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REVIEW ARTICLE

Advancements in microsponges for the management of vaginal and colorectal diseases: A comprehensive review

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ABSTRACT

The controlled-release drug delivery systems have risen dramatically allowing various factors such as the prohibitive cost of developing new entities, the expiration of existing international patents, and the discovery of new polymeric materials suitable for prolonged drug release and improvement in therapeutic efficacy. Microsponges are the porous microspheres-based polymeric delivery system that allows controlled drug release at a specific site. Microsponges are developed for the efficient delivery of active ingredients at a low dose. They help in improving stability by modifying drug release kinetics, reducing side effects, and enhancing the retention of drug entities. Microsponge compositions are stable throughout a wide pH and temperature range, making them more compatible with numerous vehicles, and ingredients. Several studies have shown that microsponges are non-irritant, non-toxic, non-mutagenic, and non-allergic with self-sterilizing properties. They are typically used for topical administration but have lately been used for oral, vaginal, and colorectal administration as well. The current review contains basic information about microsponges, their method of preparation, and various characterization parameters. The review also discusses the application of microsponges in vaginal and colorectal diseases. The latter portion of the script includes various patents and preclinical trials.

Keywords: microsponges; stability; colon; rectal diseases; vaginal diseases

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1. Introduction

The pharmaceutical industries are facing several challenges in delivering the drug to a targeting site and for controlled and sustained drug release. The drug delivery system should deliver the drugs at predetermined rates, with a controlled release rate, improved drug efficacy, and cost-effectiveness, and should be patient-compliant. Most drug delivery system requires the incorporation of high drug concentration for therapy due to their low therapeutic efficacy and there are more chances of side effects[1]. Microsponge (MS) is one of the novel patented approaches that is being widely explored by researchers and pharmaceutical industries in various pharmaceutical applications. For the first time, Won developed microsponges in 1987 and its patent was granted to Advanced Polymer System, Inc. The Company applied various developed changes in microsponge techniques to cosmetics, over-the-counter (OTC) drugs, and prescription products. Microsponges are typically porous patented polymeric systems, with interred (buried) connected voids of particle

size range 5–300 µm which are loaded with an active ingredient[2]. Microsponges are designed to deliver API (Active Pharmaceutical Ingredient) at a minimum dose and enhance stability with reduced side effects. A microsponge of approximately 25 µm can have about 25,000 pores over its surface and an internal pore structure of approximately 10 feet in length. Hence, is capable of offering a volume of about 1 mL/g which is a large reservoir with each microsponge for drug entrapment (up to 3 times its own body weight)[3].

Microsponges porous nature provides a number of benefits in drug delivery, including controlled release, increased bioavailability, drug protection, targeted delivery, reduced side effects, and taste masking. Because of these characteristics, microsponges are a diverse and useful platform for refining drug formulations and increasing therapeutic effects[4]

Research utilizing mitiglinide microsponges for prolonged drug release was prepared via quasi-emulsion solvent diffusion technique. The particle size of the microsponges was found to be ranging between 39.15–215.78 µm with an entrapment efficiency of 76.7 − 98.74% ± 1.37. The SEM studies revealed the highly porous nature of microsponges with interconnected pores, entrapping mitiglinide. Moreover, the MS was capable of sustaining the drug release (91.25 ± 2.5) for up to 24 hours, which could be attributed to the porous structure of microsponges which is responsible for controlled drug release via diffusion through the pores[5]. Similar morphological results were obtained in one of our ongoing research, **Figure 1**, the SEM image clearly indicates the particle size, spherical shape, and highly porous structures with interconnected pores encapsulating drug inside the microsponges.

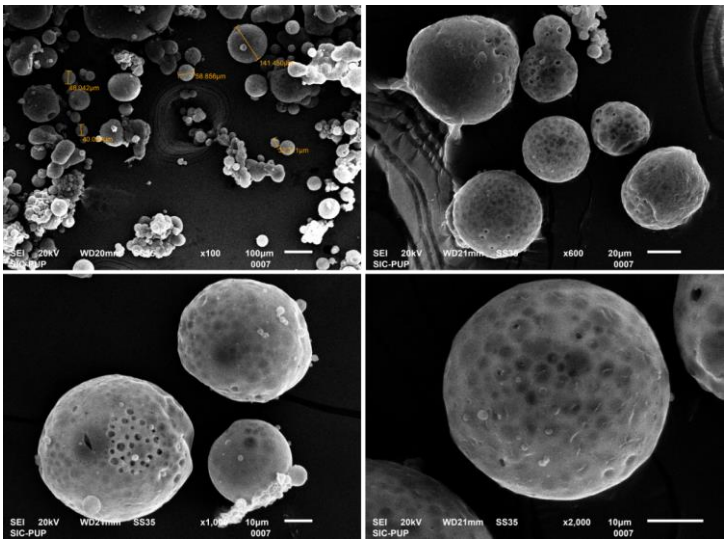

Figure 1. Structure of microsponges.

Microsponges can offer sustained and controlled drug release from formulation for up to 12 hours[6]. Abdellatif et al.[7] developed controlled-release microsponges of albendazole which retarded the drug release in a sustained manner. The possible reason for delayed or controlled drug release is due higher concentration of polymer which leads to a decrease in the number of pores over microsponge surface. Along with the release characteristics, the particle size of microsponges can be controlled by the polymer concentration. According to the findings, a rise in polymer concentration causes the organic layer's viscosity to increase, which in turn raises the polymer's diffusivity into the aqueous phase and induces larger size particles[8]. With a decrease in polymer concentration, the interfacial tension decreases, and microsponges with smaller particle sizes are formed. Microsponges also improve the solubility and bioavailability of the drug. Sustain drug release of microsponges is associated with the increased bioavailability of drugs[9]. Microsponges can be employed to incorporate solids and liquids/ oils, which are thermally (up to 130 °C), physically and chemically stable (pH range of 1–11) without the use of preservatives[10–13].

Since microsponges are a unique porous structure and encounter diverse drug delivery capabilities, it offers significant advantages when comes to drug delivery to the vagina and colorectal region. The microsponges-based vaginal drug delivery offers sustained and controlled drug release that is beneficial for conditions that require continuous drug exposure such as hormonal or infectious treatment. Microsponges adhere to the vaginal mucosa, offering prolonged drug residence for an extended period of time[14]. They also enhance the drug bioavailability by improving solubility and permeability, ensuring that the drug gets absorbed efficiently in the vaginal mucosa. Most importantly, microsponges have the potential for targeted drug delivery to the vaginal site, minimizing systemic exposure and reducing systemic side effects. In addition, microsponges facilitate less frequent dosing, improving patient compliance[15]. Moreover, microsponges are a distinctive approach for drug delivery to the colorectal region, for providing benefits for colorectal diseases. In addition to the advantages of microsponge in the vaginal region, microsponge acts a protective carrier for drug shielding from the harsh gastrointestinal environment, for their stability and effectiveness. The targeted drug delivery application of microsponges is beneficial in treating colorectal diseases such as inflammatory bowel disease, and colorectal cancer. They can also be used for delivering multiple drug simultaneously, for treating complex diseases. Since, microsponges adhere to the colorectal mucosa, providing prolonged residence and drug remains at the site for longer time[16,17].

The mechanism of drug absorption into mucosal surface via microsponges involves transcellular, paracellular and vesicular transport mechanisms. Transcellular transport comprises passive and active diffusion. Most of the drugs are absorbed via passive diffusion, driven by concentration gradients. This involves the movement of drug molecules an area of higher concentration in the gastrointestinal lumen to an area of lower concentration in the bloodstream. This process depends on the drug's physicochemical properties, including lipophilicity (ability to dissolve in lipids) and molecular size. Facilitated diffusion is a passive transport mechanism that allows specific molecules to move across cell membranes with the help of specialized proteins called transporters or carrier proteins. This process does not require energy expenditure (ATP-adenosine triphosphate) and is driven by concentration gradients, moving molecules from an area of higher concentration to an area of lower concentration. Some drugs are absorbed through active transport mechanisms, active transport is a fundamental biological process that moves molecules and ions against their concentration gradients using energy from ATP. Paracellular transport is a mechanism by which substances, such as ions and small molecules, move between adjacent epithelial or endothelial cells that form a barrier. Unlike transcellular transport, which involves substances passing through the individual cells, paracellular transport occurs through the gaps or junctions between cells. Vesicular transport mechanisms involve the movement of substances into or out of cells using membrane-bound vesicles. These vesicles are small, spherical, membrane-enclosed structures that transport various molecules, such as proteins, lipids, and other cellular components, within and between cells[18,19]. The different mechanisms of drug absorption via microsponges are depicted in **Figure 2**.

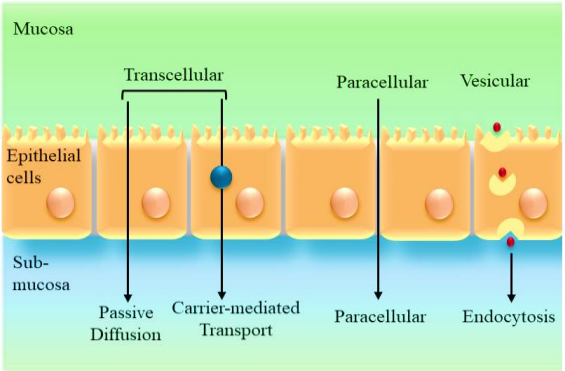

Figure 2. Drug transport mechanism via microsponges.

1.1. Preparation of microsponges

The microsponges preparation depends on the physicochemical properties of active moieties/drugs to be entrapped and their solubility characteristics with the polymer employed for microsponges preparation. For better entrapment, the drug to be entrapped should be inert with a monomer that is either fully miscible in the monomer or immiscible or slightly soluble in water. The drug must be compatible with the polymerization catalyst and polymerization conditions[20]. Also, the drug should not interfere with the spherical structure of the microsponge. Various drugs such as Domperidone, Fluconazole, Dasatinib, Indomethacin, Dicyclomine, Diclofenac sodium, Oxaliplatin[21–26], and some essential oils (such as babchi oil, citronella oil), etc, are employed for microsponge preparation[27]. Selection of a suitable polymer is also necessary for the preparation of microsponges as it defines the drug release from microsponges. Polymers utilized in the manufacture of microsponges for drug administration should have important features such as biocompatibility, controlled drug release, stability, and processability. The polymer used is determined by the unique needs of the drug delivery system, the nature of the drug, and the intended release characteristics. These qualities work together to improve the efficacy and safety of microsponge-based drug delivery systems. Polymers such as ethyl cellulose, polystyrene, Eudragit RS 100, polylactide-co-glycolic acid, Eudragit RS PO, polylactic acid, Eudragit S-100, and polyvinyl benzene are used to manufacture microsponge[28]. These polymers can form a porous structure for drug encapsulation, are biodegradable, have low toxicity, are pH-responsive, have mucoadhesive qualities, and are compatible with a wide range of drugs[29]. Other than polymers, plasticizers like glycerol, triethyl citrate, dibutyl phthalate, and stabilizers like polyvinyl alcohol are also used in microsponge development. And solvents like Dichloromethane, chloroform, ethanol, and acetone are used in microsponges to take up all the ingredients[30].

The microsponge can be prepared by either –a single-step process or a two-step process which is liquid-liquid suspension polymerization and quasi-emulsion solvent diffusion technique. The various other methods used for microsponges preparation are water-in-oil-in-water emulsion solvent diffusion method, porogen addition, oil-in-oil emulsion solvent diffusion method, lyophilization, ultrasound-assisted, electrohydrodynamic atomization, etc.

1.1.1. The liquid-liquid suspension polymerization method

It is a single-step process that involves the addition of monomers into a suitable solvent along with the active ingredient, followed by dispersing into an aqueous solution containing additives (surfactant, suspending agent, etc.) to form a suspension. After which the polymerization begins by activating the monomer via catalyst addition or increasing the temperature. Polymerization continues and leads to the creation of ladders-like structures by cross-linking of chain monomers. And the ladder causes spherical particle formation and their agglomeration leads to the formation of bunches of microsponges (like a grape). It is an advantageous technique as it can be modified to one one-step or two-step process for drug loading (**Figure 3**). But is composed of several disadvantages as well such as the unreacted monomer also getting entrapped, leaving solvent traces behind, non-uniform structure, and monomer reaction taking a long time[31,32].

Liquid-liquid suspension polymerization is a useful approach for creating customized mucosal drug delivery systems. Its precision in managing particle size and drug dispersion is critical for mucosal applications. This technique accepts both hydrophilic and hydrophobic drugs, providing a variety of drug delivery possibilities. It is suited for mucosal DDS due to its customizable release profiles, protection of labile agents, and scalability for industrial production. Polymers that are biocompatible and biodegradable provide safety, whereas mucoadhesive characteristics improve drug retention on mucosal surfaces[33].

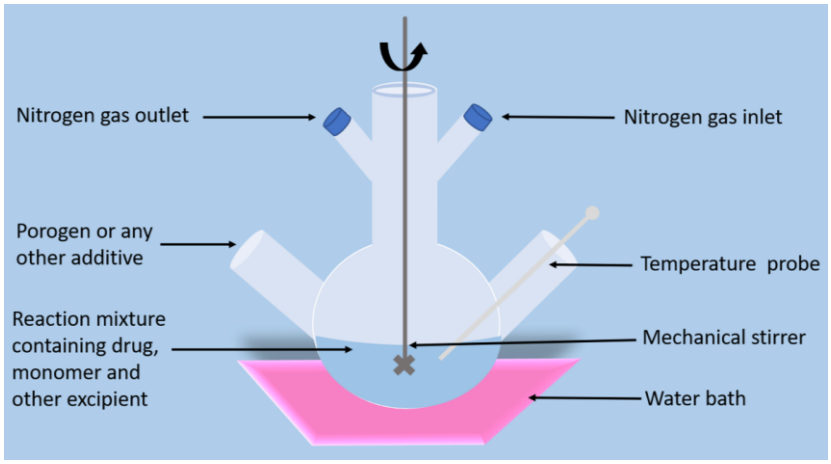

Figure 3. Liquid-liquid suspension polymerization technique.

1.1.2. Quasi-emulsion solvent diffusion technique

It is the most widely used technique for the preparation of microsponges. It is a two-step process, favorable for drugs that are sensitive to polymerization, as shown in **Figure 4**. Quasi emulsion solvent diffusion technique offers advantages such as no monomer entrapment, high drug loading, low solvent traces, and control over the size of microsponges by controlling speed. It involves the dispersion of the internal phase that contains drug and polymer into an aqueous external phase containing PVA with continuous stirring for up to 2 hours at required temperature conditions. The polymeric droplets (internal phase) disperse into the external phase and get solidified by organic solvent and water diffusion in and out of the droplet. This diffusion of the aqueous phase inside the droplet decreases the solubility of the drug and polymer, which results in drug-polymer co-precipitation. Whereas, organic phase diffusion results in the formation of porous microsponges[34,35].

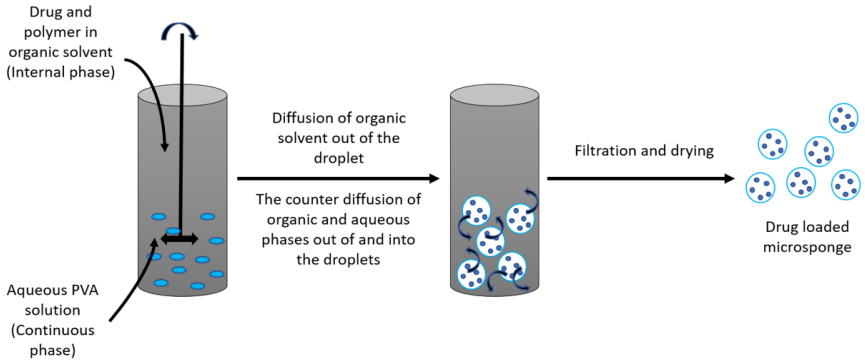

Figure 4. Quasi emulsion solvent evaporation technique.

Quasi-emulsion solvent diffusion technique is a well-established and evident method for developing controlled-release drug delivery systems. Various researchers have utilized this technique for preparing vaginal-based microsponges. Salah et al.[36] developed miconazole vaginal microsponges using a quasi-emulsion solvent diffusion technique. The microsponges showed controlled drug release and enhanced mucosal retention. In one more study, ketorolac tromethamine microsponge was prepared via quasi quasi-emulsion solvent diffusion technique and found to release the drug for up to 10 hours in a diffusion-controlled manner[37].

Microsponges can be prepared using the water-in-oil-in-water emulsion solvent diffusion method, which involves the formation of a double emulsion. It begins with the dispersion of the internal aqueous phase in an organic polymeric solution to form water in oil emulsion. The resultant emulsion is then dispersed into an

external aqueous phase containing PVA. This method can be employed for both water-soluble and water-insoluble drugs like proteins[38]. Another method known as porogen addition involves addition of porogen-like hydrogen peroxide into a polymeric solution and then dispersing it into an aqueous polymeric solution, followed by addition of initiator and the solvent is evaporated to obtain the microparticles. The other solvent diffusion-based method is oil-in-oil emulsion solvent diffusion method. In comparison to the water-in-oil-in-water emulsion method, oil-in-oil emulsion was produced using volatile organic liquid as internal phase[39]. The methods for the preparation of microsponges are shown below in (**Table 1**).

Table 1. Various methods of preparation of microsponges.

S.No.	Method	Description	Advantages/ Disadvantages
1	Liquid-liquid suspension polymerization	Dispersion of liquid droplets of monomers (insoluble in water) with stabilizer and vigorous stirring to produce polymer particles as disperse phase	**Advantage**: Can be modified to a 1 or 2-step process for drug loading. **Disadvantage**: Unreacted monomer entrapment. Long processing time. Requires 2 steps for thermolabile products.
2	Quasi-emulsion solvent diffusion	Solidification of droplets by addition diffusion of organic phase out of droplets to the external phase.	**Advantage:** Low solvent traces. No unreacted monomer entrapment. Control over microsponge size. **Disadvantage:** Not suitable for aqua-soluble drugs. Require longer reaction time for monomer. The drug needs to solubilize in volatile water-soluble solvent.
3	w/o/w emulsion solvent diffusion	This method involves formation of water in oil emulsion first, followed by dispersion in water to form double emulsion.	**Advantage:** suitable for water-soluble drug entrapment. Proteins and peptides can also be entrapped. **Disadvantage:** It utilizes surfactants which can be present as residues in the final product.
4	Porogen addition	This involves porogen addition to the matrix to form porous structures.	**Advantage:** Able to form highly porous structures with interconnected pores. **Disadvantage:** Structure can disrupt.
5	o/o emulsion solvent diffusion	Volatile organic liquid as internal phase	**Advantage:** No surfactant traces in the final product. **Disadvantage:** Vigorous washing of product is required to remove the solvent traces.
6	Lyophilization	Solvent evaporation at a fast rate to form porous particles.	**Advantage:** Offer quick reproducible results. **Disadvantage:** Cracking or shrinking of particles may occur.

1.2. Characterization of microsponges

Characterization of microsponges is required to determine their applicability for drug delivery. It supports researchers and pharmaceutical companies in optimizing formulations, predicting drug release behavior, and maintaining product quality and consistency. To examine their structure, particle size, morphology, porosity, and pore size distribution. Furthermore, measuring drug loading efficiency, drug release kinetics, and swelling behavior is critical for evaluating their effectiveness in drug delivery. A chemical composition study identifies the materials utilized, whilst thermal characteristics and stability studies evaluate their behavior under various conditions. Zeta potential measurements provide information about their surface charge. The overall applicability and dependability of microsponges in drug delivery applications are ensured by detailed characterization.

The determination of particle size and morphology is one of the key components of microsponge characterization. Microsponges come in a variety of sizes, often ranging from micrometers to nanometers, and the size distribution can have a big impact on how well they work. Particle size and shape are observed and measured using methods like dynamic light scattering (DLS) and scanning electron microscopy (SEM). Porosity and pore size distribution are crucial properties to evaluate because microsponges porous nature is their distinguishing trait. The porosity and pore size distribution of microsponges is frequently assessed using nitrogen adsorption/desorption and mercury intrusion porosimetry. Given that they affect drug loading

capacity and release kinetics, it is crucial to comprehend these factors[40,41].

Drug loading effectiveness is another key component of characterization. This variable expresses how much of the drug is loaded within the microsponges. The success of the formulation depends on accurate drug content assessment. Another important component of characterization is the drug release from microsponges. To evaluate the microsponges' capacity for prolonged and regulated drug delivery, researchers examine the release kinetics under various conditions. In order to identify the components utilized in the creation of microsponges, chemical composition analysis is crucial for quality control. This conclusion is made with the help of methods like Fourier-transform infrared spectroscopy (FTIR)[42,43]. Utilizing methods like differential scanning calorimetry (DSC) and thermogravimetric analysis, thermal characteristics of microsponges are evaluated (TGA). These tests give an idea of how the stability and drug-release characteristics of microsponges react to temperature fluctuations. Microsponges surface charges can be determined by zeta potential studies, which is important for understanding their stability and interactions with other components of pharmaceutical formulations. To assess the shelf life and long-term performance of microsponges, stability tests are carried out over time and in various environmental situations[44,45]. The different methods for the characterization of microsponges are shown below in (**Table 2**).

Table 2. Different methods for characterization of microsponges.

S.NO.	Parameter	Characterization method
1	Measurement of particle size	Optical microscope, polarizing microscope, electron microscope
2	Surface topology	Scanning electron microscopy
3	True density	Ultra-pycnometer
4	Pore structure	Mercury intrusion porosimeter
5	Compatibility	TLC, FT-IR
6	Glass transition	DSC
7	Effect of polymerization on crystallinity of drug	XRD
8	Resiliency	Considering release as a function of cross-linking
9	Release study	Dissolution test apparatus

2. Vaginal pathophysiology

The female reproductive consists of ovaries, fallopian tubes, uterus, vagina, vulva, accessory glands, and external genital organs. Out of which vagina is the flexible, fibromuscular tube measuring 6 to 8 cm in length crucial connecting vulva with the cervix of the uterus and then to the uterine cavity[46]. The vaginal opening is situated in the posterior portion of the vulvar vestibule, at the back of the urethral opening. The vaginal canal consists of an outermost fibrous adventitia, middlemost smooth muscle cells, and an innermost layer of mucosa[47,48]. Vaginal fluid is the limiting factor in vaginal drug delivery as it can lead to drug dilution, poor drug retention, and bioadhesion. The other limiting factors for vaginal drug delivery are the various enzymes like amino-peptides and lysozymes which interfere with drug activities and pH of the vagina. Despite all these barriers, vagina is the most feasible site for drug delivery due to its enormous surface area, abundant blood supply, absence of hepatic first-pass effect and gastrointestinal absorption, high mucosal permeability to several medications, and flexibility of self-insertion[49,50].

The vagina is the most prone area to infections. The possible reasons for vaginal infections are douching, changes in hormone level, birth control pills, intercourse, pregnancy, breastfeeding, medications (like

antibiotics), and certain medical conditions such as diabetes, high blood pressure, HIV, or AIDS. As a result of these conditions, the vagina may experience itching, burning, pain, vaginal discharge, and strong odor[51,52]. The major vaginal infections are of three types namely yeast infection, bacterial vaginosis, and trichomoniasis or trichomonas vaginitis. The yeast infections are caused by the fungus candida causing vaginal itching, thick white discharge, and vulva redness. Lactobacilli is a vaginal-friendly bacteria, when it gets low in number, the Gardnerella overgrows causing bacterial vaginosis. Bacterial vaginosis leads to thick white discharge and fishy odor with no burn or itching. Furthermore, Trichomoniasis, the true sexually transmitted disease is caused by Trichomonas vaginalis passed from one to another partner during intercourse[53]. For treating these disorders many vaginal formulations such as creams, ointments, powders, and suppositories are used that exhibit shorter residence time and undergo a natural clearance process in the vaginal lumen, irritation, and burning in the vaginal area. Microsponges, bioadhesive films, microspheres, vaginal gels, nanosystems, liposomes, etc. are the novel approaches used nowadays for achieving long-term retention of a dosage form in the vagina and to withstand vaginal pH and vaginal secretions[54,55].

2.1. Application of microsponges in vaginal diseases

Microsponges are composed of porous microspheres that entrap various mate-rials such -as medications, emollients, essential oils, sunscreens, and fragrances. Vaginal administration of microsponges offers several advantages such as controlled release characteristics, reduced local adverse effects, better patient compliance, improved retention in the vagina and enhanced drug therapeutic efficacy, high encapsulation efficiency, and sustained drug release. Microsponges consist of large numbers of interconnecting pores within a non-collapsible structure, after application onto the mucus membrane, microsponges reside in the tiny crevices and folds and gradually release the entrapped material[56,57]. They act as a depot of active components and provide sustained as well as controlled drug release with avoidance of adverse effects at a minimal dose[58]. Microsponges placed inside, are subjected to muscular pressure through the body movements of the patient, which contributes to the partial release of the drug into the vaginal canal[59].

Microsponges have been proven to show better retention and improved therapeutic efficacy. In one of the studies, miconazole had been used to develop microsponge gel for treating vaginal candidiasis. The microsponges were produced using quasi-emulsion technique and were introduced into carbopol gel, further evaluated for viscosity and bioadhesion characteristics. The microsponges showed controlled release characteristics, reduced local adverse effects, better patient compliance, improved retention in the vagina, and enhanced drug therapeutic efficacy[36]. Microsponge gel of metronidazole (MTZ) was also formulated for superficial surgical wound infections and bacterial infections of the vagina, genital tract, intestine, bones, mouth, rosacea, and skin ulcers. MTZ microsponges were developed by w/o/w emulsion solvent evaporation process and they exhibited enhanced drug retention time, improved therapeutic efficacy for up to 24 hours, and improved patient compliance[57]. In another study, Butoconazole nitrate (BN) microsponges were prepared by lyophilization. The result reported that BN microsponges have high stability for up to 3 months concerning drug release profile and their physical properties, and are biodegradable within 24 h[58]. The microsponges are also known for sustained and controlled drug release in the vagina. Amir[59] formulated the metronidazole-loaded microsponge for the treatment of vaginal infections (bacterial vaginosis) and the microsponges showed a controlled/sustained drug release. Sildenafil citrate microsponge was formulated by Aboud et al.[60], for infertility management in women. The developed microsponges displayed sustained release of the therapeutic

agent with reduced adverse effects.

Microsponges are well known for improving drug bioavailability. Itraconazole microsponges were formulated by using emulsification for the treatment of vaginal candidiasis and the microsponges showed controlled drug release, better drug retention, and improved drug bioavailability[61]. Khattab and Nattouf[62] developed the clindamycin (potent antibacterial drug) encapsulated microsponges gel using the emulsion solvent diffusion technique. The formulated microsponges were used for the treatment of infections of the skin, female reproductive system, and internal body organs. The micro-sponges showed high entrapment efficiency, controlled drug release, and better patient compliance. Sertaconazole-loaded microsponges were prepared in the study by employing quasi-emulsion solvent diffusion process. The microsponges were examined for drug content, encapsulation efficiency, and in vitro drug release rate. The microsponges offered controlled drug release and better patient complianc[63]. Oxiconazole nitrate microsponges were formulated by a quasi-emulsion solvent diffusion technique and evaluated for particle size, encapsulation efficiency, and in vitro drug release studies. The developed microsponges exhibit controlled drug release and better patient compliance[64].

Hussien[65] formulated the microsponge drug delivery system of ketoconazole by employing quasi-emulsion technique and evaluated for particle size, and in vitro drug release. The prepared microsponges had a faster drug release rate. Miconazole nitrate is a known compound for its anti-candidal activity. Microsponges of miconazole were entrapped in a gel for treating fungal infections of the skin, vagina, intestine, and mouth. The results depicted good spread ability of gel and displayed better antifungal action[66]. In another study tiotioconazole-loaded ethyl cellulose microsponges were prepared using emulsification technique and were used for the treatment of vaginal fungal infection (Candida albicans). The microsponges displayed enhanced patient compliance, controlled as well as sustained drug release[67]. Gupta et al.[68] developed and evaluated the clotrimazole-loaded microspheres to treat vaginal candidiasis by using spray dried method. The developed microsystem exhibits enhanced antifungal activity, and non-irritant, controlled intra-vaginal drug release.

Various microsponges preparation utilized for treating vaginal disorders are listed in (**Table 3**).

Table 3. Microsponges preparation for treatment of vaginal disorders.

Drug	Polymer	Method of preparation	Disease	Remarks	Ref.
Miconazole (MCZ)	Eudragit RS100	Quasi emulsification	Vaginal candidasis	Controlled release characteristics, reduced local adverse effects, better patient compliance, improved retention in vagina, and enhanced drug therapeutic efficacy	[36]
Metronidazole (MTZ)	Ethylcellulose, Xanthan gum, Polyvinyl alcohol (PVA)	w/o/w emulsion solvent evaporation	Bacterial vaginosis, Genital tract infection	Enhanced drug retention time, therapeutic efficacy was maintained up to 24 h, improved patient compliance	[57]
Butoconazole nitrate (BN)	Hydroxypropyl methylcellulose (HPMC), Chitosan, Carbopol 934, carboxymethylcellulose	Lyophilization	Vaginal Fungus infection (Candida albicans), vulvovaginitis	High stability, biodegradable sponges within 24 h	[58]
Metronidazole	Carbomer, Triethanolamine	Emulsification	Bacterial vaginosis	Controlled drug release, better retention	[59]
Sildenafil-citrate	Poloxamer 407, Polyvinyl alcohol	Emulsification	Infertility management	Sustained release of therapeutic agent, reduced adverse effect	[60]

	(PVA), chitosan				
Itraconazole	Carbomer	Emulsification	Vaginal candidiasis	Controlled drug release, better retention, improved bioavailability	[61]
Clindamycin (CLN)	Carbopol 934, Ethylcellulose, PVA	Emulsion solvent diffusion	Bacterial vaginosis	High entrapment efficiency, controlled drug release, minimized adverse effects, enhanced patient compliance	[62]
Sertaconazole	Eudragit RS100	Quasi emulsion solvent diffusion	Vaginitis	Controlled drug release, better patient compliance	[63]
Oxiconazole nitrate	Eudragit S100, Eudragit L100	Quasi emulsion solvent diffusion	Fungus infection	Better patient compliance sustained release of therapeutic agent	[64]
Ketoconazole	Eudragit RS, Eudragit E100	Quasi emulsion solvent diffusion	Fungus infection (Candidiasis)	Better flow characteristics, rapid release of drug from dosage form	[65]
Miconazole nitrate	Carbopol 940, HPMC	Emulsification	Vaginal fungus infection	Controlled drug release, better antifungal action	[66]
Tioconazole	Ethylcellulose	Emulsification	Fungal infection	Enhanced patient compliance, controlled as well as sustained drug release	[67]
Clotrimazole	Eudragit RS100, Eudragit RL100, HPMC, Carbopol, Sodium carboxymethylcellulose	Spray drying	Vaginal candidiasis	Enhanced antifungal activity, nonirritant, controlled intra-vaginal drug release	[68]

3. Colorectal pathophysiology

The colorectal region, which includes the colon (large intestine) and rectum, is an important portion of the digestive system. Beginning with the cecum in the bottom right abdomen, the colon ascends as the ascending colon, crosses horizontally as the transverse colon, lowers along the left side as the descending colon, and finally forms an S-shaped sigmoid colon, connecting to the rectum[69–72]. The rectum is about 15–20 cm long in adults, with a surface area of approximately 200–400 cm^2 an average fluid volume of around 1–3 mL, and neutral pH of 7–8. It acts as a temporary storage site for stool before defecation, signaled by stretch receptors. Stretch receptors signal the rectum to act as a temporary storage site for stool before defecation. The anus (external opening), is surrounded by sphincter muscles that govern stool release[73,74]. The superior and inferior mesenteric arteries feed blood to the region, and lymph nodes aid in drainage and immunological function. The enteric nervous system and autonomic nerves control motility, and the gut microbiota in the colon have a remarkable impact on digestion and overall health[75–78]. This anatomical knowledge is essential for correctly detecting and managing numerous colorectal illnesses such as colorectal cancer, diverticular disease, inflammatory bowel disease, and functional bowel disorders[79–81]. For drug delivery, the colorectal region offers significant advantages. It allows for the treatment of diseases within the colorectal region while minimizing systemic side effects. Drugs delivered rectally avoid first-pass metabolism in the liver, resulting in increased bioavailability. Colonic drug delivery systems enable sustained drug release, resulting in a longer therapeutic effect, which is especially advantageous for chronic disorders. The colon's steady pH environment improves drug stability, while tailored formulations allow for precise drug administration. These are useful in addressing a variety of colorectal disorders, including colorectal cancer, diverticular disease, inflammatory bowel disease, IBS (Crohn’s disease, ulcerative colitis), colon polyps, chronic anal and functional bowel disorders, as well as providing optimal patient care[82,83].

The protective mucus layer in the colon restricts drug absorption, and enzymatic breakdown by gut bacteria in the colon can impair drug bioavailability. The complex microbial population in the colon can metabolize medications, affecting their characteristics and efficacy, and pH variations in the colon can affect drug solubility and stability. Furthermore, the colonic epithelium's decreased permeability relative to the small

intestine, as well as the presence of a mucosal immune system, offer problems to drug distribution and clearance. Anatomically, the folds of the colon and the rectum's small surface area might cause unequal drug dispersion and complicate topical delivery. Conventional therapies are ineffective in treating colorectal diseases because active therapeutic agents are unable to reach the target site in the optimal required concentration due to drug degradation in the upper GIT, requiring a large drug dose to pass through the GIT and reach the target site, which is associated with adverse side effects. Such limitations are overcome by developing colon target site-specific drug delivery systems. Colon-specific drug delivery is achieved by employing microsponges, pH-sensitive polymers, microspheres, and nanosystems[84,85].

3.1. Application of microsponges in colorectal diseases

Microsponges overcome all barriers associated with colorectal region as they exhibit target site-specific drug delivery, better control over drug release, reduced dose as well as decreased dose frequency, better patient compliance, effective local and therapeutic action, and prolonged drug action.

Furthermore, because macrophages in the colon can selectively take up micro-sponges, they may provide effective local action. In one of the studies, Gupta et al.[86] formulated 5-Fluorouracil encapsulated microsponges for treating colorectal cancer by employing modified quasi-emulsion solvent diffusion technique. In-vitro drug release studies were conducted in simulated gastric fluid for 2 hours, simulated intestinal fluid for 6 hours, and colonic fluid for 16 hours. The microsponges displayed bibasic drug release, better patient compliance and were found to be a leading approach for colon-targeted drug delivery systems.

Jain et al.[87] prepared the Eudragit S-100-based microsponges encapsulating dicyclomine for colonic delivery in the treatment of irritable bowel syndrome using quasi-emulsion solvent diffusion technique. In vitro, release study concluded that colon-specific microsponges start releasing the drug around the sixth hour correspondence to the arrival in the colon. The microsponges exhibit colonic target site-specific drug delivery, which is readily uptaken by colon macrophages, and offer effective local therapeutic action.

The MS of flurbiprofen was formulated by quasi-emulsion solvent diffusion technique. They were found to offer targeted site-specific delivery with uniform drug distribution in the colon[88]. The prolonged-release colon-targeted dicyclomine entrapped eudragit microsponges were prepared for the treatment of irritable bowel syndrome, employing quasi emulsion solvent diffusion technique. The results concluded that the drug was stable in all formulations, and provides prolonged drug action. It was also suggested that microsponges could be used for local action because macrophages in the colon can take them up[89].

Paracetamol (PCM) entrapped eudragit microsponges were formulated for colon targeting with a purpose to treat inflammatory bowel diseases (IBD) by using a quasi-emulsion solvent diffusion process. The microsponges were compressed into tablets that began drug releasing at the sixth hour, corresponding to the time the drug reached the proximal colon, which suggested a new approach for colon-specific drug delivery system[90]. In a study, meloxicam (MLX) microsponges for colon-targeted delivery were formulated with modified quasi-emulsion solvent diffusion method. The in vivo study in rabbits suggested microsponges to be the ideal candidate for treating colorectal cancer and displayed up to 8 hours colonic luminal retention with targeted site-specific action[91]. Kumari et al.[92] developed the prednisolone colon-targeted microsponges by employing the quasi-emulsion solvent diffusion method using ethyl cellulose, polyvinyl alcohol, and triethyl citrate. Later the microsponges were compressed into tablet using the direct compression method. The microsponges showed a maximal amount of drug release in the colon, decreased adverse side effects, and reduced dose as well as dose frequency. The researchers formulated resveratrol entrapped microsponges for colon-targeted delivery and later compressed into tablet form. The microsponges offer targeted colon site-specific drug release and enhanced therapeutic efficacy of drugs in the treatment of IBS, and colon cancer[93].

In another study, curcumin-entrapped microsponges were prepared for colon targeting by employing

quasi-emulsion solvent diffusion technique. The pharmacodynamics study revealed that curcumin MS has a substantial effect in reduction of edema, and hemorrhage in the colon and was found to be a promising tool for treating ulcerative colitis[94].

To treat Anal fissures, scientists formulated the diltiazem encapsulated microsponges in the form of rectal gels using a 23-factorial design. The ex-vivo studies of optimized formulation indicated prolonged/delayed drug release for up to 24 hours. These findings suggested that local chronic anal fissure therapy may be improved by using diltiazem hydrochloride-loaded microsponges dispersed in rectal gels[95]. Naproxen-entrapped microsponges for colon targeting are formulated by Kardile et al.[96], for treating colon infections by employing a quasi-emulsion solvent diffusion process. The in vivo findings demonstrated that an increase in the drug: polymer ratio regulates the naproxen release rate for colon targeting, and an improved batch of naproxen microsponge was further developed in the form of tablets.

Microsponges loaded with 5-amino salicylic acid were developed using the quasi-emulsion diffusion technique. Different formulations having drug: polymers in ratios 1:1,1:1.5,1:1.5 were prepared. The results depicted that microsponges provide prolonged drug release with zero order release kinetics[97]. D'souza and More[98] developed fluticasone acetonide entrapped microsponges by utilizing the quasi-emulsion diffusion technique for itching and inflammation. Morphological characteristics were examined using SEM. The prepared microsponges provide prolonged drug release with improved patient compliance. Various microsponges preparation utilized for treating vaginal disorders are listed in (**Table 4**).

Table 4. Microsponges preparation for the treatment of colorectal diseases.

Drug	Polymer	Method of preparation	Disease	Remarks	Ref.
5-Fluorouracil	Eudragit RS-100, HPMC, Eudragit S100, Eudragit L100	Quasi-emulsion solvent diffusion	Colorectal cancer	Better patient compliance, colon targeted system as well as proper tight control over drug release in combination with calcium alginate beads	[86]
Dicyclomine	Eudragit S-100, PVA, HPMC, sodium carboxymethylcellulose (Na-CMC)	Quasi-emulsion solvent diffusion	Irritable bowel syndrome (IBS)	Colonic target site-specific drug delivery, readily uptaken by colon macrophages, effective local therapeutic action	[87]
Flurbiprofen	Eudragit RS-100, HPMC, microsponge 5640, PVA, Na-CMC	Quasi-emulsion solvent diffusion	Inflammatory bowel	Targeted site-specific delivery, avoids release of drugs in small intestine. Uniform drug distribution in the colon	[88]
Dicyclomine	Eudragit RS-100, PVA	Quasi-emulsion solvent diffusion	Irritable bowel syndrome	Prolonged drug release characteristics, effective local action	[89]
Paracetamol	Eudragit RS-100, HPMC, PVA, Na-CMC	Quasi-emulsion solvent diffusion	Inflammatory bowel syndrome	Readily up taken by colonic macrophages, effective local action	[90]
Meloxicam	Eudragit RS-100, HPMC, PVP	Quasi-emulsion solvent diffusion	Colorectal cancer	Colonic luminal retention up to 8 h, target site-specific action	[91]
Prednisolone	Eudragit S100, ethyl cellulose, PVA, Na-CMC	Quasi-emulsion solvent diffusion	Ulcerative colitis, Crohn's disease	Targeted site-specific delivery, reduction in dose as well as dose frequency	[92]
Resveratrol (RES)	Chitosan, PVA	Quasi-emulsion solvent diffusion	Colon cancer, ulcerative colitis	RES-loaded microsponges in combination with chitosan and pectin matrix provide targeted colon site-specific drug release and enhanced therapeutic efficacy.	[93]
Curcumin	Eudragit L100, PVA	Quasi-emulsion solvent diffusion	Inflammatory bowel diseases	Natural anti-inflammatory agent, safe, inexpensive therapy	[94]
Diltiazem hydrochloride	Eudragit RS100, Poloxamer 407, methylcellulose, PVA	Quasi-emulsion solvent diffusion	Chronic anal fissures	Better permeation and high drug retention, improved patient compliance	[95]

Naproxen	Eudragit RS-100, PVA	Quasi-emulsion solvent diffusion	Crohn's disease, ulcerative colitis	Targeted drug delivery, reduced dose as well as dose frequency, improved patient compliance	[96]
5-Amino salicylic acid	Eudragit S100, Eudragit L100, Eudragit RS-100, PVA	Quasi-emulsion solvent diffusion	Inflammatory bowel disease	Better control over drug release rate, prolonged drug release	[97]
Fluocinolone acetonide	Eudragit, carbopol 934	Quasi-emulsion solvent diffusion	Crohn's disease, ulcerative colitis	Controlled drug release, improved patient compliance	[98]
Dexamethasone	PVA, Tween 80, dichloromethane, and methanol	Quasi-emulsion solvent diffusion	Ulcerative colitis	*In vivo* studies revealed remarkable improvement in ulcerative colitis rat model	[99]

4. Patents

Dean et al.[100] received the patent for developing vaginal microsponges. The invented microsponges exhibited a crosslinked collagen matrix with an open-to-surface porous structure, average particle size in the vicinity of 100 to 1000 microns, and were biodegradable, provided controlled drug release, and showed better patient compliance. This patent was assigned to Verax Corp. (Germany). A patent was awarded to Embil[101], for the formulation of analgetic cream consisting of salicylate in silicone oil and microsponges that provides sustained delivery of menthol (counter-irritant) with decreased skin irritation, increased cooling effect and displayed enhanced antifungal activity as well as better patient acceptance. Wright et al.[102] awarded a patent for developing microsponges that were biodegradable and provided delayed release of the biologically active agent. This patent was assigned to Alkermes Pharma Ireland Ltd. Dean et al.[103] received the patent for the invention of microsponges that displayed appropriate pore structure, size, and volume along with exhibited ease of colon insertion and biocompatibility. Love et al.[104] were awarded a patent for developing vaginal microsponges that provide sustained drug release, better stability, and vaginal retention. Tamarkin et al.[105] received a patent for the invention of the poloxamer foamable pharmaceutical compositions composed of a copolymer, such as a cross polymer of methyl methacrylate and glycol dimethacrylate. The prepared microsponges were non-toxic, provided sustained/controlled drug release, and showed enhanced patient compliance. Tamarkin et al.[106] were awarded a patent for the invention of the foamable vehicle, vitamin, and flavonoid pharmaceutical compositions that were stable against degradation. Patented microsponges showed enhanced stability, reduced adverse effects, and high reproducibility. Bernick et al.[107] received a patent for the invention of estradiol capsule microsponges for vaginal insertion The prepared formulation was used in the treatment of vulvovaginal atrophy. Kharlampieva and Yancey[108] received a patent for the invention of biodegradable microsponges of polylactic acid (PLA) with titania nanoparticles (NPs). The developed formulation was biocompatible, biodegradable, and non-toxic. Dean et al.[109], were awarded a patent for the invention of microsponges that showed enhanced antifungal action and controlled/sustained drug release. Ahn et al.[110] were awarded a patent for developing microsponges that were biodegradable, biocompatible, and exhibited reduced toxicity as well as better patient acceptance. Dean et al.[111] received a patent for the invention of vaginal microsponges that were biocompatible, biodegradable, provided controlled drug release, and showed enhanced patient compliance. This patent was assigned to Cellex Biosciences Inc. Various patented microsponges preparation utilized for treating vaginal and colorectal disorders are listed below in (**Table 5**).

Table 5. Various patents granted for microsponges.

Patent no.	Application	Ref.
WO1986005811A1	Microsponges have crosslinked collagen matrix with open-to-the-surface porous structure, average particle size in the vicinity of 100 to 1000 microns, are biodegradable, provide controlled drug release, and exhibit better patient compliance.	[100]
WO2004014397A1	Salicylate-dispersed silicone oil microsponges showed decreased skin irritation with a cooling effect. The microsponges also displayed enhanced antifungal activity and better patient acceptance.	[101]
US20050271702	The biodegradable polymeric sustained release microsponges offer delayed release of biologically active agents.	[102]
US4863856A	Crosslinked collagen structure with particle size in the range 100–1000 microns, the appropriate	[103]

	volume for immobilization of bioactive agent, biocompatible, biodegradable, ease of insertion.	
US7426776B2	The microsponges result in sustained drug release, better stability, and enhanced vaginal retention.	[104]
US8709385B2	The microsponges were found to be non-toxic, and offer sustained/controlled drug release and improved patient compliance.	[105]
US20080069779A1	Microsponges showed enhanced drug stability, reduced adverse effects, and high reproducibility.	[106]
US9180091B2	The microsponges offered ease of insertion, enhanced safety while insertion, and minimal vaginal discharge was observed.	[107]
WO2012177535A3	Biocompatible, biodegradable, non-toxic, photocatalytic nanocomposite microsponges	[108]
CA1288370C	The microsponges result in enhanced antifungal action with controlled/sustained drug release	[109]
KR101900387B1	biodegradable, biocompatible, and exhibited reduced toxicity as well as better patient acceptance	[110]
US100783A1	Biostable, biocompatible, controlled drug release	[111]

5. Pre-clinical case report

Pre-clinical studies are beneficial in drug development and obtain extensive data on preliminary efficacy, pharmacokinetics, toxicity, and safety information required before clinical trials of the compound. In the context of this review, various information has been collected on the pre-clinical efficacy of microsponges in vaginal and colorectal disorders. The brief information on microsponges intended for vaginal and colorectal diseases is as follows. To determine the therapeutic efficacy of miconazole (MCZ) in vaginal candidiasis, a microsponge gel of MCZ was formulated using quasi-emulsion method and evaluated in female Wistar rats. The result suggested enhanced anti-fungal and encapsulation efficiency of MCZ in comparison to marketed products. Also, the microsponges showed better drug retention in the vagina due to bioadhesion[46].

Curcumin is a well-known herbal bioactive compound that is commonly used for its anti-inflammatory activity. To treat inflammatory bowel disease colon-targeted curcumin-loaded microsponges were prepared and the therapeutic effectiveness was confirmed by using Wistar albino rats. The result of in-vivo investigation revealed quick healing of colon ulcers and the results of histopathology studies depicted that curcumin-entrapped microsponges are an ideal tool for treating ulcerative colitis as micro-sponges lead to a significant reduction in pathological parameters in comparison to free curcumin[79]. In another pre-clinical study diltiazem HCl encapsulated microsponges were developed for the treatment of chronic anal fissures. The study was performed using the mucosa of pig rectum. At appropriate time intervals, the percentage of drug permeation through mucosa was measured, and found that the initial burst effect was minimized by microsponges. The microsponges displayed enhanced permeation and better mucoadhesive characteristics[80].

6. Conclusion

Microsponges are microporous-based polymeric system that seeks the advantages of scientists due to their numerous advantages such as reduced side effects, stability, better retention, industrial development, and much more. The selection of suitable preparation methods, polymer, and solvent systems are challenging parameters for preparing microsponges. A lot of work has already been published on microsponges but micro-sponges for vaginal and colorectal application are limited. The present review describes the standard method for the preparation of microsponges and the emerging characterization techniques for evaluating microsponges. Despite advancements in microsponges development techniques, some unexplored grey areas require thorough research regarding the critical process, material attributes, biocompatibility, and toxicity studies are need to be addressed for a better understanding of microsponges.

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Conflict of interest

The authors declare no conflict of interest.

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