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Modern Drug Delivery Systems for De-Addiction: Focus on Advanced Formulation Technologies for Smoking Cessation With Emphasis on Microsponge Systems

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ABSTRACT

Addiction is a chronic, relapsing disorder marked by compulsive substance use, neuroadaptation, and a high risk of recurrence. Among the various forms of substance dependence, tobacco addiction remains the most prevalent, contributing substantially to the global burden of cardiovascular, respiratory, and neurological disease. Current pharmacological options for smoking cessation — including nicotine replacement therapy and antidepressants — are limited by poor bioavailability, extensive first-pass metabolism, fluctuating plasma levels, frequent dosing, and inconsistent patient compliance. These shortcomings have driven interest in advanced drug delivery systems capable of controlled, sustained drug release. Transdermal, buccal, nasal, and nanocarrier-based platforms have improved therapeutic outcomes to some extent, but issues of stability, consistency, and long-term efficacy persist. Microsponge drug delivery systems have emerged as a particularly promising alternative because their porous, non-collapsible structure allows high drug loading and controlled, prolonged release. This review examines the systemic effects of addiction and smoking, evaluates the limitations of existing smoking-cessation therapies, and surveys advanced formulation technologies, with particular emphasis on microsponge systems as a platform for improving delivery efficiency, patient compliance, and therapeutic outcomes in de-addiction therapy. Further clinical validation is needed to establish their full potential.

Keywords: Smoking cessation; microsponge drug delivery; controlled release; advanced formulation technologies; de-addiction; drug delivery systems.

INTRODUCTION

Addiction is the compulsive engagement in rewarding stimuli despite adverse consequences, arising from complex interactions between environmental, psychological, and neurobiological factors that create dependency and make quitting difficult [1,2]. De-addiction refers to the process of reducing or eliminating dependence on addictive substances through a combination of pharmacological and behavioural therapies [3]. Substance addiction remains a major global health problem because of its impact on morbidity, mortality, and socioeconomic burden [4], and cigarette smoking in particular continues to be one of the leading preventable causes of death worldwide [5]. Smoking is strongly associated with lung cancer, cardiovascular disease, and chronic obstructive pulmonary disease (COPD), making it a key target for de-addiction therapy [6].

Pharmacotherapy plays a central role in addiction treatment by reducing cravings, relieving withdrawal symptoms, and preventing relapse [7]. However, conventional drug delivery methods are often limited by short half-life, extensive first-pass metabolism, low and variable bioavailability, and the need for frequent dosing [8]. These limitations reduce treatment effectiveness, increase side effects, and lower patient adherence [9]. Because tobacco products are widely available and nicotine is highly addictive [5], smoking remains the most common form of addiction. Nicotine crosses the blood–brain barrier rapidly and stimulates the release of dopamine, reinforcing addictive behaviour [10]; repeated use produces neuroadaptation and dependence that make quitting difficult and increase the risk of relapse [11]. These challenges highlight the need for improved drug-delivery strategies that enhance treatment efficacy and compliance. Advanced formulation technologies address the shortcomings of conventional methods by providing controlled and sustained drug release, increased bioavailability, and reduced dosing frequency [12,13]. This review focuses on novel formulation technologies — particularly microsponge systems — for improving smoking-cessation therapy.

SYSTEMIC EFFECTS OF ADDICTION ON THE HUMAN BODY

Substance misuse affects multiple organ systems, producing serious physiological and psychological consequences. Chronic exposure to addictive drugs alters brain neurotransmitter systems that mediate motivation, reward, and behaviour, with the dopaminergic system particularly affected in the development of dependence [2,10]. Substance misuse can impair memory, cognition, and decision-making, and contributes to psychiatric conditions such as psychosis, depression, and anxiety [14]. Cardiovascular complications — including hypertension, arrhythmia, myocardial infarction, and stroke are common [6], along with damage to the liver and kidneys, impaired immune function, and endocrine disturbance [4]. Addiction is further characterised by psychological dependence: compulsive drug-seeking behaviour and an inability to stop despite negative consequences [1]. Table 1 summarises these systemic effects.

System	Effects of Substance Abuse	Mechanism	Ref.
Central Nervous System	Impaired memory, reduced attention, poor decision-making, cognitive dysfunction	Alters neurotransmitter activity, particularly dopamine signalling, changing brain function and promoting dependence	1,15
Psychological health	Anxiety, depression, mood disturbance, psychotic symptoms	Long-term use disrupts the neurotransmitter balance regulating mood and behaviour	14,15
Cardiovascular System	Elevated blood pressure, arrhythmia, myocardial infarction, stroke	Increased sympathetic activity, vasoconstriction, and oxidative stress strain the cardiovascular system	4,6
Respiratory System	Reduced lung function, chronic airway inflammation, greater infection susceptibility	Toxins damage the respiratory epithelium, impair mucociliary clearance, and promote inflammation	6
Immune System	Decreased immune function, increased infection risk	Interferes with immune cell activity, weakening pathogen defence	16
Endocrine System	Hormonal imbalance and metabolic alteration	Interferes with hormone secretion and endocrine regulation	16
Liver	Injury, inflammation, impaired hepatic function	Oxidative stress from toxic metabolites causes progressive liver damage	16
Kidneys	Decline in renal function and waste elimination	Drug-induced toxicity and reduced filtration capacity	16
Behavioural effects	Persistent craving, compulsive use, difficulty stopping	Repeated reward-pathway stimulation reinforces addictive behaviour	1,15
Overall health	Progressive multi-system deterioration of physical and mental health	Combined neurological, psychological, and systemic effects of chronic abuse	1,4,6,14,15,16

Table 1: General Systemic Effects of Substance Abuse on the Human Body

Tobacco smoke contains more than 7,000 chemicals, many of which are toxic, mutagenic, or carcinogenic, and its effects extend well beyond addiction and the central nervous system to nearly every organ system (Table 2).

System Affected	Health Effects of Smoking	Major Toxic Components	Ref.
General Health	Leading preventable cause of disease and premature death worldwide	Nicotine, tar, carbon monoxide, carcinogens	17,18
Addiction / CNS	Nicotine reaches the brain rapidly, stimulating dopamine release and reinforcing dependence	Nicotine	19
Cardiovascular System	Established risk factor for coronary artery disease, hypertension, peripheral arterial disease, stroke, and aortic aneurysm	Nicotine, carbon monoxide, tar	24–26
Cardiovascular Mechanisms	Increases heart rate and blood pressure, impairs endothelial function, promotes platelet aggregation, inflammation, and atherosclerosis	Nicotine, carbon monoxide	27
Respiratory System	Damages airways and lung tissue; contributes to COPD, worsens asthma, reduces pulmonary function	Tar, carbon monoxide, toxic gases	28,34
Reproductive System	Reduces fertility; increases risk of pregnancy complications, fetal growth restriction, and adverse neonatal outcomes	Nicotine, carbon monoxide	29
Oral Health	Linked to periodontal disease, delayed wound healing, tooth loss, and oral mucosal lesions	Tar, nicotine	29
Cancer Risk	Primary risk factor for lung cancer; also linked to cancers of the oral cavity, larynx, oesophagus, pancreas, and bladder	PAHs, tobacco-specific nitrosamines	30–32
Genetic Damage	Induces DNA mutation and genomic instability, driving abnormal cell proliferation	PAHs, TSNAs	32,35, 43
Immune System	Weakens host defence, increases infection susceptibility, slows wound healing	Toxic smoke constituents	18,21
Passive Smoking	Second-hand smoke raises respiratory and cardiovascular risk, especially in children and pregnant women	Environmental tobacco smoke	22
Socio-economic Impact	Raises healthcare costs, reduces productivity, causes disability and premature mortality	Tobacco smoke toxicants	17,18
Overall, Health Impact	Affects nearly every organ system, reducing quality of life and life expectancy	Multiple toxic constituents	23–31

Table 2: Systemic Effects of Smoking

RATIONALE FOR DE ADDICTION AND SMOKING CESSATION THERAPY

Nicotine addiction is a chronic, relapsing condition driven by dopamine-mediated reward pathways that produce tolerance and dependence [10,37]. Withdrawal symptoms — irritability, anxiety, poor concentration, and cravings — together with psychological stress and environmental cues, commonly trigger relapse and make quitting difficult [10,11,37]. Counselling and behavioural therapy can help, but heavily dependent smokers often require pharmacological support [37,38]. Beyond the addiction itself, tobacco smoke contains nicotine, carcinogens, and carbon monoxide that raise the risk of cancer, respiratory disease, and cardiovascular disease, and non-smokers exposed to second-hand smoke face similar risks [36,39]. Smoking also imposes a substantial economic burden through healthcare costs and lost productivity [36]. Because conventional dosage forms frequently produce uneven drug levels and poor compliance, advanced drug delivery systems capable of sustained, controlled release are essential to improve cessation outcomes and long-term sobriety [8,12].

CURRENT THERAPIES FOR SMOKING CESSATION

Smoking-cessation therapies aim to reduce nicotine dependence, relieve withdrawal symptoms, and prevent relapse. Both pharmacological and non-pharmacological options are available, and medication is generally most effective when combined with behavioural support (Table 3).

No	Drug/Class	Examples	Mechanism of Action	Advantages	Limitations	Ref.
1	Nicotine Replacement Therapy (NRT)	Gum, patch, lozenge, inhaler, nasal spray	Delivers controlled nicotine doses to relieve withdrawal and cravings while avoiding tobacco smoke toxins	Reduces withdrawal symptoms; available in multiple dosage forms	Local irritation; requires consistent adherence; risk of continued nicotine dependence	33
2	Partial Nicotinic Receptor Agonist	Varenicline	Partial agonist at α4β2 nicotinic receptors; blunts nicotine's reinforcing effects	Among the most effective pharmacotherapies; reduces cravings and withdrawal	Nausea, insomnia, vivid dreams, occasional mood disturbance	7,44
3	Plant-based Alkaloid	Cytisine	Partial nicotinic receptor agonist; reduces cravings and withdrawal	Cost-effective with promising efficacy	Limited availability; fewer long-term studies	40
4	Tricyclic Antidepressant	Nortriptyline	Inhibits norepinephrine/serotonin reuptake, easing withdrawal	May help patients unable to use first-line therapies	Sedation, dry mouth, constipation, anticholinergic effects	41
5	Antihypertensive Agent	Clonidine	Suppresses sympathetic activity, reducing withdrawal and cravings	Alternative when standard therapies fail or are contraindicated	Hypotension, dry mouth, dizziness, sedation	11
6	Combination Therapy	NRT + Varenicline	Combines nicotine replacement with partial receptor stimulation for better craving control	May improve long-term abstinence versus monotherapy	Higher cost and adverse-effect incidence	42
7	Oral Tablet	Bupropion HCl	Non-nicotine agent; reduces cravings and delays relapse	Particularly useful in smokers with co-existing depression	Insomnia, dry mouth, headache; rare seizure risk — contraindicated in seizure disorders	37,45

Table 3: Current Pharmacological Therapies for Smoking Cessation

LIMITATIONS OF CURRENT SMOKING CESSATION THERAPIES

Pharmacokinetic limitations: Oral agents such as bupropion undergo extensive hepatic first-pass metabolism, limiting systemic bioavailability, and often produce fluctuating plasma concentrations that reduce therapeutic consistency [46,47].

Poor patient compliance: Treatment courses lasting weeks to months, combined with irritating patches, gums, and frequent dosing schedules, contribute to poor adherence [48,49].

Adverse effects: Bupropion can rarely cause seizures, dry mouth, and insomnia; NRT may cause oral or skin irritation; and varenicline is

associated with nausea and neuropsychiatric symptoms — all of which reduce compliance [47,50].

Inadequate craving control: Existing therapies do not replicate the rapid nicotine surge produced by smoking, leaving patients vulnerable to breakthrough cravings and relapse [46,47].

Limited site-specific delivery: Most conventional systems cannot target specific absorption sites in the gastrointestinal tract, reducing therapeutic efficacy [51].

Dose dumping and plasma fluctuation: Burst release from immediate-release formulations causes peak-trough fluctuations that compromise efficacy and increase the likelihood of adverse effects [49,51].

Incomplete management of psychological dependence: Pharmacotherapy alone does not address the behavioural component of nicotine addiction, leaving many patients psychologically dependent despite treatment [46,47].

NEED FOR ADVANCED DRUG DELIVERY SYSTEMS

Conventional dosage forms are limited by fluctuating drug levels, reduced bioavailability, and poor adherence. Advanced drug delivery systems address these challenges by providing:

- Controlled and sustained drug release
- Reduced dosing frequency
- Improved bioavailability
- Enhanced patient compliance

ADVANCED DRUG DELIVERY SYSTEM FOR SMOKING CESSATION

Several advanced delivery platforms have been developed to overcome the disadvantages of conventional smoking-cessation dosage forms, aiming for controlled release, improved bioavailability, fewer doses, and better compliance.

TRANSDERMAL DRUG DELIVERY

Transdermal systems, particularly nicotine patches, are among the most widely used cessation aids. By delivering drug through the skin directly into systemic circulation, they bypass hepatic first-pass metabolism and maintain steady plasma concentrations over 16–24 hours, reducing withdrawal symptoms and dosing frequency [10,38]. However, skin absorption is slow, onset of action is delayed, and local irritation, erythema, or itching may occur at the application site [10].

BUCCUL AND SUBLINGUAL DRUG DELIVERY

Nicotine gums, lozenges, and sublingual tablets deliver drug across the oral mucosa directly into the bloodstream, providing faster onset than transdermal routes while avoiding first-pass metabolism [37]. Their rapid release makes them useful for controlling acute cravings, and the highly vascularised sublingual mucosa enhances absorption. Limitations include a short duration of action, the need for frequent dosing, and adverse effects such as gastric upset, throat irritation, and, if chewed too quickly, reduced effectiveness [11,37].

NASAL AND PULMONARY DRUG DELIVERY

Nasal and pulmonary systems exploit the large, highly vascularised mucosal surface area of the nose and lungs to achieve rapid systemic absorption, which is useful for managing sudden cravings [11,42]. Nicotine nasal sprays produce plasma concentrations resembling those achieved by smoking, while inhalers mimic the behavioural ritual of smoking. Local irritation nasal burning, coughing, throat discomfort, can reduce acceptability, and variation in administration technique affects delivery consistency [42].

NANOCARRIER BASED DRUG DELIVERY

Nanoparticles, liposomes, and nano emulsions enable targeted delivery, controlled release, and improved drug solubility and stability [12,13]. Nanoparticles protect drugs from degradation and prolong circulation time, while liposomes accommodate both lipophilic and hydrophilic agents and can be engineered for tissue-specific targeting to limit systemic effects. However, complex and costly manufacturing, difficulty scaling to industrial production, stability concerns,

and regulatory hurdles constrain their broader clinical use [13].

Despite these advances, achieving ideal controlled release with minimal side effects, consistent absorption, and strong patient adherence remains difficult. These limitations have prompted growing interest in microsponge drug delivery systems, which may offer controlled release, improved stability, and better compliance for smoking cessation.

ADVANTAGES OF MICROSPONGE SYSTEMS OVER OTHER DELIVERY PLATFORMS

Over conventional formulations: Conventional topical products release active ingredients rapidly, forming a saturated surface layer that the skin absorbs in bulk, often increasing irritation. Microsponges instead release actives slowly over time, reducing side effects such as irritation without compromising efficacy — illustrated by benzoyl peroxide microsponge formulations, which retain efficacy with markedly less irritation than conventional preparations [52].

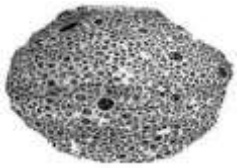
Over ointments: Ointments are often disliked for their oily feel and require a high concentration of active ingredient, increasing the risk of sensitivity, irritation, and odour, along with rapid evaporation and vehicle incompatibility. Microsponge systems avoid these issues while sustaining activity beneath the skin surface [53].

Over liposomes and microencapsulation: Liposomes and microcapsules release their contents abruptly once the enclosing wall or membrane ruptures, and liposomes additionally suffer from low drug capacity, poor thermal stability, and susceptibility to microbial degradation. Microsponges, by contrast, remain stable across a pH range of 1–11 and temperatures up to 130°C, are compatible with a wide range of carriers, and self-sterilise through an average pore size of 0.25 µm that excludes microorganisms, while accommodating a drug payload of 50–60% [54].

MICROSPONGE TECHNOLOGY

The proprietary polymeric Microsponge Delivery System (MDS) consists of porous, non-collapsible microspheres with an extensively interconnected internal pore network that permits controlled release of active substances (Figure 1). A typical 25 µm microsponge may contain up to 25,000 pores, with a total internal pore length equivalent to several metres when uncoiled, and a pore volume of roughly 1 mL/g — sufficient to retain a substantial drug load. Microsponge diameters generally range from 5–300 µm, with surface areas of 20–500 m^2/g and pore volumes of 0.1–0.3 cm^3/g, allowing each particle to carry several times its own weight in active material [58]. Because they can also absorb skin secretions, microsponges help reduce surface oiliness, and their flexible polymer matrix accommodates a wide range of active ingredients, improving efficacy, mildness, and tolerability [59].

Microsponges are uniform, highly cross-linked polymer spheres that are chemically inert, insoluble, and mechanically robust enough to withstand the high shear used during manufacturing. They are designed to deliver active



material efficiently at the lowest effective dose while improving stability, reducing side effects, and modifying the drug-release profile [60].

Fig 1: Microsponges

CHARACTERISTICS OF MICROSPONGE

- Stable across a pH range of 1–11 and at temperatures up to 130°C.
- Compatible with most carriers and chemicals.
- Self-sterilizing the ~0.25 µm average pore size excludes microbial ingress.
- Cost-effective, with a high payload (50–60%) while remaining free-flowing. [70]

METHOD OF PREPARATION

LIQUID- LIQUID SUSPENSION POLYMERIZATION

This method is based on free-radical suspension polymerization, typically carried out in a three-necked flask fitted with a thermometer, condenser, and stirrer. The aqueous phase (surfactant and dispersant) is combined with the drug and monomer(s), and polymerization is initiated by heat, catalyst, or initiator; water-insoluble pore forming diluents may also be added. Cross-linking of monomer chains forms polymer 'ladders' that fold into spherical particles, which aggregate into clusters and bind together to form microsponges. After polymerization, the entrapped liquid diffuses out, leaving the porous structure; a two-step process can be used for drugs sensitive to polymerization conditions. The main drawback is possible entrapment of unreacted monomer residues [72,73].

QUASI- EMULSION SOLVENT DIFFUSION METHOD

An external aqueous phase containing polyvinyl

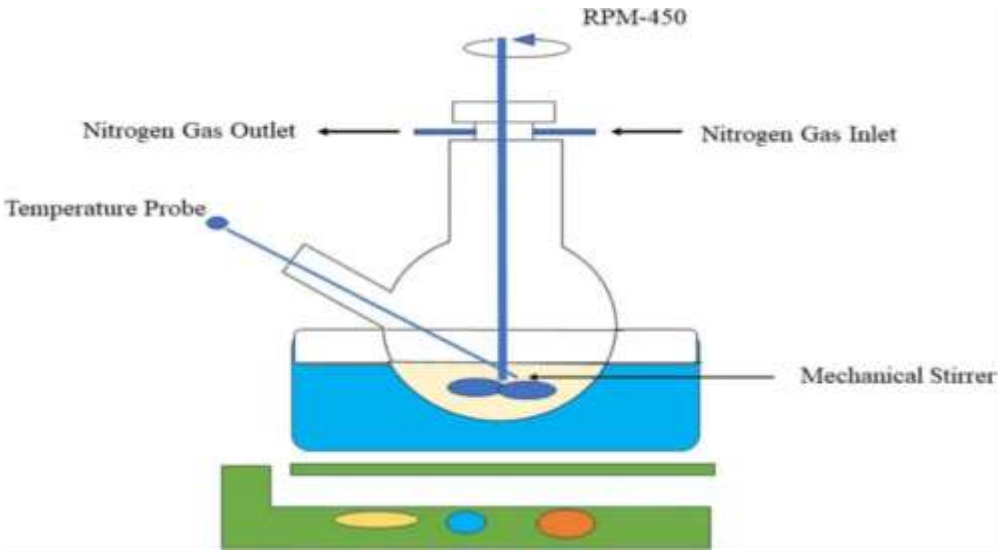


Figure 2: Reaction vessel for microsponge preparation by liquid–liquid suspension polymerization

drug and polymer dissolved in a volatile solvent alcohol (PVA) is mixed with an internal phase of such as ethanol or acetone, forming a quasi-emulsion under vigorous stirring. As solvent evaporates from the resulting globules, insoluble microparticles form; these are filtered and dried in a heated oven. Water and organic solvent counter-diffuse across the droplets during solidification, producing the porous matrix [72,73].

POROGEN ADDITION

A porogen such as sodium bicarbonate or hydrogen peroxide replaces the internal aqueous phase of the w/o/w emulsion. The porogen is dispersed in the polymer solution and redispersed in the PVA-containing aqueous phase; after an initiator is added, the organic solvent is evaporated.

Hydrogen peroxide produces interconnected pores with a uniform spacing of 5–20 µm [72,75].

WATER-IN-OIL-IN-WATER(W/O/W) EMULSION

An internal aqueous phase is dispersed in an organic polymer solution containing an emulsifier such as span, polyethyleneimine, or stearyl amine to form a w/o emulsion, which is then redispersed in an external PVA-containing aqueous phase to create a double emulsion. This method can entrap both water-soluble and water-insoluble drugs, including proteins and other thermolabile compounds; xanthan gum has also been used to stabilise the internal emulsion [73,74].

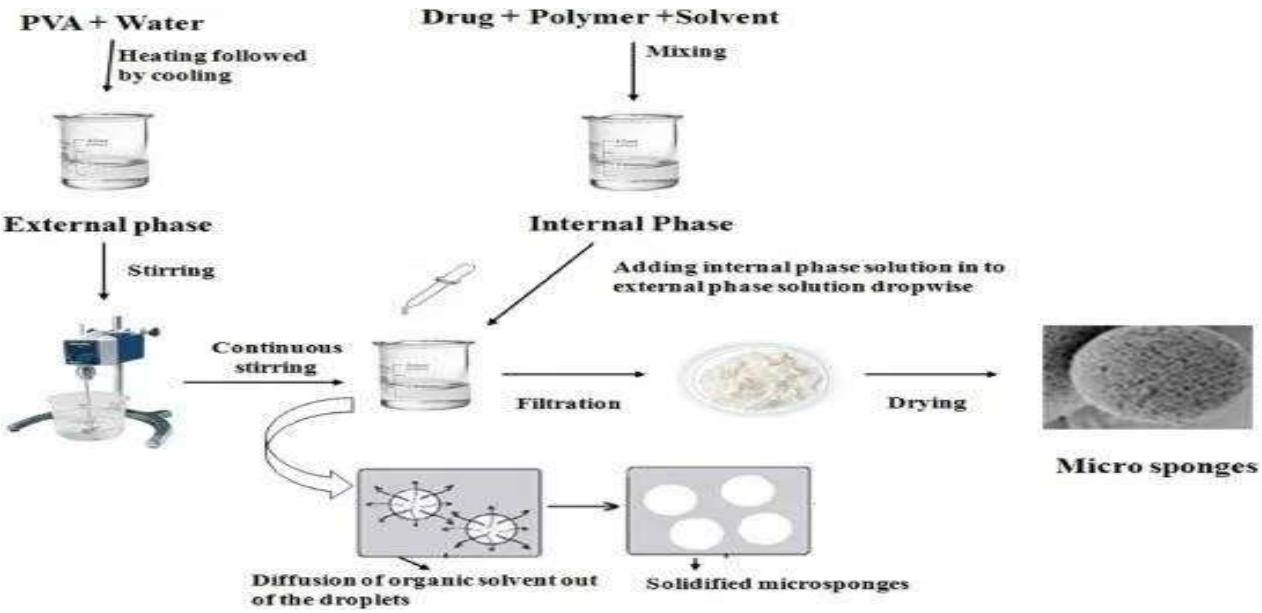


Figure 3: Preparation of microsponges by quasi-emulsion solvent diffusion

Figure 4: Microsponge preparation by porogen addition

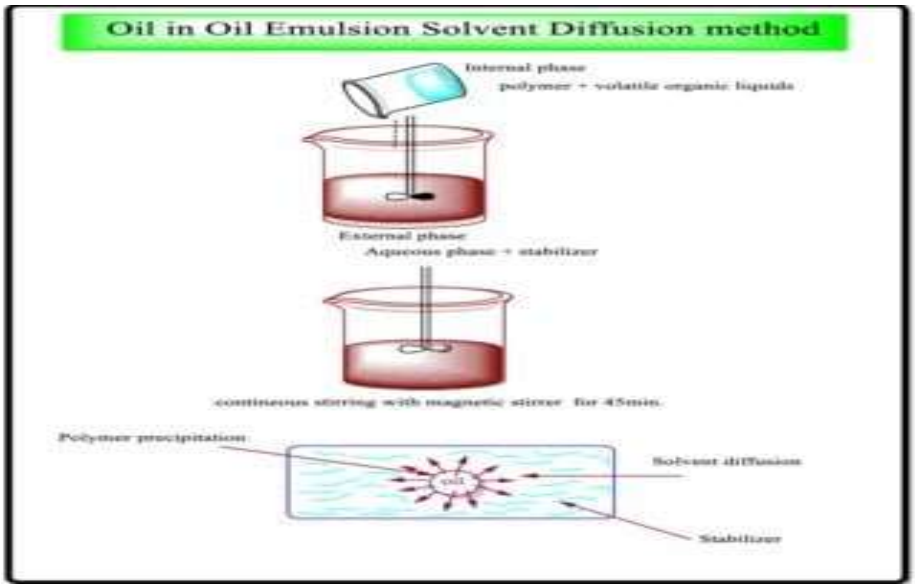


Figure 5: Oil-in-oil emulsion solvent diffusion

OIL-IN-OIL EMULSION SOLVENT DIFFUSION

Unlike the w/o/w method, the internal phase here is a volatile organic solvent, continuously stirred and evaporated at a controlled rate; a mixture of fixed oil (e.g., corn or mineral oil) and dichloromethane is commonly used as the external phase, with polylactide-co-glycolide as the polymer. For example, Eudragit RS-100 microsponges loaded with hydroxyzine HCl were prepared by adding the internal phase dropwise to a liquid-paraffin dispersion medium under stirring. Choice of solvent and external phase depends on the physicochemical properties of the drug and polymer [75].

LYOPHILLIZATION

Gelation-prepared microspheres are incubated in a chitosan hydrochloride solution and then freeze-dried, rapidly removing solvent to create a porous structure. The process is fast and efficient, but rapid solvent loss can shrink or fracture the particles [76].

VIBRATING ORIFICE AEROSAL GENERATOR (VOAG) METHOD

Lipid-bilayer mesoporous silica particles are synthesised via evaporation-induced surfactant templating in aerosol microdroplets generated by a VOAG. A tetraethyl orthosilicate stock solution, prepared by refluxing with ethanol, water, and dilute hydrochloric acid, is diluted in a surfactant-containing solvent and atomised into monodisperse droplets, which are then encapsulated by liposomes. The resulting particles are suited to targeted drug delivery [75,76].

ULTRASOUND ASSISTED PRODUCTION

This technique modifies liquid–liquid suspension polymerization to produce nano sponges using diphenyl carbonate as a cross-linker and β-cyclodextrin as the monomer. Particle size is controlled through heating and sonication; after cooling, the product is ground into coarse particles and washed with ethanol and distilled water. The resulting cross-linked β-cyclodextrin microparticles are porous and serve as effective drug carriers, though residual crosslinking agent may remain trapped [76,77].

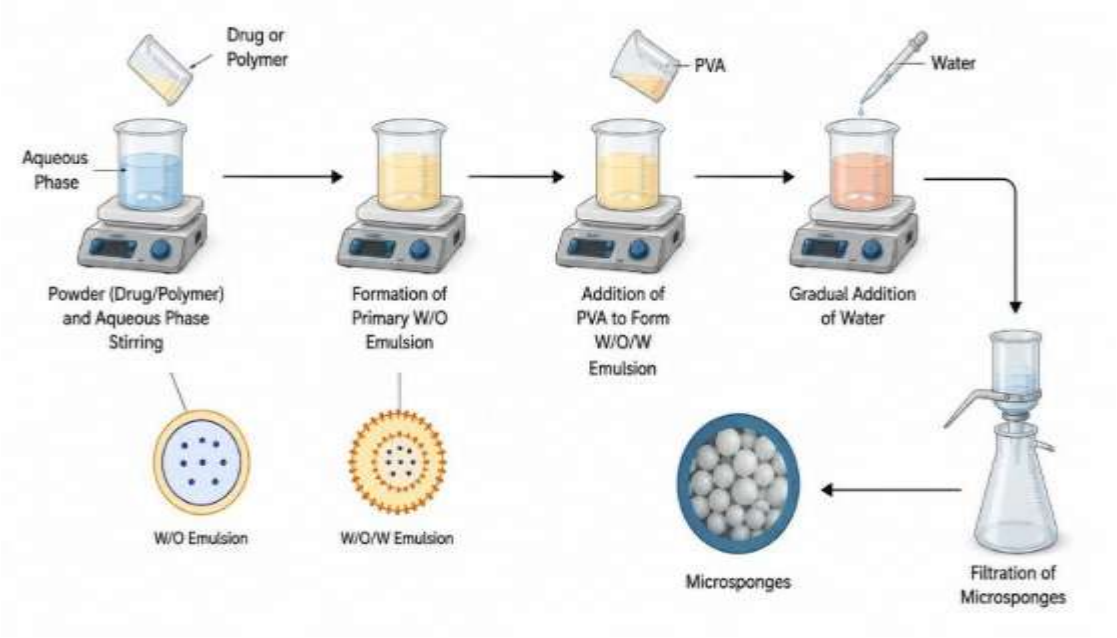


Figure 6: Ultrasound-assisted production of microsponges

DRUG RELEASE MECHANISM OF MICROSPONGES

The active ingredient loaded into microsponges is not enclosed by a continuous membrane, allowing it to move freely between the particle and the surrounding vehicle until equilibrium is reached. Upon application, skin absorption depletes the active ingredient from the vehicle, disturbing this equilibrium and triggering diffusion of drug from the microsponge into the vehicle and then into the skin. Once the vehicle is exhausted, residual microsponge particles on the stratum corneum continue to release active ingredient over time. Because this mechanism depends on the vehicle having low solubilising power for the active, formulation of microsponge systems departs from the conventional approach of maximising active solubility in the vehicle used for standard topical products [73,74].

FACTORS AFFECTING DRUG RELEASE FROM MICROSPONGES

Solubility: Release into aqueous media such as sweat depends on the drug's external-phase solubility, the concentration gradient, and the extent of the microsponge network [78].

Pressure: Compression or rubbing of the microsponge releases entrapped actives onto the skin; the amount released depends on the sponge's resilience and capacity [58,80].

Temperature: Release is temperature-dependent, since many entrapped actives are too viscous to flow from the microsponge at room temperature; skin warmth increases flow and release [79].

pH: Coating modifications allow microsponges to be designed for pH-responsive drug release [79].

EVALUATION OF MICROSPONGES [81,82]

Particle size: Determined by laser diffractometry or similar techniques; particles of 10–25 µm are preferred for topical use, as particles above 30 µm can feel gritty. Drug release is assessed by plotting cumulative release against time for different particle-size fractions **Morphology and surface topography:** Gold–palladium-coated microsponges are examined by scanning electron microscopy (SEM) to assess surface structure and the ultrastructure of fractured particles (Figure 7).

Loading efficiency and production yield: Loading efficiency (%) is calculated as actual

drug content divided by theoretical drug content, multiplied by 100. Production yield (%) is calculated as the practical mass of microsponges divided by the theoretical mass, multiplied by 100.

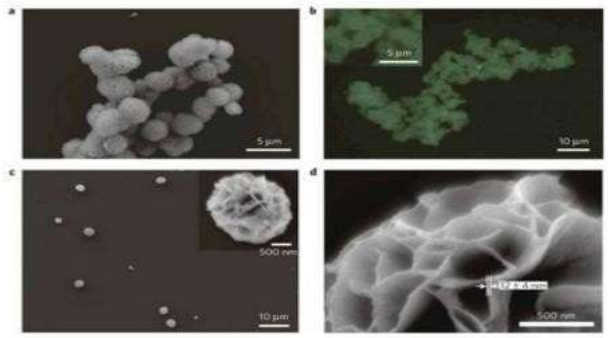


Fig 1: SEM imeges of Microsponges

Porous structure: Mercury intrusion porosimetry characterises pore volume, diameter, surface area, bulk and apparent density, and percent porosity — parameters that influence both drug-retention capacity and release duration.

Dissolution testing: Performed using a modified 5 µm stainless-steel mesh basket with USP XXIII dissolution apparatus, in a medium selected to maintain sink conditions appropriate to the drug's solubility.

Real density: Measured by helium ultra-pycnometry, averaged over multiple readings.

Additional in vitro characterisation: FTIR is used to assess drug–polymer compatibility [84]; DSC evaluates the thermal behaviour of the drug, polymer, and their physical mixture, typically heated from 40–430°C at 20°C/min [84]; and accelerated stability studies at 4±1°C, 25±2°C, and 37±5°C (75% relative humidity) assess physicochemical, microbiological, and therapeutic stability over storage [85,86]. Data are typically analysed by one-way ANOVA and Student's t-test, with $p<0.05$ considered significant [84].

Safety evaluation: Anti-inflammatory activity is commonly assessed using a croton-oil-induced mouse ear-oedema model, comparing ear thickness before and 6 hours after treatment with free versus microsponge-entrapped drug [86]. Primary eye irritation is assessed in rabbits at 1-, 24-, 48-, and 72-hours post-instillation, with observation extended up to 21 days where needed to assess reversibility [86]. Further safety characterisation includes oral toxicity studies in rats, bacterial mutagenicity testing, and thin-layer chromatography (TLC)-based compatibility studies.

APPLICATIONS OF MICROSPONGE DRUG DELIVERY SYSTEM

Figure 8: Summarised uses of microsponges in various formulations

Application Area	Drug	Polymer / Method	Use	Outcome
Oral	Ibuprofen	Eudragit RS acrylic polymer	Controlled oral delivery	Sustained release via regulated intraparticle density
Oral	Ketoprofen	Quasi-emulsion solvent diffusion, Eudragit RS100	Controlled oral delivery	Direct-compression sustained-release tablets
Oral	Prednisolone	Quasi-emulsion solvent diffusion, Eudragit RS100	Colon-specific release	Reduced upper-GI release; fewer systemic effects
Oral	5-Fluorouracil	Oil-in-oil emulsion solvent diffusion, Eudragit RS100	Sustained colon-cancer delivery	>95% entrapment with sustained release
Topical	Various actives	Polymer-based porous microsponge gel	Sustained topical release	High loading with prolonged, controlled release
Bone/Tissue Engineering	PMMA composite	PMMA, hydroxyapatite, tricalcium phosphate	Bone substitute material	Scaffold support promoting tissue regeneration
Intranasal	Sumatriptan	Ethyl cellulose; quasi-emulsion solvent diffusion	Migraine treatment	Improved nasal residence time and bioavailability
Intranasal	Insulin	Eudragit RS100; solvent diffusion	Diabetes management	Enhanced nasal absorption, prolonged effect
Inhalational	Salbutamol	PLGA; emulsion solvent evaporation	Asthma / COPD treatment	Controlled pulmonary release, reduced dosing
Inhalational	Budesonide	Ethyl cellulose; spray drying	Respiratory anti-inflammatory	Improved lung deposition, less systemic exposure
Intravaginal	Clotrimazole	Eudragit RS100; quasi-emulsion solvent diffusion	Vaginal fungal infection	Prolonged local retention, less irritation
Intravaginal	Metronidazole	Ethyl cellulose; solvent evaporation	Bacterial vaginosis	Sustained release, improved compliance

Table 4: Applications of Microsponge Drug Delivery System [55,56,61,63–67,86]

ADVANTAGES OF MICROSPONGE DRUG DELIVERY SYSTEM [68,69]

- Provides continuous, sustained activity for up to 12 hours
- Greater patient compliance due to higher tolerance and less discomfort
- May enhance overall therapeutic efficacy
- Superior chemical, physical, and thermal stability
- Non-toxic, non-allergenic, non-mutagenic, and non-irritating
- Can incorporate immiscible ingredients
- Greater flexibility in formulation
- Higher payload and easier formulation compared with liposomes and microencapsulation

FORMULATION NOTES AND DOSAGE FORMS

Microsponge-based products can be developed as lotions, gels, creams, tablets, implants, injections, and other formats. Selected examples include benzoyl-peroxide lotions for acne [89]; diclofenac sodium, fluconazole, hydroxyzine HCl, and glabridin/benzoyl-peroxide gels for inflammation, dermatitis, and pigmentation disorders [90–93]; fluconazole and miconazole nitrate creams for fungal infections and acne [94,56]; and tablets containing terbinafine HCl, glabridin, benzoyl peroxide, flurbiprofen, dicyclomine, meloxicam, and paracetamol for conditions ranging from musculoskeletal pain to colon-targeted delivery [88,73,95–99]. Implant and injectable formats have also been explored, including PLGA implants for skin tissue engineering [100] and basic fibroblast growth factor injections [101], alongside other benzoyl peroxide, mefenamic acid, and ibuprofen-based systems [102–104].

COMMERCIAL PRODUCTS BASED ON MICROSPONGE TECHNOLOGY

No.	Product Name	Drug Used	Pharmaceutical Use	Manufacturer
1	Glycolic Acid Moisturizer w/SPF 15	Glycolic acid	Anti-wrinkle, soothing	AMCOL Health & Beauty Solutions, US
2	Retin-A Micro	Tretinoin	Acne vulgaris	Ortho-McNeil Pharmaceutical, US
3	Carac Cream 0.5%	Fluorouracil	Actinic keratoses	Dermik Laboratories, US
4	Retinol 15 Night Cream	Retinol	Anti-wrinkle	Sothys, Paris, France
5	EpiQuin Micro	Hydroquinone & retinol	Hyperpigmentation	SkinMedica Inc., US
6	Micro Peel Plus	Salicylic acid	Acne (peeling)	Biomedic, UK
7	Oil-Free Matte Block SPF 20	Zinc gluconate	Sunscreen	Dermalogica, UK
8	Lactrex 12% Moisturizing Cream	Ammonium lactate	Moisturizer	SDR Pharmaceuticals, US
9	Dermalogica Oil Control Cream	Salicylic acid	Skin protectant	Dermalogica Skin Care, UK
10	Ultra Guard	Dimethicone	Protects baby skin	Scott Paper Company, US
11	NeoBenz Micro	Benzoyl peroxide	Anti-acne	SkinMedica Inc., US**(55,98,105)**

Table 5: Commercial Products Based on Microsponge Technology

PATENTS FILED RELATED TO MICROSPONGES

Patent No.	Inventors	Year
US4690825	Won, Richard	1987
US4863856	Dean RC Jr et al.	1989
US5292512	Schaefer et al.	1989
US5135740	Katz et al.	1992
US5679374	Fanchon, Chantal et al.	1994
US5316774	Eury, Robert P et al.	1994
US5725869	Lo, Ray J. R.	1996
US6395300	Straub et al.	1999
US6211250	Tomlinson et al.	2001
US20030232091	Shefer et al.	2002
US20040247632	Cattaneo, Maurizio	2004
US20050271702	Wright, Steven G et al.	2005***(106)***

Table 6: Patents Filed Related to Microsponges

CASE STUDIES: MICROSPONGE DELIVERY IN PRACTICE

CASE 1: KETOROLAC (CHRONIC PAIN WITH GI RISK)

Presentation	A 52-year-old male with chronic lower-back pain on long-term NSAID therapy developed epigastric discomfort and mild gastritis, confirmed by endoscopy, prompting a need for a safer delivery strategy.
Method	Ketorolac microsponges were prepared by quasi-emulsion solvent diffusion using the pH-sensitive polymer Eudragit S-100 and compressed into tablets with a protective coating to prevent gastric release.
Results	Drug release was negligible (<10%) in simulated gastric fluid (pH 1.2) over 2 hours, rising sharply (>80%) at intestinal/colonic pH (6.8–7.4), correlating with reduced gastric irritation and analgesia lasting up to 24 hours.
Discussion	The pH-sensitive polymer remains intact in the stomach and dissolves at higher intestinal pH, releasing drug through combined erosion and diffusion while avoiding direct gastric mucosal contact and prostaglandin inhibition.
Conclusion	Colon-targeted microsponge systems can improve the gastrointestinal safety profile of ketorolac and other NSAIDs. **[107]**

CASE 2: IBUPROFEN (RHEUMATOID ARTHRITIS)

Presentation	A 60-year-old woman with rheumatoid arthritis on ibuprofen 400 mg three times daily experienced poor adherence and fluctuating pain relief due to rapid drug elimination.
Method	Ibuprofen microsponges were prepared with Eudragit RS100 by quasi-emulsion solvent diffusion and filled into sustained-release capsules.
Results	Dissolution followed Higuchi kinetics, with controlled release over 12–24 hours, potentially allowing once- or twice-daily dosing with consistent analgesia.
Discussion	Diffusion across the porous polymer matrix creates a tortuous release path that prevents sudden plasma spikes and the resulting inconsistent pain control.
Conclusion	Microsponge-based ibuprofen delivery may improve adherence and sustain therapeutic levels in chronic inflammatory conditions. [55]

CASE3: CURCUMIN (INFLAMMATORY BOWEL DISEASE)

Presentation	A 40-year-old patient with mild ulcerative colitis prescribed curcumin for its anti-inflammatory effect showed a poor response due to the drug's low solubility and rapid metabolism.
Method	Curcumin microsponges were prepared with ethyl cellulose by quasi-emulsion solvent diffusion to enhance solubility and protect the drug from degradation.
Results	Dissolution increased to ~90%, versus ~10–15% for the pure drug, correlating with improved intestinal availability and anti-inflammatory effect.
Discussion	The porous structure increases surface area and wettability, while the polymer matrix protects curcumin from enzymatic degradation; release occurs via diffusion.
Conclusion	Microsponge technology can enhance the therapeutic efficacy of poorly soluble natural compounds such as curcumin. [61]

RECENT ADVANCES IN MICROSPONGE DRUG DELIVERY

TISSUE ENGINEERING

Conventional vascular grafts made of expanded polytetrafluoroethylene (ePTFE) or Dacron work well for large-diameter vessels such as the aorta but are prone to thrombosis in small-calibre arteries because they are recognised as foreign material, often necessitating further bypass surgery. In one study, small-calibre vascular grafts made from polyglycolic acid (PGA) and poly-L-lactic acid (PLLA) fibres incorporating collagen microsponges were tested in dogs; the biodegradable scaffold supported vessel patency without cell-seeding pretreatment or anti-thrombotic therapy, and the animals recovered without adverse effects [108–112].

RNA INTERFERENCE (RNAi) DELIVERY

RNAi is a natural antiviral defence mechanism in which the enzyme Dicer cleaves double-stranded RNA into ~22-nucleotide siRNA fragments that silence complementary target mRNA. Delivering siRNA remains challenging because of poor oral permeability, immunogenicity, and the need for repeated dosing. Microsponge-based delivery addresses these issues using rolling-circle transcription: RNA polymerase and nucleoside triphosphates act on a circular DNA template to generate long RNA polymers that self-assemble into RNAi microsponges, which are then coated with polyethyleneimine (PEI) to form ~200 nm nanoparticles, each carrying more than 500,000 siRNA precursors (Figure 9) [113,114].

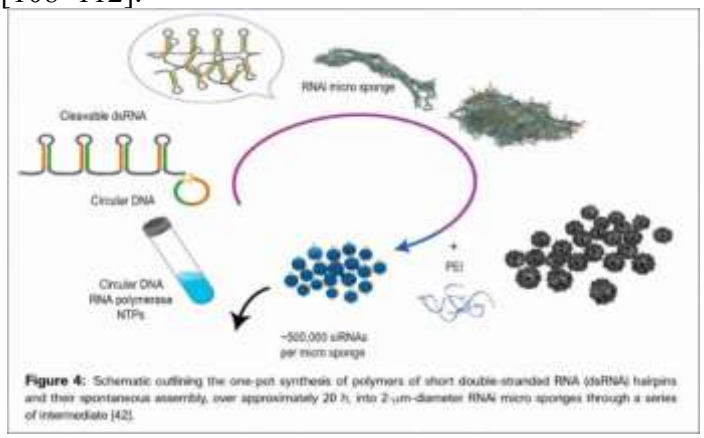


Figure 4: Schematic outlining the one-pot synthesis of polymers of short double-stranded RNA (dsRNA) hairpins and their spontaneous assembly, over approximately 20 h, into 2-μm-diameter RNAi micro sponges through a series of intermediate [42].

Figure 9: One-pot synthesis of dsRNA hairpins and their self-assembly into RNAi microsponges, followed by PEI-mediated nanoparticle formation for siRNA delivery

CURRENT CHALLENGES AND FUTURE OUTLOOK

Despite improved stability, controlled release, and reduced side effects, microsponge systems face several unresolved challenges. Achieving consistent drug loading and uniform particle size remains difficult, particularly for water-soluble drugs, and residual organic solvents raise toxicity and environmental concerns. Scaling production from laboratory to industrial scale is complicated, since small changes in formulation variables affect porosity, entrapment, and release behaviour. Polymer selection is critical, as drug–polymer incompatibility can compromise stability and efficacy, and structural collapse or drug crystallisation during storage can affect long-term stability. Limited clinical trial data, the absence of standardised evaluation criteria, and unresolved reproducibility and safety questions continue to slow regulatory approval, while high production costs and complex manufacturing further limit commercial development.

Looking ahead, the high drug-loading capacity and porous architecture of microsponge systems make them well suited to reducing dosing frequency and maintaining steady plasma concentrations — benefits particularly relevant to chronic conditions such as smoking-cessation therapy, where they may help reduce withdrawal symptoms and relapse rates. Combining microsponge technology with nanotechnology and stimuli-responsive polymers could further improve bioavailability, stability, and site-specific targeting, while advances in manufacturing and scale-up may improve regulatory acceptance and commercial viability.

CONCLUSION

Addiction, and tobacco addiction in particular, remains a major global health burden with wide-ranging systemic effects, and current smoking-cessation therapies are constrained by poor bioavailability, fluctuating drug levels, and inconsistent patient compliance. Advanced drug delivery systems — especially microsponge technology — offer a promising route to controlled, sustained drug release, improved stability, and better adherence. Beyond topical use, microsponge platforms are being extended to oral, nasal, inhalational, and biopharmaceutical delivery, broadening their therapeutic relevance while reducing toxicity, irritation, and mutagenic potential relative to conventional systems. Continued research, formulation optimisation, and clinical validation will be essential to fully establish microsponge-based systems as a safe, effective, and patient-friendly platform for de-addiction therapy and beyond.

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