months following the implantation. In each animal, thrombus formation was not observed. Two months post-implantation, histological examination using hematoxylin/eosin staining and immunostaining revealed that all grafts exhibited robust in situ cellularization. The polymerase chain reaction technique, employed to quantify the cell population, detected a significant presence of smooth muscle and endothelial cells two months post-implantation. After six months, the tissue architecture of the patch in the large transplantation model closely resembled that of native tissue, indicating its potential as an innovative surgical material for cardiovascular system restoration [41, 74].

2.10 Different analysis showing the difference between different conventional and advanced delivery systems

2.10.1 Conventional drug delivery systems

Topical administration

- Traditional methods such as eye drops and ointments are frequently employed in ocular drug delivery owing to their widespread acceptance among patients and the convenience they offer for self-application [75].
- The constrained ocular bioavailability poses a substantial obstacle when utilizing conventional drug delivery systems, thereby affecting the efficiency of drug administration. In this, case microsponges offer a better bioavailability minimizing the limitations observed in conventional systems [76].

2.10.2 Advanced drug delivery systems

2.10.2.1 Novel drug delivery systems (NDDS) Novel drug delivery systems (NDDS) have been devised to address the shortcomings associated with conventional formulations, aiming to enhance drug release kinetics, augment drug penetration, and elevate antifungal efficacy.

Research findings indicate that novel drug delivery systems exhibit superior performance compared to conventional formulations in terms of drug release, permeation, and antifungal efficacy, underscoring their advantage in ocular drug delivery [77].

2.10.3 Specific differences

2.10.3.1 Performance Advanced delivery systems, such as microsponges, exhibit enhanced efficacy regarding drug release, permeation, and therapeutic outcomes when compared to conventional systems.

Microsponges are engineered to optimize drug administration through the augmentation of drug bioavailability and the precise targeting of particular tissues or cellular entities, thereby resulting in enhanced therapeutic efficacy [78].

2.10.3.2 Antibacterial delivery Nano-liposomal delivery systems have surfaced as effective transporters for antibacterial agents, providing benefits in encapsulation efficiency, antibacterial mechanisms, and interactions with bioactive compounds [79].

2.10.3.3 Drug loading and release Innovative approaches, such as supercritical CO_2 impregnation, have demonstrated elevated drug loadings and extended drug release durations in contrast to conventional soaking methodologies, underscoring the significance of novel techniques in drug delivery systems [80].

2.11 Marketed products of microsponges

Listed in Table 2.

2.12 Patent information

Patented information is listed in Table 3.

2.13 Recent advancements of Microsponges as drug delivery systems

By altering the process of creating microsponges, several innovations have been created, including nanoferrosponges, nanosponges, and microbeads. β-CD nanosponges by using β-CD (beta-cyclodextrin—is a cyclic oligosaccharide commonly used to improve drug solubility and stability in pharmaceutical formulations) is beneficial for trapping of hydrophilic as well as hydrophobic drugs. Several drugs, including flurbiprofen, dexamethasone, doxorubicin, itraconazole, and serum albumin, were administered orally using these methods. In order to make these nanosponges, the β-CD molecule must be cross-linked using biphenyl carbonate. These nanosponge carrier drug delivery systems are particularly

Table 2 A list of marketed products of microsponges [25, 45, 81–85]

Product name	Manufacturer	Advantages	References
Retinol 15 night cream	Biomedic, sothys	Retinol 15, a night-time therapy cream that utilizes a microsponge system and pure retinol, consistently improves skin discoloration and visibly reduces fine lines and wrinkles	[25, 81, 82]
EpiQuin micro	Skin Medica Inc	Microsponge® encapsulation of retinol and hydroquinone facilitates their gradual release into the skin, potentially mitigating irritation, and enhancing efficacy over time	[25, 81, 83]
Aramis fragrances	Aramis Inc	An effective antiperspirant spray with 24-h longevity, utilizing microsponge technology to gradually disperse fragrance, facilitated by the absorbent properties of the microsponge, controlled by environmental factors, offering a free-flowing powder texture	[81, 83, 85]
Ultra guard	Scott paper	Diaper rash protection for babies' skin using a dimethicone-containing microsponge system	[45, 81, 85]
Retino-A-Micro	Ortho-McNeil Pharmaceutical, Inc	Tretinoin encapsulated within patented porous microspheres at concentrations of 0.1% and 0.04% via microencapsulated drug delivery systems is effective for the topical treatment of acne vulgaris	[45, 81, 82]
Fluorouracil cream, 0.5%	Dermik Laboratories, Inc. Berwyn, PA 19312 USA	A patented porous microsphere (microsponge) composed of poly(methyl methacrylate-*co*-glycol dimethacrylate) and dimethicone effectively encapsulated 0.5% fluorouracil within the Carac cream formulation	[25, 81, 82]
Sports cream RS and XS	Embil Pharmaceutical	Microsponge® Delivery System (MDS) encapsulates topical agents with analgesic, anti-inflammatory, and counterirritant properties, tailored for addressing musculoskeletal disorders	[25, 81, 83]
Salicylic acid exfoliating peel 20 and 30	Biophora	Penetrative BHA Exfoliation Treatment with Microsponge Technology, containing 20% to 30% salicylic acid, effectively reduced fine wrinkles, acne, and discoloration. This treatment is especially suited for robust skin types or when expedited results are desired	[81, 83, 85]
Line eliminator dual retinol facial treatment	Avon	Retinol, or vitamin A, in MDS is a lightweight cream that fights wrinkles instantly and over time	[25, 45, 83]
Retinol cream	Biomedic	Microsponge technology enhances retinol retention and, ensures maximal efficacy while minimizing discomfort, thereby supporting the maintenance of healthy mucous membranes, skin, and hair through topical application	[25, 84, 85]
Oil-balancing lotion	Fountain Cosmetics	A lightweight lotion with microsponges absorbs excess oil, providing a matte finish while the skin response complex treats inflammation and tightness in oily, breakout-prone skin	[81, 83]
Lactrex™ 12% moisturizing cream	SDR Pharmaceuticals, Inc., Andover, NJ,.S.A. 07821	LactrexTM incorporates a 12% concentration of lactic acid as a neutral ammonium salt and ammonium lactate, aiding in skin exfoliation. Glycerin and water are included to moisturize and soften dry, flaky, and cracked skin, enhancing its efficacy	[82, 83, 85]

Table 2 (continued)

Product name	Manufacturer	Advantages	References
Dermalogica oil control lotion	John and Ginger Dermalogica skin care Products	Leveraging moisturizing botanicals, oil-absorbing Microsponge® technology, and an antibacterial skin response complex, this feather-light lotion promotes skin purification, soothing, and hydration	[45, 81, 84]
Micro peel plus	Biomedic	Utilizing Microsponge® technology, the MicroPeel® Plus procedure employs salicylic acid microcrystals to stimulate cellular regeneration, surpassing conventional superficial chemical peels in effectively eliminating dead skin cells without causing harm	[62, 81, 83]
Oil free matte block spf-20	Dermalogica	This sunscreen, utilizing microsponge technology, regulates oil production, provides UV protection, and maintains a matte appearance. Green tea extracts in an oil-free solution reduce inflammation, whereas absorbent microsponges, such as cornstarch and vinyl dimethicone/methicone silica, effectively remove surface oils, enhancing their efficacy	[81, 83, 85]
Glycolic acid moisturizer w/SPF 15	AMCOL Health and Beauty Solutions, Inc. USA	Anti-wrinkle and soothing agent	[82, 85]
NeoBenz®Micro	Intendis Inc. Morristown	It is a keratolytic agent with antibacterial properties	[45, 82]

Table 3 Patent information on microsponges [86–103]

Patent no.	Publication date	Invention	References
CN107469141B	2020-08-18	A medical dressing containing microsponge and preparation method thereof	[86]
JP6688386B2	2020-04-28	Hyaluronic acid microsponge and method for producing the same	[87]
KR101900387B1	2018-09-20	Microsponges having controlled solubility and improved redissolution property	[88]
US7426776B2	2008-09-23	Nonwoven towel with microsponges	[89]
WO2000072827A2	2000-12-07	Porous drug matrices and methods of manufacture thereof	[90]
US5955109A	1999-09-21	Methods and compositions for topical delivery of retinoic acid	[91]
US5679374A	1997-10-21	Anti-acne composition for the simultaneous treatment of the surface layers and deep layers of the skin, and use thereof	[92]
US5725869A	1998-03-10	Microsphere reservoirs for controlled release application	[93]
US5316774A	1994-05-31	Blocked polymeric particles having internal pore networks for delivering active substances to selected environments	[94]
US5292512A	1994-03-08	Cosmetic or pharmaceutical composition containing microspheres of polymers or of fatty substances filled with at least one active product	[95]
US5145675A	1992-09-08	Two-step methods for the preparation of controlled release formulations	[96]
US5100783	1992-03-31	Weighted microsponge for immobilizing bioactive material	[97]
US4997753A	1991-03-05	Weighted collagen microsponge for immobilizing bioactive material	[98]
CA1288370C	1991-09-03	Weighted collagen microsponge	[99]
WO1986005811	1986-09-10	Weighted microsponge for immobilizing bioactive material	[100]
US4863856A	1989-09-05	Weighted collagen microsponge for immobilizing bioactive materials	[101]
US4861714A	1989-08-29	Weighted collagen microsponge for immobilizing bioactive material	[103
US4690825A	1987-09-01	Method for delivering an active ingredient by controlled time release utilizing a novel delivery vehicle which can be prepared by a process utilizing the active ingredient as a porogen	[103]

helpful for incorporating cytotoxic medications into targeted drug delivery for malignant cells**.** Additionally, they noted enhanced ribonucleic acid (RNA) stability and a somewhat successful small interfering RNA(siRNA) encapsulation procedure. This strategy could result in new therapeutic avenues for the delivery of siRNA [26, 104, 105].

2.14 Future prospects

A microsponge is made up of several interconnected voids housed in a non-collapsible framework that can hold a broad range of materials. Today, scientists are focusing more on the delivery of sunscreen, anti-acne, anti-dandruff, and agents that can also be used in the delivery of thermolabile substances like vaccines, proteins, peptides, and deoxyribonucleic acid-based therapeutics. It is also employed in the field of tissue engineering and in controlled drug release systems for medications necessitating extended therapeutic regimens. The outer surface of the sphere is typically porous, allowing substances to flow into and out of it. In these investigations, optimization techniques are used to get the greatest possible result from several formulations. Employs efficient and safe methods for delivering active substance. Moreover, parenteral and pulmonary drug administration using these porous devices has been researched. As microsponge particles find utility as a cell culture medium, their potential extends to stem cell cultivation and cellular regeneration within the organism. Prospective uses of microsponge carrier systems encompass cosmetic applications. Furthermore, the flexibility of the formulation offers advantages across diverse sectors, paving the way for innovative medication delivery systems.

3 Conclusion

Microsponges are a revolutionary drug delivery technology with versatile applications. Ranging in size from 5 to 300 µm, these porous microspheres offer controlled release, stability, and reduced side effects. Synthesized through techniques like quasi-emulsion solvent diffusion, they found use in dermatological and oral drug delivery. Advantages include prolonged drug release, adaptability, and high loading capacity, although challenges exist, such as solvent use. Evaluation methods ensure quality, and various preparation techniques contribute to their versatility. Triggered drug release mechanisms enhance effectiveness. Marketed products and patents highlight their commercial viability and ongoing innovations. Microsponges represent a promising frontier in drug delivery, with potential across pharmaceutical and cosmetic domains.

Abbreviations

MDS	Microsponge delivery system
DCM	Dichloromethane
SEM	Scanning electron microscope
BPO	Benzoyl peroxide
DNA	Deoxyribonucleic acid
HPMC	Hydroxypropyl methylcellulose
XRD	X-ray powder diffraction
DSC	Differential scanning calorimetry
bFGF	Basic fibroblast growth factor
FA	Fluocinolone acetonide
FTIR	Fourier transform infrared analysis
B-CD	Beta-cyclodextrin
PLGA	Poly(lactic-*co*-glycolic acid)
(5-FU)	5-Fluorouracil
PBS	Phosphate-buffered saline
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
RNA	Ribonucleic acid
NDDS	Novel drug delivery systems

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