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MICROSPONGE-BASED DRUG DELIVERY FOR ANTI-INFLAMMATORY THERAPY: FORMULATION STRATEGIES, CHARACTERIZATION, THERAPEUTIC PERFORMANCE AND TRANSLATIONAL CHALLENGES

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ABSTRACT:
Microsponge drug delivery systems have been developed to overcome the limitations of conventional dosage forms through controlled drug release, improved drug stability and bioavailability, reduced adverse effects and improved patient compliance as an advanced porous polymeric carrier platform. These highly porous cross-linked microspheres with a unique three-dimensional structure have generally a diameter between 5-300 μm that allows efficient drug encapsulation and sustained site-specific release of active medicinal components. The review describes the fundamentals of microsponge formulation, major techniques of fabrication, such as quasi-emulsion solvent diffusion, liquid–liquid suspension polymerization, spray drying, and electrospinning, and the influence of polymers, such as Eudragit RS100, Eudragit RL100, ethyl cellulose, chitosan, and poly (lactic-co-glycolic acid) (PLGA) on the formulation performance. Further, it covers the characterisation methodologies, drug release processes and kinetic models of microsponge systems. The therapeutic applications for topical, oral, ophthalmic, intranasal, intravaginal and herbal drug administration have also been highlighted. Among the preparation methods used in the literature reviewed, quasi-emulsion solvent diffusion was the most frequently used method because of its simplicity, reproducibility, high encapsulation efficiency, and suitability for sustained drug release while Eudragit RS100 and ethyl cellulose were consistently identified as the preferred polymers due to their excellent controlled-release characteristics. Most applications are still topical formulations, although recent studies indicate an increasing interest in multifunctional and targeted delivery systems for a variety of therapeutic pathways. Despite significant advances in formulation development and laboratory evaluation, large-scale production, regulatory standardization, long-term stability, clinical validation and commercialization issues still pose barriers to wider pharmaceutical acceptance. Some of the emerging trends that are projected to further enhance the adaptability and clinical applicability of this delivery platform are Quality by Design (QbD), biodegradable polymers, green manufacturing technologies, smart stimulus-responsive systems and nanotechnology-integrated microsponges. In conclusion, microsponge technology is a promising next-generation drug delivery system with great potential to improve therapeutic efficacy, safety and patient compliance and further multidisciplinary research is still needed for its successful translation into clinical and commercial practice.

KEYWORDS: Microsponge drug delivery system; Controlled drug release; Quasi-emulsion solvent diffusion; Eudragit; Polymeric microspheres; Drug delivery; Sustained release; Nanotechnology.

INTRODUCTION

Novel drug delivery systems are gaining importance in pharmaceutical research since the available dosage forms do not provide controlled, site specific and sustained drug delivery. However, the use of conventional topical delivery systems such as creams, ointments and lotions have certain disadvantages such as poor drug retention, greasiness, unpleasant odor, skin irritation, frequent application and poor patient compliance necessitates the development of advanced carrier systems which improve the therapeutic efficacy with little or no adverse effects (1–5). The Microsponge Drug Delivery System (MDDS) is a novel drug delivery technique which offers promising technology for controlled and targeted drug administration (2,4,5). Microsponges are highly cross-linked porous polymeric microspheres with a diameter usually between 5 and 300 μm, having an interconnected network of pores and capable of trapping a wide range of active medicinal compounds (2,4). The porous architecture provides continuous medication release with less systemic absorption, enhanced drug stability and reduced local pain (2,4,5). Microsponge technology was developed (2,3) to overcome the problems associated with the current carrier systems such as liposomes, microcapsules, microspheres and nanoparticles. Microsponges provides improved control of drug release, better thermal, physical and chemical stability (2,3). Microcapsules discharge its contents on rupture . Liposomes are characterized by poor physicochemical stability and limited drug entrapment efficiency . Their high drug loading capacity, compatibility with other pharmaceutical excipients, and ability to protect active ingredients from degradation, have made them even more essential in pharmacy (2–5).

Microsponge technology was originally developed for topical medication delivery, but has subsequently been extended to oral and transdermal drug delivery systems. It has been shown in numerous studies to have the ability to cure dermatological disorders, acne, fungal infections, inflammatory skin diseases, cosmetic formulations and sunscreen preparations (1, 4, 5). In recent years, microsponges filled with herbs have attracted substantial interest because they can provide the therapeutic effects of herbal bioactives with regulated drug release, better stability, increased patient compliance and reduced dose frequency (1,3). Herbal microsponge of Bryophyllum pinnatum and herbal sunscreen formulations demonstrate the utility of this delivery mechanism for improving absorption and therapeutic efficiency (1,3).

In recent years, the study on microsponge has been concentrated on the optimization of the methods for the manufacture such as quasi emulsion solvent diffusion, liquid-liquid suspension polymerization, selection of polymer, particle size, encapsulation efficiency and drug release properties (1-5) . These advancements widen the scope of application of microsponge technology in the area of pharmaceutical and cosmetic making it one of the most promising controlled drug delivery system available today.

However, the commercialization of microsponge-based formulations currently faces various barriers such process standardization, scale-up, reproducibility, regulatory approval and lack of extensive clinical evidence (4,5). The future study should aim to use clinically validated formulations, novel biodegradable polymers, herbal bioactive compounds and multifunctional delivery systems to fully harness the therapeutic potential of the microsponge technology.

1.1 Why Are Anti-inflammatory Drugs Formulated as Microsponges?

Many of the top causes of chronic pain and disability worldwide are inflammatory disorders such as rheumatoid arthritis, osteoarthritis, psoriasis, dermatitis, acne vulgaris and musculoskeletal injuries. NSAIDs and corticosteroids are still the principal therapeutic agents for the management of these disorders, due to their capability to block inflammatory mediators and to relieve pain. However, despite their extensive clinical usage, conventional oral and topical formulations have many pharmacokinetic and therapeutic limitations that affect therapy efficacy and patient safety (6–9).

NSAIDs are linked to systemic side effects, particularly in long-term therapy. As these medications block cyclooxygenase (COX-1 and COX-2) enzymes systemically, long-term therapy is often associated with gastrointestinal irritation, gastric ulceration, bleeding, renal failure, hepatotoxicity, and cardiovascular problems (7,10–13). Moreover, several NSAIDs such as diclofenac, aceclofenac, meloxicam and piroxicam are characterized by poor water solubility (Biopharmaceutics Classification System Class II) with delayed dissolution, variable gastrointestinal absorption and lower oral bioavailability (7,11,14). Extensive first-pass metabolism and relatively short biological half-lives further require repeated doses to maintain therapeutic plasma concentrations, therefore raising the chance of adverse drug reactions and limiting patient compliance (7,10,12).

Extensively developed are many formulations such creams, gels, lotions and ointments for topical therapy of inflammatory disorders to avoid systemic toxicity. The advantage of topical administration is that it avoids first-pass metabolism and reduces systemic drug exposure (8,9,15). However, typical topical formulations also have significant problems. The stratum corneum is a good physiological barrier and prevents the passage of most anti-inflammatory medications into the deeper layers of the skin (8,15,16). In addition, typical gels and creams usually show a quick release of the medication soon after application, leading to an initial burst effect followed by a rapid drop in drug concentration. This generally demands a regular reapplication to maintain therapeutic efficacy (6,8,15,17). Furthermore, drug loss owing to sweating, washing, friction from clothing, and environmental exposure reduces the drug residence time at the site of application (8,16).

A further important disadvantage of typical topical preparations is the local irritation of the skin. High concentrations of free medication which is produced quickly after application especially with continuous treatment may induce erythema, burning sensation, itching, dryness, contact dermatitis and skin sensitization (8,15,18). Moreover, the unstable medications can degrade with exposure to light, oxygen and moisture that leads to decreased shelf-life and lower therapeutic activity (6,19).

Microsponge medication delivery devices have been designed as an efficient approach to bypass these drawbacks. Microsponges are highly porous polymeric microspheres, typically 5–300 μm in diameter, capable of entrapping active medicinal substances inside an interconnected porous matrix (6,19–21). Unlike conventional dosage forms, the drug is entrapped in the polymeric network and slowly released by diffusion and external stimuli such hydration of the skin, temperature, pH or mechanical rubbing (6,20,22). Microsponges provide sustained and regulated drug release, sustain therapeutic concentrations for longer periods and minimize the burst release phenomenon observed in conventional formulations (6,19,21).

Moreover, the porous architecture of microsponges significantly improves the formulation stability by protecting the encapsulated medicines from environmental deterioration due to light, oxidation and hydrolysis (6, 19, 23). In addition, the slow release of the drug considerably lowers local irritation, as only a little amount of drug is present on the skin surface at any given time (6,20,23). This controlled release behavior not only increases therapeutic efficacy, but also decreases the dosing frequency, improves patient compliance and minimizes systemic absorption, thus lowering the risk of gastrointestinal and cardiovascular adverse effects associated with chronic NSAID therapy (6,7,10,21).

Microsponge delivery systems have successfully incorporated several anti-inflammatory drugs, including diclofenac sodium, diclofenac diethylamine, aceclofenac, lornoxicam, meloxicam, ketoprofen, piroxicam, ibuprofen, indomethacin, celecoxib, hydrocortisone, and betamethasone (6,19,21,24). In vitro and in vivo studies have consistently shown that these formulations have improved drug entrapment efficiency, prolonged release profiles, enhanced skin retention,

increased local bioavailability, reduced skin irritation and superior anti-inflammatory activity compared to conventional formulations (6,19–21,24,25).
However, despite these promising discoveries, there are still significant obstacles ahead to transfer the microsponge technology into clinical practice. Most of the published studies are mainly focused on formulation development, physicochemical characterization and evaluation of in vitro drug release, while relatively few studies involve pharmacokinetic studies, long-term stability assessment, toxicity evaluation, large-scale manufacturing, regulatory issues and randomized clinical trials (6,19,21,23).
Previous reviews have covered the synthesis, characterisation and medicinal uses of microsponge. However, a focused and critical synthesis of microsponge-based delivery of anti-inflammatory agents is still limited, particularly in relation to drug–polymer relationships, formulation variables, release mechanisms, skin retention, pharmacodynamic outcomes, translational barriers and clinical relevance.

2. METHODS

2.1 Preparation Methods of Anti-inflammatory Drug-Loaded Microsponges

The preparation technique is an important factor for the particle size, drug entrapment efficiency, release behavior, and therapeutic performance of anti-inflammatory drug-loaded microsponges. While many manufacturing methods have been documented, the most prevalent procedures are quasi-emulsion solvent diffusion (QESD) and liquid–liquid suspension polymerization, as they allow the production of extremely porous microsponges with prolonged drug release and high encapsulation efficiency. (20,22,23)

2.1.1 Advantages of Preparation Methods for Anti-inflammatory Drug Delivery

The microsponge production methods increase the formulation performance of the anti-inflammatory medications such as diclofenac diethylamine, aceclofenac, indomethacin, ketoprofen, celecoxib, curcumin, and piroxicam to a great extent by forming porous polymeric matrices, which ensure the controlled release of the drug. This sustained release results in the maintenance of therapeutic levels of the drug at the site of inflammation, reduces the dose frequency, and limits the gastrointestinal and local side effects of conventional formulations (20,26,27).
One of these approaches, quasi-emulsion solvent diffusion, is able to provide great control over particle size, surface morphology and drug loading by optimisation of stirring speed, polymer concentration and solvent composition. Besides, this process gives good manufacturing yield, repeatability and compatibility with hydrophobic anti-inflammatory medicines and hence is the chosen preparation method in the majority of the published research (28,29). Further, the microsponge formulations generated using these procedures possess good physicochemical stability and prolonged drug release for a protracted period of time to enhance the therapeutic efficiency.

2.1.2 Limitations of Preparation Methods

Conventional microsponge preparation methods have numerous limitations, despite their advantages. Most formulations need volatile organic solvents such as dichloromethane, ethanol or acetone, which raises issues about residual solvent toxicity and environmental safety (26). In polymerization based approaches, residual monomers or initiators can be retained within the polymeric matrix, necessitating significant purification before medicinal use (22). Furthermore, the tuning of the formulation factors such as polymer concentration, drug to polymer ratio, emulsifier concentration and stirring speed is generally time-consuming and directly effects the encapsulation efficiency and drug release behavior. It is also tricky to scale up for industrial manufacture since it is hard to maintain batch-to-batch consistency.

2.2 Comparison of Major Preparation Techniques

2.2.1 Quasi-Emulsion Solvent Diffusion

The quasi-emulsion solvent diffusion method is the most common method for the manufacture of anti-inflammatory drug-loaded microsponges. The studies of aceclofenac, diclofenac, celecoxib, indomethacin and ketoprofen all showed high manufacturing yield, spherical porous particles, outstanding encapsulation efficiency and sustained drug release for 8-12 h. Polymerization processes are not present, decreasing the chance of residual monomer contamination. But the method is less appropriate for highly water soluble medicines because drug diffusion into the exterior aqueous phase can diminish entrapment efficiency.(20, 27,29)

2.2.2 Liquid-Liquid Suspension Polymerization

Liquid-liquid suspension polymerization provides good control of particle size and high yield of manufacturing, hence it is appropriate for industrial scale production. However, prolonged reaction durations and the likelihood of residual monomers are serious limits, especially for pharmaceutical formulations for long-term topical application. (22)

2.2.3 Spray Drying

Spray drying is a viable industrial production method to produce dry microsponge powders in a short time. However, high temperature exposure can lead to the degradation of thermolabile anti-inflammatory medicines or phytoconstituents such as curcumin and other natural bioactive chemicals resulting in lower formulation stability.(30).

2.2.4 Supercritical Fluid Technology

Supercritical fluid technology has appeared as an eco-friendly alternative for the preparation of microsponges with extremely homogeneous shape and low organic solvent usage. However the pharmaceutical application of this technique is now limited due to the need for complex instruments and substantial operational expenditures. (31)

3. POLYMERS USED IN ANTI-INFLAMMATORY DRUG-LOADED MICROSPONGES

Polymers are the major structural components of microsponge systems and are responsible for encapsulation of drugs, porosity, mechanical strength and drug release kinetics. The significance of choosing the right polymer is especially relevant for anti-inflammatory medications, as prolonged drug release results in less frequent dosage, less systemic exposure, and minimized gastrointestinal irritation linked to long-term NSAID use. (20,22).

3.1 Advantages of Polymers

The most widely studied polymers for anti-inflammatory microsponge formulations are synthetic polymers such as Eudragit RS100, Eudragit RSPO, Eudragit S100 and ethyl cellulose, which offer good drug entrapment efficiency, prolonged release and strong mechanical stability. Generally, higher polymer concentrations result in more porous matrices which increase drug diffusion and hence extend anti-inflammatory efficacy and reduce dosage frequency (26,32).

Biodegradable polymers such PLA and PLGA have also gained substantial attention because they degrade into non-toxic metabolites while offering long-term regulated medication delivery. Moreover, natural polymers such as chitosan and cellulose derivatives promote biocompatibility and are being extensively explored for herbal anti-inflammatory compositions.(33)

3.2 Limitations of Polymers

Polymers provide benefits, but formulation issues arise in choosing one. A high concentration of polymer increases viscosity, resulting in an increase in particle size and a decrease in medication loading efficiency. Conversely, a low polymer content might lead to weak microsponges with poor structural integrity. Processing of some polymers additionally involves the use of volatile organic solvents which adds to formulation complexity and potential residual solvent contamination. Besides, hydrophilic polymers are often incompatible with emulsion techniques for creating microspheres because they tend to permeate into the aqueous exterior phase. (6, 20,21,22)

3.3 Commonly Used Polymers in Anti-inflammatory Microsponge Formulations

Eudragit RS100 is the most commonly reported polymer for anti-inflammatory medications among the polymers available due to its outstanding permeability qualities and sustained-release properties. It has been utilized successfully in microsponge formulations of diclofenac, aceclofenac, celecoxib, indomethacin, and ketoprofen. Another commonly used polymer is ethyl cellulose, which gives a sustained release of medication and great compatibility in topical applications. Polyvinyl alcohol (PVA) is often used as an emulsifying and stabilizing agent during preparation, in which the concentration of PVA is important for particle size, production yield, and encapsulation efficiency.(20, 22,26,28,29)

3.4 Effect of Drug-to-Polymer Ratio

One of the most critical parameters in the formulation of anti-inflammatory microspheres is the drug-to-polymer ratio, which affects the performance of the microspheres. Higher polymer content often leads to stronger polymeric walls, which in turn leads to slower drug diffusion and extended anti-inflammatory effect. Several investigations on diclofenac, aceclofenac, celecoxib, and indomethacin have consistently established the effect of polymer ratio on prolonged drug release, encapsulation efficiency, and formulation stability. (26,27,32).

Table 1: Effect of Drug-to-Polymer Ratio

Parameter	Effect on Microsponges
Drug: Polymer ratio	Increases matrix density and diffusion path length, thereby reducing drug release; however, the effect depends on polymer type, porosity, and drug solubility.
Polymer concentration	Polymer concentration → particle formation → porosity → drug release
PVA concentration	Higher concentration → smaller particles; decreased production yield
Stirring rate	Higher speed → smaller particles; improved encapsulation
Dichloromethane volume	Increased volume → more porous structure; higher drug release

Table 2: Characterization Methods (20-36)

Parameter	Technique(s)	Reference Standard
Particle size	Laser diffraction, optical microscopy, DLS	ISO 13320, ISO 22412
Surface morphology	SEM, TEM	ASTM E986, ISO 29301
Pore structure	Mercury intrusion porosimetry	ASTM D4404
Production yield	Gravimetric	—
Drug content / EE	UV-Vis, HPLC	ICH Q2(R2), USP ⟨857⟩
Compatibility	FTIR, DSC, XRD	ASTM E1252, ASTM E967/E968, USP ⟨941⟩
True density	Helium pycnometry	—

Parameter	Technique(s)	Reference Standard
Dissolution / release	USP apparatus, Franz cell	USP ⟨711⟩, FDA SUPAC-SS
Resiliency	Texture analyzer	—
Zeta potential	Electrophoretic light scattering	ISO 13099-2

4. Release Mechanisms and Kinetics 19,23,24,37,38-43

The microsponges release medicines through numerous triggering mechanisms:

1. Pressure-activated: rubbing releases trapped material. The amount released is dependent on sponge qualities.
2. Temperature-dependent: Increased flow of viscous agent at high skin temperature
3. pH responsive: Modified coating enables site-specific release
4. Solubility-activated: Actives are hydrophilic and soluble in aqueous solutions (perspiration)

4.1 Diffusion-controlled release 44,45,46,47

In diffusion-controlled systems, drug molecules diffuse through the interconnected pores and polymeric matrix of the microsponge into the surrounding medium, with the release rate influenced by pore size, porosity, drug concentration gradient, polymer density, and drug–polymer interactions. Increasing polymer concentration may increase the diffusion path length and retard drug release, although the effect is formulation-dependent.

4.2 Dissolution-controlled release 44,45,46,47

In dissolution-controlled release, the drug must first dissolve in the surrounding aqueous medium before diffusing through the porous matrix. Therefore, drug solubility, wettability, particle size, and polymer–drug interactions can determine the overall release rate. This mechanism is particularly relevant to poorly water-soluble drugs incorporated into hydrophobic polymeric systems.

4.3 Polymer relaxation/swelling 44,45,46,47

Hydrophilic or swellable polymers can absorb the release medium, resulting in polymer swelling and chain relaxation, which increases the mobility of drug molecules and facilitates their diffusion through the matrix. The extent of swelling depends on polymer hydrophilicity, cross-linking, pH, and environmental conditions. This mechanism is more relevant to hydrophilic or swellable polymer-based advanced microsponge systems.

4.4 Erosion/degradation-controlled release 44,45,46,47

In biodegradable polymeric systems, drug release may occur through surface erosion, bulk degradation, hydrolysis, or gradual breakdown of the polymer matrix, leading to progressive liberation of the entrapped drug. This mechanism is particularly relevant to biodegradable polymers such as PLGA and PLA and can be modulated by polymer composition, molecular weight, and degradation characteristics.

4.5 Stimulus-responsive release 44,45,46,47

Stimulus-responsive systems are designed to alter drug release in response to specific internal or external stimuli, including pH, temperature, enzymes, redox conditions, light, or other environmental triggers. Such systems may enable spatial and temporal control of drug release and represent an emerging direction for advanced microsponge and porous drug-delivery platforms, particularly for site-specific therapy

Table 3: Release kinetics

Model	Equation	What It Indicates	Typical Application
Zero-order	$Q_t = Q_0 + K_0 t$	Constant release rate independent of concentration	Ideal for sustained delivery; rare in microsponges
First-order	$\log C_t = \log C_0 - \frac{K_1 t}{2.303}$	Release rate proportional to remaining drug	Soluble drugs with initial burst
Higuchi	$Q = K_H \sqrt{t}$	Diffusion-controlled release from insoluble matrix	Most common for microsponges
Korsmeyer-Peppas	$\frac{M_t}{M_\infty} = Kt^n$	Mechanism determination based on diffusional exponent (n)	Used to distinguish Fickian vs. non-Fickian transport
Hixson-Crowell	$W_0^{1/3} - W_t^{1/3} = K_{HC} t$	Erosion-controlled release	Rarely dominant in microsponges

Comparative evidence of microsponge-based delivery systems for anti-inflammatory therapy

Drug / active	Therapeutic application	Polymer/carrier	Preparation method	Dosage form/route	Key formulation findings	In vitro / ex vivo performance	In vivo anti-inflammatory evidence
Lornoxicam	Arthritis / rheumatoid	Cellulosic polymers; ethyl	Quasi-emulsion solvent	Microsponge-loaded	Extensive characteriza	Sustained release;	Optimized formulation

Drug / active	Therapeutic application	Polymer/carrier	Preparation method	Dosage form/route	Key formulation findings	In vitro / ex vivo performance	In vivo anti-inflammatory evidence
48	arthritis	cellulose-based system	diffusion	topical gel; transdermal	tion including SEM, FTIR, DSC, XRD, BET and texture analysis	optimized formulation followed Super Case II transport	produced 72% reduction in inflammation within 4 h in carrageenan-induced rat paw edema model; Transcutol P and microneedle-assisted delivery were used
Aceclofenac 49	Rheumatoid arthritis	Cellulosic polymer	Quasi-emulsion solvent diffusion	Microsponge-loaded Carbopol gel	Optimized microsponges incorporated into Carbopol gel	Sustained-release formulation reported	Anti-inflammatory activity evaluated in an arthritis model
Aceclofenac + Piperine 50	Osteoarthritis	Microsponge system; Carbopol gel	Quasi-emulsion solvent diffusion	Transdermal microsponge gel	Piperine incorporated as a potential bioenhancer	Entrapment efficiency reported in the range of 50.37–80.76%; in vitro drug release values reported as 71.18–91.8% for the investigated formulations	Histopathological evaluation showed reduction in inflammatory cells in the optimized formulation; reported anti-osteoarthritic activity
Curcumin 51	Colonic inflammation / inflammatory bowel disease	Eudragit L100/S100; cyclodextrin inclusion complex	Microsponge preparation with experimental design optimization	Oral colon-targeted microsponge	pH-sensitive Eudragit polymers and PVA pore former; Design Expert used for optimization	Optimized microsponges showed approximately 3-fold increase in drug release rate compared with pure drug	Anti-inflammatory activity evaluated using an acetic acid-induced rat colitis model; recovery of normal colonic morphology was reported
Curcumin 52	Inflammatory bowel disease	Cyclodextrin-based microsponge system	Fabrication and optimization of curcumin-loaded microsponges	Colon-targeted oral microsponge	Designed to improve curcumin solubility, stability and local colonic delivery	Controlled/targeted release system designed to retain drug at the colon	Pharmacodynamic evaluation demonstrated potential anti-inflammatory activity in experimental colitis
Celecoxib 28	Arthritis / inflammatory pain	Microsponge polymeric matrix; formulation-specific	Quasi-emulsion solvent diffusion	Topical microsponge cream	Designed to improve delivery of poorly water-soluble celecoxib	Controlled-release topical formulation reported	Formulation developed for anti-inflammatory/arthritis applications; quantitative in vivo evidence should be extracted from the full paper before inclusion

Drug / active	Therapeutic application	Polymer/carrier	Preparation method	Dosage form/route	Key formulation findings	In vitro / ex vivo performance	In vivo anti-inflammatory evidence
Ketoprofen 48	Arthritis / inflammatory pain	Cellulosic/hydrophilic–hydrophobic polymer system	Microsponge preparation	Topical microsponge formulation	Microsponge system designed for high loading and controlled drug release	Sustained release reported for up to 8 h	Anti-inflammatory efficacy should be cited from the original study if an in vivo model was used

Proposed evolution of microsponge and sponge-based systems for anti-inflammatory drug delivery

Proposed generation	Delivery system	Representative example	Main objective	Current evidence
First generation 48	Conventional microsponge	Lornoxicam-loaded cellulosic microsponge gel	Controlled and sustained topical delivery for arthritis	Preclinical evidence; in vivo anti-inflammatory activity demonstrated
Second generation 49	Drug-loaded microsponge gel	Aceclofenac, celecoxib	Improve local NSAID delivery and provide sustained drug release	Formulation and preclinical evidence
Third generation 50	Microsponge + bioenhancer	Aceclofenac + piperine	Combine controlled delivery with potential bioenhancement	Emerging formulation/preclinical evidence
Fourth generation 52	Site-specific microsponge	Curcumin-loaded colon-targeted microsponge	Localized delivery to the colon for inflammatory bowel disease	Preclinical evidence; pharmacodynamic evaluation in experimental colitis
Fifth generation 53	Nanosponge / advanced sponge hydrogel	Aceclofenac-loaded nanosponge hydrogel	Enhance topical permeation, sustained release and anti-inflammatory activity	Recent preclinical evidence; published in IJAP

Polymers used in microsponge drug delivery

Polymer	Type	Advantages	Limitations	Drug compatibility	Release behavior	Representative anti-inflammatory application
Eudragit RS100 54	Synthetic, pH-independent, water-insoluble acrylic polymer	Controlled drug release; permeability can be modulated by polymer composition	Organic solvent may be required depending on preparation method; non-biodegradable	Suitable for a range of drugs; demonstrated with diclofenac and other anti-inflammatory drugs	Sustained/controlled	Diclofenac sodium microsponge; also topical anti-inflammatory systems
Ethyl cellulose 55	Synthetic, hydrophobic cellulose derivative	Good film-forming properties; useful for sustained-release systems	Non-biodegradable; hydrophobicity may limit release of highly water-soluble drugs	Particularly suitable for many hydrophobic drugs	Sustained/controlled	Naproxen microsponge
PLGA 56	Biodegradable synthetic copolymer	Biodegradable, biocompatible; tunable degradation and drug release	Relatively expensive; more complex processing; acidic degradation products may affect some drugs	Broad compatibility; particularly useful for encapsulation of small molecules and biological agents	Controlled/sustained; degradation- and diffusion-dependent	Investigational anti-inflammatory delivery, including corticosteroids and other anti-inflammatory agents
Chitosan 57	Natural polysaccharide	Biocompatible, biodegradable, mucoadhesive;	pH-dependent solubility; batch-to-batch variability;	Suitable for hydrophilic drugs, proteins, peptides and some natural	Controlled; pH- and matrix-dependent	Herbal/biological anti-inflammatory actives; evidence more commonly reported in

Polymer	Type	Advantages	Limitations	Drug compatibility	Release behavior	Representative anti-inflammatory application
		pH-responsive properties	limited solubility at neutral/alkaline pH	bioactives		chitosan nanoparticles/microparticles than classical microsponges

5. Research Trends 33, 58-61

Microsponge drug delivery system: Recent studies on microsponge drug delivery system indicate a major shift from conventional topical preparations to oral drug delivery applications such as sustained release tablets and capsules due to their excellent compressibility, enhanced bioavailability and extended drug release profile. At the same time, researchers are looking at sophisticated fabrication processes such as electrospinning, spray drying, supercritical fluid technology and three-dimensional (3D) printing to have more control over particle size, porosity, morphology and drug-loading efficiency. Another important trend is the increasing use of biodegradable polymers, especially poly (lactic-co-glycolic acid) (PLGA) and poly (lactic acid) (PLA that allow the development of biocompatible and biodegradable microsponges for oral, parenteral and implantable drug delivery systems with predictable degradation characteristics. In addition, combination medication therapy has received great interest, where microsponges are designed to encapsulate numerous therapeutic agents for synergistic efficacy with decreased dose frequency and side effects . The development of nanosponge technology, specifically cyclodextrin based cross-linked nanosponges, has significantly extended the scope of porous drug carriers via enhancing the solubility, stability, and targeted administration of poorly water-soluble medicines. Furthermore, modern formulation development is increasingly based on the concept of Quality by Design (QbD), using Design of Experiments (DoE), factorial design and response surface methodology to optimize critical formulation parameters, improving product quality and ensuring reproducibility in manufacturing. Taken together, these new characteristics suggest a shift in microsponge technology from conventional topical applications to multifunctional, patient-centric, and precise drug delivery platforms with broader therapeutic prospects.

6. Knowledge Gaps 33,58,59

Significant advancements have been made in microsponge drug delivery devices, although some knowledge gaps persist. Large scale manufacture of microsponges is still a challenge due to batch to batch variability, solvent removal and process improvement. There is also an absence of regulatory advice unique to microsponge formulations leading to a dependence on standards of conventional particle dose forms. Accelerated stability experiments have shown encouraging outcomes but there is limited long term real time stability data. Also, robust in vitro-in vivo correlation (IVIVC) models, especially for topical preparations, are not fully developed. The use of biodegradable polymers such as PLGA and PLA needs additional study in terms of degradation behavior, long-term safety and sustained drug release. Moreover, most of the published research are limited to preclinical models, and there is a dearth of well-designed clinical trials to establish safety and therapeutic efficacy in humans. Finally, the employment of organic solvents such as dichloromethane in the microsponge fabrication process leads to issues regarding environmental and occupational safety, underscoring the necessity for greener and more sustainable manufacturing processes.

7. Clinic Potential 20, 28

The successful loading of several anti-inflammatory drugs in the microsponge drug delivery devices highlights the adaptability of this technology in improving therapeutic outcomes. Microsponges loaded with diclofenac diethylamine have showed sustained drug release, longer topical retention, and increased anti-arthritic efficacy, showing their promise for localized therapy of inflammatory joint conditions (Osmani et al., 2015). Similarly, lornoxicam-loaded cellulosic microsponge gels showed regulated drug release and considerable anti-inflammatory action in arthritic animal models, thus underlining their applicability for long-term care of arthritis (He et al., 2020). Ketoprofen microsponges also revealed altered release properties which allow for sustained therapeutic effects and a decreased administration frequency (Comoglu et al., 2003). Moreover, curcumin-loaded microsponges have been found to improve the stability of the phytoconstituent, offer continuous drug release, and boost skin deposition, thus overcoming the constraints associated with its poor bioavailability (Bhatia and Saini, 2018). Topical microsponge formulations loaded with celecoxib have also recently showed high drug entrapment efficiency, sustained drug release and good therapeutic potential for the treatment of arthritis (Bornare et al., 2024). Overall, these results suggest that microsponge-based formulations can improve localized drug delivery, prolong therapeutic action, reduce systemic drug exposure, and increase anti-inflammatory efficacy, supporting their potential use in the management of chronic inflammatory disorders such as arthritis, psoriasis, dermatitis, and other inflammatory skin diseases.

7.1 Translational challenges 21,22,65-67

The clinical translation of microsponge-based drug delivery devices faces many hurdles, despite the promising preclinical results. It is difficult to scale up the quasi-emulsion solvent diffusion approach because of problems in achieving consistent particle size, porosity and drug loading. Further complicating industrial production is batch-to-batch variability, residual organic solvents and restricted availability of pharmaceutically approved polymers. Sterilization and long-term storage can cause moisture absorption and polymer breakdown that can alter the porosity structure of microsponges and impair stability and drug release. In addition, standardized continuous manufacturing procedures are not yet fully established, resulting in higher production costs. Most crucially, data from controlled

clinical trials are scarce and there are currently no dedicated regulatory guidelines for pharmaceutical products based on microsponge technology, hampering their commercial translation. Thus, further development of formulation optimization, scalable production, clinical validation and regulatory standardization is needed to enable effective commercialization.

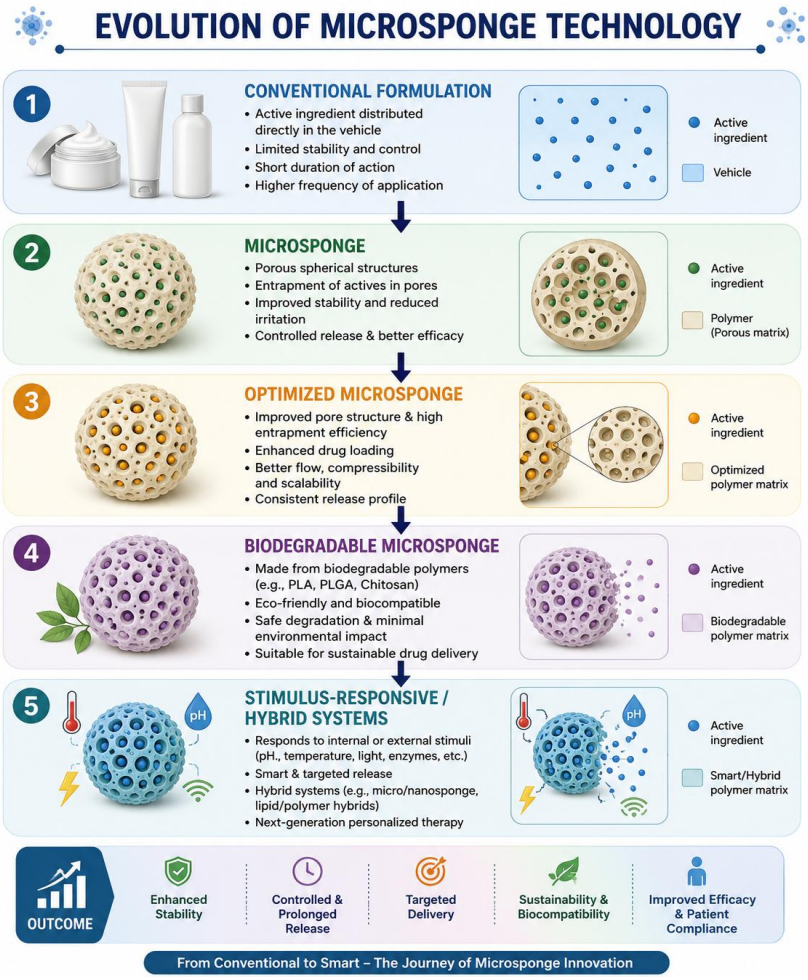
8.Patents and Marketed products 19,21, 67-75

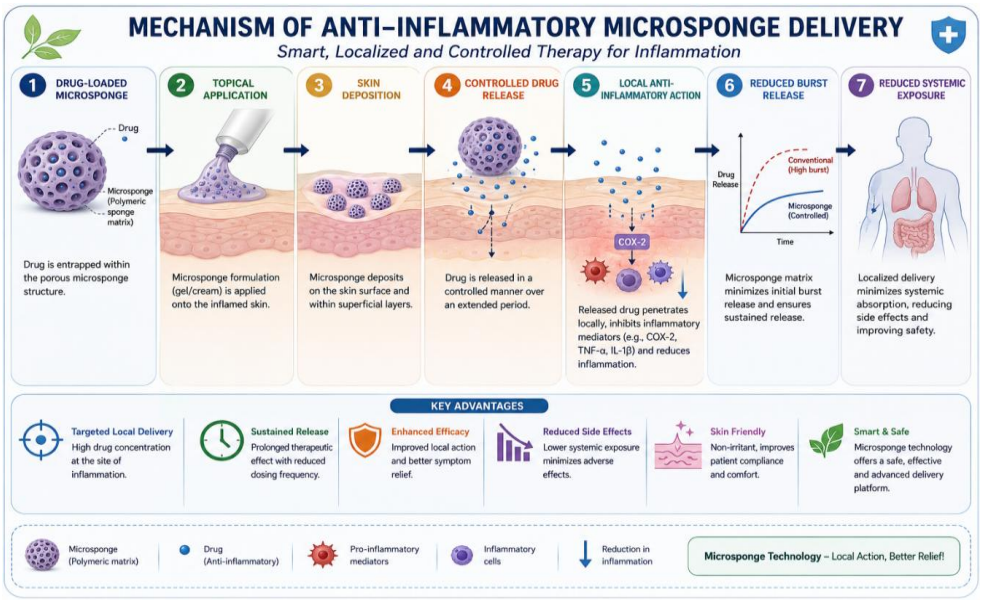
Patents on microsponge based drug delivery systems have increased substantially over the last two decades indicating growing interest in enhancing formulation processes and broadening therapeutic uses. Recent innovations are aimed at the development of new fabrication methods, optimization of porous polymer matrices, controlled and sustained drug release, improved topical retention and development of hybrid delivery systems by combining microsponges with hydrogels, nanofibers and lipid based carriers. These technological advances are designed to enhance drug loading, formulation stability, scalability, and patient compliance, hence increasing the therapeutic utility of microsponge devices. However, in spite of the continual development of patents, only a few medicinal items based on microsponge have been commercialized. In dermatology, the most commercial success has been seen with products such as Retin-A Micro® (tretinoin) for acne vulgaris, Carac® (5-fluorouracil) for actinic keratosis, and benzoyl peroxide microsponge formulations that reduce skin irritation without sacrifice of therapeutic benefit. Moreover, microsponge technology has been extensively used in cosmetic formulations comprising sunscreens, vitamins and scents for regulated topical distribution. Nevertheless, the commercial translation of oral and parenteral microsponge formulations is still restricted, underscoring the need for further clinical validation, scalable production and regulatory approval.

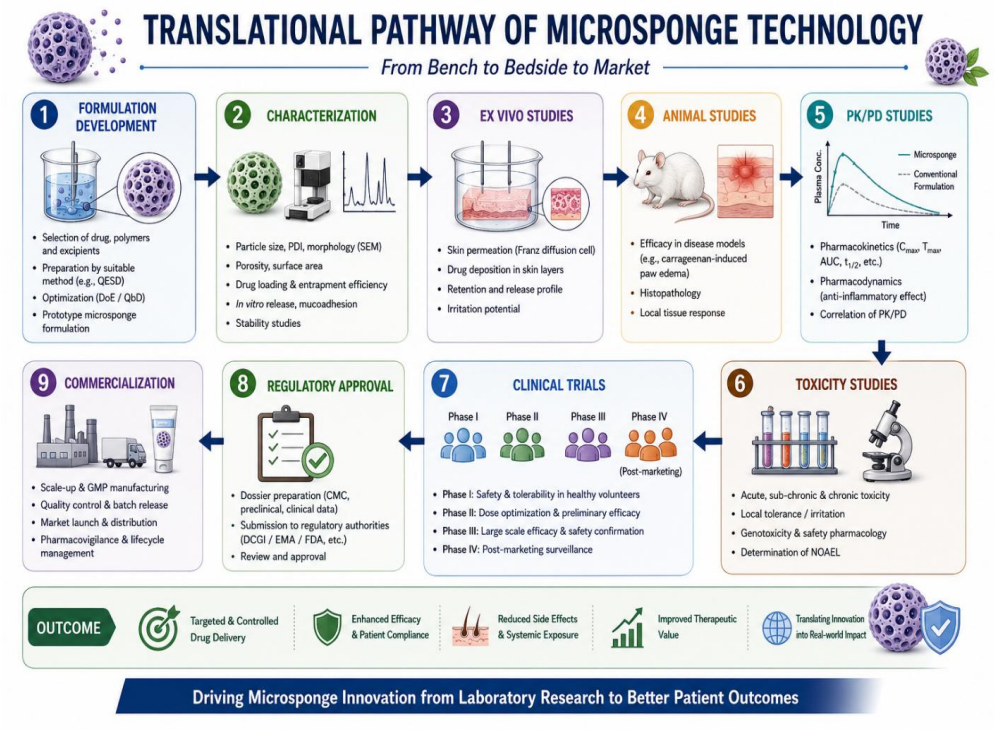
9. Future perspectives

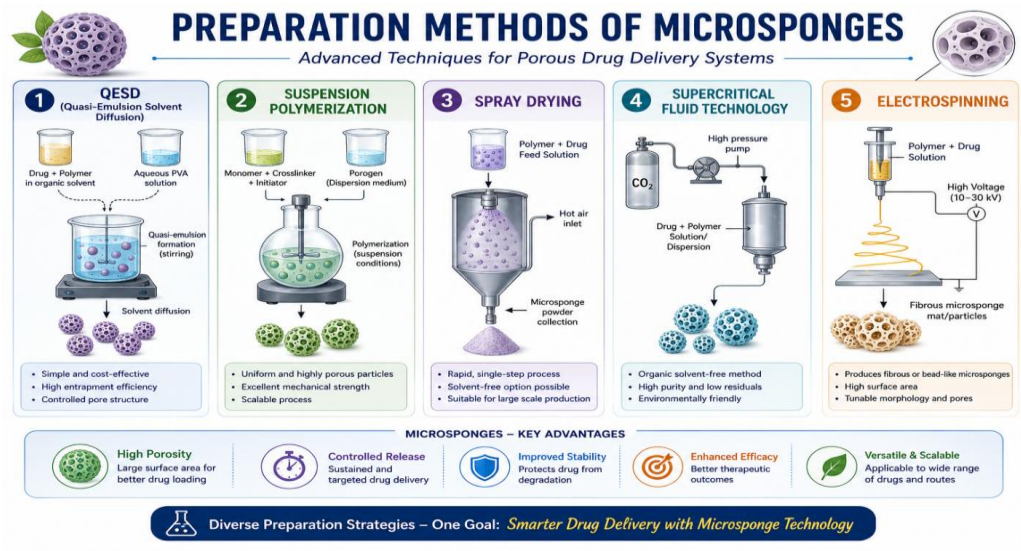
The future promise of microsponge technology in future may be in the intelligent systems that can adjust to change in temperature, pH, enzyme activity or ROS to regulate the controlled release of drugs. This is a more accurate way to deal with inflammatory problems. The formulations can be improved in terms of biocompatibility and efficacy using biodegradable and natural polymers, hybrid composites, and 3D printed materials. In addition, the integration of Artificial Intelligence (AI), Machine Learning (ML), and Quality by Design (QbD) concepts is anticipated to assist in the selection of suitable polymers, formulation optimization, and drug release prediction. The combination of antioxidants, corticosteroids, phytochemicals and nonsteroidal anti-inflammatory medications (NSAIDs) may be more beneficial when administered in combination. For successful clinical translation, extensive multi-center trials, uniform regulations, continuous manufacturing technologies and economically and environmentally viable production processes are required.

Plagiarism Microsponge




MECHANISM OF ANTI–INFLAMMATORY MICROSPONGE DELIVERY
Smart, Localized and Controlled Therapy for Inflammation
1 DRUG-LOADED MICROSPONGE
Drug
Microsponge (Polymeric sponge matrix)
Drug is entrapped within the porous microsponge structure.
2 TOPICAL APPLICATION
Microsponge formulation (gel/cream) is applied onto the inflamed skin.
3 SKIN DEPOSITION
Microsponge deposits on the skin surface and within superficial layers.
4 CONTROLLED DRUG RELEASE
Drug is released in a controlled manner over an extended period.
5 LOCAL ANTI-INFLAMMATORY ACTION
COX-2
Released drug penetrates locally, inhibits inflammatory mediators (e.g., COX-2, TNF-α, IL-1β) and reduces inflammation.
6 REDUCED BURST RELEASE
Drug Release
Conventional (High burst)
Microsponge (Controlled)
Time
Microsponge matrix minimizes initial burst release and ensures sustained release.
7 REDUCED SYSTEMIC EXPOSURE
Localized delivery minimizes systemic absorption, reducing side effects and improving safety.
KEY ADVANTAGES
Targeted Local Delivery
High drug concentration at the site of inflammation.
Sustained Release
Prolonged therapeutic effect with reduced dosing frequency.
Enhanced Efficacy
Improved local action and better symptom relief.
Reduced Side Effects
Lower systemic exposure minimizes adverse effects.
Skin Friendly
Non-irritant, improves patient compliance and comfort.
Smart & Safe
Microsponge technology offers a safe, effective and advanced delivery platform.
Microsponge (Polymeric matrix)
Drug (Anti-inflammatory)
Pro-inflammatory mediators
Inflammatory cells
Reduction in inflammation
Microsponge Technology – Local Action, Better Relief!


TRANSLATIONAL PATHWAY OF MICROSPONGE TECHNOLOGY
From Bench to Bedside to Market
1 FORMULATION DEVELOPMENT
• Selection of drug, polymers and excipients
• Preparation by suitable method (e.g., QESD)
• Optimization (DoE / QbD)
• Prototype microsponge formulation
2 CHARACTERIZATION
• Particle size, PDI, morphology (SEM)
• Porosity, surface area
• Drug loading & entrapment efficiency
• In vitro release, mucoadhesion
• Stability studies
3 EX VIVO STUDIES
• Skin permeation (Franz diffusion cell)
• Drug deposition in skin layers
• Retention and release profile
• Irritation potential
4 ANIMAL STUDIES
• Efficacy in disease models (e.g., carrageenan-induced paw edema)
• Histopathology
• Local tissue response
5 PK/PD STUDIES
Plasma Conc.
Microsponge
Conventional Formulation
Time
• Pharmacokinetics (Cmax, Tmax, AUC, t1/2, etc.)
• Pharmacodynamics (anti-inflammatory effect)
• Correlation of PK/PD
6 TOXICITY STUDIES
• Acute, sub-chronic & chronic toxicity
• Local tolerance / irritation
• Genotoxicity & safety pharmacology
• Determination of NOAEL
7 CLINICAL TRIALS
Phase I
Phase II
Phase III
Phase IV
(Post-marketing)
• Phase I: Safety & tolerability in healthy volunteers
• Phase II: Dose optimization & preliminary efficacy
• Phase III: Large scale efficacy & safety confirmation
• Phase IV: Post-marketing surveillance
8 REGULATORY APPROVAL
• Dossier preparation (CMC, preclinical, clinical data)
• Submission to regulatory authorities (DCGI / EMA / FDA, etc.)
• Review and approval
9 COMMERCIALIZATION
• Scale-up & GMP manufacturing
• Quality control & batch release
• Market launch & distribution
• Pharmacovigilance & lifecycle management
OUTCOME
Targeted & Controlled Drug Delivery
Enhanced Efficacy & Patient Compliance
Reduced Side Effects & Systemic Exposure
Improved Therapeutic Value
Translating Innovation into Real-world Impact
Driving Microsponge Innovation from Laboratory Research to Better Patient Outcomes


PREPARATION METHODS OF MICROSPONGES
Advanced Techniques for Porous Drug Delivery Systems
1 QESD (Quasi-Emulsion Solvent Diffusion)
Drug + Polymer in organic solvent
Aqueous PVA solution
Quasi-emulsion formation (stirring)
Solvent diffusion
• Simple and cost-effective
• High entrapment efficiency
• Controlled pore structure
2 SUSPENSION POLYMERIZATION
Monomer + Crosslinker + Initiator
Porogen (Dispersion medium)
Polymerization (suspension conditions)
• Uniform and highly porous particles
• Excellent mechanical strength
• Scalable process
3 SPRAY DRYING
Polymer + Drug Feed Solution
Hot air inlet
Microsponge powder collection
• Rapid, single-step process
• Solvent-free option possible
• Suitable for large scale production
4 SUPERCRITICAL FLUID TECHNOLOGY
High pressure pump
CO2
Drug + Polymer Solution/ Dispersion
• Organic solvent-free method
• High purity and low residuals
• Environmentally friendly
5 ELECTROSPINNING
Polymer + Drug Solution
High Voltage (10–30 kV)
Fibrous microsponge mat/particles
• Produces fibrous or bead-like microsponges
• High surface area
• Tunable morphology and pores
MICROSPONGES – KEY ADVANTAGES
High Porosity
Large surface area for better drug loading
Controlled Release
Sustained and targeted drug delivery
Improved Stability
Protects drug from degradation
Enhanced Efficacy
Better therapeutic outcomes
Versatile & Scalable
Applicable to wide range of drugs and routes
Diverse Preparation Strategies – One Goal: Smarter Drug Delivery with Microsponge Technology

CONCLUSION

Microsponge technology is an emerging controlled drug delivery system that improves drug stability, sustained release and reduces adverse effects. Quasi-emulsion solvent diffusion with Eudragit or ethyl cellulose is the most commonly used method of preparation because of its simplicity and high encapsulation efficiency. Despite extensive development in topical, oral and targeted delivery, large scale manufacturing, regulatory guidelines and limited clinical data are the major obstacles in commercializing microsponge technology. Future research should focus on scalable manufacturing, standardized guidelines and clinical validation for wider pharmaceutical use of microsponge based drug delivery systems.

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