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Review Article

AN UP-TO-DATE REVIEW: MICROSPHERES AS A NEW DRUG DELIVERY SYSTEM

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ABSTRACT

The application of microsphere systems in drug preparations has seen a significant increase in recent years for various purposes. Microsphere systems can be utilized in a range of drug preparations, utilizing polymer types that are appropriate for the intended release target. Microspheres offer numerous benefits and can be used in various applications, including spacer applications, medication administration, and medical diagnostics. Microspheres have minimal negative effects, a more extended therapeutic effect, require fewer doses, and provide more consistent medication absorption. Additionally, they are adaptable, offer effective encapsulation, and are cost-effective. This overview was compiled to provide an up-to-date summary of the latest developments in new drug delivery systems utilizing microsphere dosage forms. Literature from Scopus, ScienceDirect, and PubMed from 2019 to 2022 was searched to provide the latest information. The use of microsphere systems is categorized into various new drug delivery routes, including gastroretentive, colon, nasal and pulmonary, parenteral, ocular, and topical applications.

Keywords: Microspheres, Microparticles, New drug delivery, Polymer, Route of drug use

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INTRODUCTION

Microspheres are a form of drug delivery system using polymers. Polymer comes from the Greek word "meros", meaning large molecules with repeated arrangements connected by covalent bonds. Spherical particles, known as microspheres, have dimensions in the high nanometer to micron range [1]. Microspheres are adaptable objects with special qualities that make them useful for a variety of uses. Their process of synthesis enables customization and control over the material's size, shape, and composition. The choice of method for preparing microspheres is highly dependent on the type of polymer that adapts to the desired properties of the microspheres and the particular application to be used. Microsphere systems are often used to modify drug delivery systems. For example, galantamine pamoate microspheres developed using the solvent evaporation emulsion method could provide extended release of the drug for 24 d *in vitro* and the plasma drug concentration remained stable for 17 d *in vivo* when tested in rats [2]. Another study by Bolourchian and Bahjar [3] reported an extended-release diltiazem hydrochloride preparation, which was formulated in microsphere dosage forms using Eudragit RL and RS polymers by a similar method. Tilmicosin microspheres using gelatin polymers can also provide a sustained release effect that has the potential to be used in veterinary clinics [4]. Sodium bicarbonate formulated in ethyl cellulose microspheres also showed extended drug release for up to 40 h [5]. Microspheres can also be used to extend drug release in the stomach (i.e., a gastroretentive system). Amoxicillin trihydrate microspheres formulated using *Sterculia foetida* and pullulan polymers can form a mucoadhesive system in the stomach [6].

The microsphere system can also be used to increase the bioavailability of drug preparations. Preparation of asenapine maleate (ASM) microspheres as an agent for schizophrenia therapy using poly(lactic acid-co-glycolic) can significantly increase the bioavailability of the drug [7]. Salbutamol sulfate microspheres made using cross-linked chitosan and carrageen an can increase their bioavailability 1.61 times compared to salbutamol tablets on the market [8]. Likewise, the biodegradable alginate microsphere formulation of doxorubicin with a high concentration of $NaHCO_3$ can increase the cytotoxicity effect *in vitro* assays using hepatocellular carcinoma-derived cell lines [9]. Apart from being a drug delivery system, the microsphere system can also be used as a method to mask the unpleasant taste of drugs. Research on the manufacture of ibuprofen microspheres with octadecanol and glycerin monostearate as the ingredients shows that the release profile and flavor masking effect are strongly influenced by the preparation process in the preparation of ibuprofen microspheres [10].

This review was conducted to look at development trends in research on the use of microspheres in various application routes from 2019 to 2022. A literature search was conducted based on publications indexed by Scopus, ScienceDirect, and PubMed related to the use of microspheres in drug administration. The journals obtained were then analyzed based on inclusion criteria, namely journals published from 2019 to 2022, which are journals in the pharmaceutical field and in English. The exclusion criterion for selecting a journal was that it was not a review journal. This research is expected to provide an overview of the development of the use of the microsphere system in various routes of drug administration. This review will provide an overview of considerations in formulating microsphere preparations. However, this review article is limited to only providing information regarding the considerations for selecting polymers for different application routes and the methods used to manufacture microspheres.

Gastroretentive microspheres drug delivery

A gastroretentive system is a form of delivery system that is formulated so that medicinal ingredients can last longer in the stomach. Modifications of the system using various types of polymers have been carried out to produce microspheres that can last longer in the gastrointestinal tract. The development of microsphere formulations for gastroretentive delivery systems was not only intended for gastrointestinal drugs but also for drugs with systemic effects such as pregabalin, gabapentin, furosemide, simvastatin, and alogliptin. In general, these microspheres are formulated to increase the residence time of drugs in the stomach to increase their bioavailability [11–15].

The choice of polymer varies greatly, which also determines the method used for the preparation of microspheres. Polymers that can expand and float in gastric juices are typically selected for the gastroretentive system. The emulsion solvent evaporation method is the most widely used in formulation because of its ease in the manufacturing process. In this method, the polymer solution is dispersed in an organic solvent to form an emulsion, which is then evaporated to form microspheres. Several ionic-charged polymers have also been used to produce gastroretentive microspheres via the ionic gelation method, such as the *Bletilla striata* polysaccharide

formulation using alginate, famotidine using *Mimosa pudica* seed mucilage as a natural mucoadhesive polymer, famotidine using locust bean gum (LBG) and polyvinyl alcohol (PVA), amoxicillin trihydrate using semi-interpenetrating *Sterculia foetida-pullulan*, and pregabalin using pectin. The addition of a cross-linking agent has also been carried out to increase the bond strength between polymers to extend the drug release time [6, 13, 16-18].

Flotation and swelling degrees are two of the most important parameters determining the success of gastroretentive microsphere formulations [13]. Several microsphere formulations for *in vitro* drug release followed the kinetics described by Higuchi and Korsmeyer Peppas and were diffusion-regulated. The non-fiction form of the *in vitro* drug release mechanism was governed by the polymer's expansion and contraction. Microspheres have the twin benefits of flotation and mucoadhesiveness to boost oral bioavailability and release medications in a regulated manner to lower the necessary frequency of administration, thus enhancing patient compliance [15, 17, 19].

Table 1: Summary of gastroretentive microspheres drug delivery

No.	Active substance	Polymer	Method	References
1	Itraconazole	Ethyl cellulose as a low-density polymer and Eudragit E100 as a release modifier	Emulsion solvent diffusion-evaporation	[19]
2	*Bletilla striata* polysaccharide	Sodium Alginate	Ionotropic gelation	[16]
3	Simvastatin	HPMC K4M as carrier polymer and Eudragit RSPO	Spray drying	[11]
4	Famotidine (FX) and clarithromycin (CLX)	Thiolated polyacrylic acid (TPA)	Emulsion solvent evaporation	[20]
5	Famotidine	*Mimosa pudica* seed mucilage as a natural mucoadhesive polymer	Ionic gelation	[17]
6	Lafutidine	Chitosan	Emulsion solvent evaporation	[21]
7	Famotidine	Locust bean gum (LBG) and polyvinyl alcohol (PVA)	Emulsion cross-linking	[18]
8	Lafutidine	Eudragit Grades	Emulsion Solvent Evaporation	[22]
9	Pregabalin	Ethyl cellulose (EC) and polyvinyl pyrrolidone (PVP)	W/O/O multiple emulsion	[12]
10	Amoxicillin trihydrate	Sterculia foetida-pullulan-based semi-interpenetrating polymer	Emulsion crosslinking	[6]
11	Pregabalin	Pectin	Ionotropic Gelation	[13]
12	Alogliptin	Cellulose acetate butyrate (CAB) and polyethylene oxide (PEO)	Emulsion solvent evaporation	[14]
13	Furosemide	Ethyl cellulose (EC) and hydroxypropyl methylcellulose (HPMC)	Emulsion solvent volatilization	[23]
14	Gabapentin	HPMC K100	Solvent evaporation	[15]
15	Nifedipine	Poloxamer 407 and carbopol 934	Single emulsion cross-linking	[24]

Colon microspheres drug delivery

The use of the microsphere system as an effort to target drugs for the colon is widely used. The choice of polymer type plays an important role. The polymers selected have to be able to survive through the upper gastrointestinal tract so that the drug can be delivered to the colon. In general, this system is developed for drugs that act locally in the colon or have limitations when they are in the gastrointestinal tract.

This delivery system is used for some nonsteroidal anti-inflammatory agents, such as flurbiprofen (a BCS II-class drug), which is used to treat ulcerative colitis. Ileocolonic flurbiprofen mucoadhesive microspheres are formulated to prevent gastric side effects but also improve patient compliance. Utilizing chitosan as a polymer, core microspheres were prepared using an emulsification-crosslinking process. They were then coated with enteric coating polymers, such as Eudragit L100 and Eudragit S100, using an emulsion solvent evaporation process to create a colon-specific delivery system. The drug-loaded microspheres had a spherical form with a rough surface. The microspheres also showed a sustained and desired drug release profile *in vitro* [25].

The use of Eudragit class polymers, which are pH-sensitive, is the choice of various drug formulations for colonic delivery [26–28]. Mesalamine microspheres, intended to treat inflammation of the colon, have been previously prepared using the ionic gelation technique, which included the use of sodium alginate and pectin as release modifiers and calcium chloride as a crosslinking agent. Eudragit S100 has a coating polymer that aids in medication release at the desired location. *In vitro* drug release of mesalamine from the microspheres examined in pH 7.4 phosphate buffer using the USP dissolving device II showed a maximum release of 99.75% at a maximum time of 9 h [29].

Site-specific delivery of drugs to areas of the colon is of great interest for the local treatment of many colonic disorders, such as ulcerative colitis and colon cancer. The delivery system must be able to prevent hydrolysis and degradation of the drug. The use of jackfruit seed starch and its thiol derivatives as drug carriers for the large intestine is quite potential. A previous study reported the isolation of starch from jackfruit seeds using the water extraction method, followed by modification using the thioglycolic acid esterification procedure. Microspheres were then prepared using the thiolated starch using an ionic gelation process with ibuprofen as the model drug. Thiolated starch microspheres released the most drug at pH 7.4 in the presence of caecal content in rats for up to 24 h, compared to pH 1, 2, and pH 6.8, which followed first-order release kinetics. These findings imply that using thiolated jackfruit seed starch as a long-term drug delivery carrier for the colon could be beneficial [30].

Another natural polymer that has potential as a delivery system through the colon is fenugreek seed mucilage and sodium alginate, which can be made into microspheres using the ionic gelation method. Its ability to survive gastric fluid conditions makes this polymer able to deliver 5-fluorouracil for the treatment of colon cancer [31]. The use of pectin and Na CMC polymers on progesterone microspheres showed pH-dependent swelling, insignificant drug release in the simulated gastric fluid, and a sustained release pattern in the simulated small intestinal fluid. These findings support the capacity of a novel carrier system to enhance the oral bioavailability of progesterone while maintaining clinical efficacy [32]. The use of pH-sensitive polymers such as alginate is also used in colonic delivery preparations. The choice of polymer will certainly affect the preparation method to be carried out, as in the case of ionically charged polymers, researchers generally use ionic gelation techniques to form strong cross-linked bonds between polymers [28, 33, 34].

Nasal and pulmonary microspheres drug delivery system

Nasal and pulmonary drug delivery systems are starting to develop as an alternative route for delivering drugs that have problems when administered orally and for local treatment of the respiratory tract. These systems are generally used for drugs that have small doses. The use of the nasal and pulmonary microspheres utilizes the existing mucosa in the respiratory system. The use of mucoadhesive polymers helps increase the bioavailability of drugs delivered through the nasal and pulmonary systems.

Chitosan polymer is one of the most widely used polymers in nasal and pulmonary delivery systems. Its non-toxic, biocompatible,

antibacterial, and biodegradable properties have been significantly proven in several studies applied in the biomedical and pharmaceutical fields. The amine group in chitosan determines various properties of chitosan, such as cationic properties, ability to control drug release, mucoadhesive properties, *in situ* gelation, antimicrobial properties, permeation enhancement, and so on. Chitosan microspheres as nasal and pulmonary preparations can increase the drug's residence time, which is longer in the nasal cavity, thereby increasing the effect of drug therapy locally and systemically [38–41]. Ethyl cellulose is a component in some chitosan microsphere formulations. The efficiency of drug entrapment and matrix drug release is anticipated to be influenced by this biopolymer, which is intended to be inert, food-grade, water-insoluble, non-ionic, and nonreactive [42, 43]. To maximize bioavailability via the nasal route, several methodologies, such as applying mucoadhesive formulations that adhere to the mucous membranes, can address the problem of mucociliary clearance. Potential mucoadhesive polymers used include polylactic-co-glycolic acid, alginate, gellan gum, pectin, and hypromellose [44-49].

Ciprofloxacin HCl microspheres based on carrageenan polymers as a dry powder inhalation dosage form have been previously reported. The microspheres were successfully prepared via the ionic gelation method and have been shown to improve drug bioavailability and release mechanisms in the pulmonary system [50]. In addition to local treatment in the nose, several current studies are also focusing on the manufacture of nasal mucoadhesive microspheres for drug delivery to the brain, such as rivastigmine microspheres using chitosan and ethyl cellulose polymers by solvent evaporation and donepezil microspheres with a carrier matrix based on mannitol and chitosan using spray drying, both intended for treating Alzheimer's disease and a sprayable dexamethasone sodium phosphate formulation for regulating neuroinflammatory processes in patients with severe COVID-19 [41, 43, 51].

Table 2: Summary of colon microspheres drug delivery

No.	Active substance	Polymer	Method	References
1	Dicyclomine hydrochloride chitosan	Ethylcellulose as a low-density polymer and Eudragit E100 as a release modifier	Emulsion crosslinking and solvent evaporation	[26]
2	Ibuprofen	Thiolated jackfruit seed starch	Ionic gelation	[30]
3	Puerarin	Alginate	Emulsification/internal gelation	[33]
4	Flurbiprofen	Chitosan microspheres were coated with Eudragit L-100 and Eudragit S-100	Emulsion solvent evaporation	[25]
5	Progesterone	Pectin and Na CMC	Ionic gelation	[32]
6	Mesalamine	Sodium alginate and pectin	Ionic gelation	[29]
7	5-fluorouracil	fenugreek seed mucilage-sodium alginate	Ionotropic gelation	[31]
8	*Lactobacillus rhamnosus* GG (LGG)	Eudragit® S100	Spray drying	[27]
9	Fluorouracil and Oxaliplatin	Alginate and guar gum polymers for Fluorouracil. Alginate and chitosan polymers for Oxaliplatin. Coated with Eudralgit s100	Ionotropic gelation	[28]
10	Epigallocatechin gallate	Chitosan (CS) and Gum acacia (GA)	Water-in-oil emulsion crosslinking	[35]
11	Curcumin and Epigallocatechin gallate	Chitosan (CS) and Gum acacia (GA)	Water-in-oil emulsion crosslinking	[36]
12	Meloxicam	Sodium alginate and Eudragit-coating	Ionotropic gelation	[37]
13	Piroxicam	Pectin and Zein	Ionic Gelation	[34]

Table 3: Summary of nasal and pulmonary microspheres drug delivery

No.	Active substance	Polymer	Method	References
1	Levofloxacin	Poly (lactic-co-glycolic acid)	Modified Double Emulsion Solvent Evaporation Method With Premix Membrane Homogenization	[44]
2	Sildenafil Citrate	Sodium Carboxymethyl Cellulose, Sodium Alginate, And Sodium Hyaluronate	Spray-Drying	[45]
3	Ciprofloxacin HCl	Carrageenan	Ionic Gelation	[50]
4	Melatonin	Pectin and Hypromellose	Spray-Drying	[46]
5	Lurasidone HCl	Chitosan and Eudragit L 100	Spray-Drying	[52]
6	Tetanus toxoid	Trimethyl chitosan	Ionic gelation	[53]
7	Ropinirole hydrochloride	Alginate	Spray-Drying	[54]
8	Astragalus polysaccharide	Chitosan	Spray-Drying	[38]
9	Granisetron	Chitosan	Emulsification cross-linking	[39]
10	Donepezil Hydrochloride	Gellan gum	Spray-Drying	[47]
11	Mometasone furoate	Poly (lactic-co-glycolic acid)	Solvent evaporation	[55]
12	Meloxicam	Chitosan	Spray-Drying	[40]
13	Lercanidipine	Bovine serum albumin	Solvent Evaporation	[56]
14	Domperidone	Chitosan-ethyl cellulose	Solvent Evaporation	[42]
15	Dexamethasone sodium phosphate	Pectin and Hypromellose	Spray-Drying	[51]
16	Rivastigmine	Ethylcellulose and Chitosan	Solvent Evaporation	[43]
17	Naloxone	Lactose monohydrate	Modified spray drying	[57]
18	Exenatide	Poly (lactic-co-glycolic acid)	Double emulsion (w/o/w) solvent evaporation	[48]
19	Donepezil	Chitosan and mannitol-based	Spray-Drying	[41]
20	Vitamin D3	Poly (lactic-co-glycolic acid)	Solvent extraction	[49]
21	Hydrocortisone sodium succinate	Chitosan and HPMC	Orifice ionic gelation	[58]

Parenteral microspheres drug delivery system

In recent years, microsphere dosage forms have also been used for parenteral delivery systems. Microspheres are used as a depot system to obtain a controlled drug delivery system for parenteral preparations. For instance, glatiramer acetate (GA) microspheres have been previously developed to prevent the recurrence of multiple sclerosis. This drug is generally used through repeated subcutaneous

injections every day or twice a week due to the fast clearance of the drug in the body. For this reason, a parenteral microsphere system was developed in the form of an implant using poly (lactic-co-glycolic acid) polymer to release the drug continuously and gradually so that the patient does not need to be injected repeatedly [59]. Human chorionic gonadotropin hormone microspheres have also been formulated for a similar purpose to treat fertility problems in women and increase sperm count in men [60].

Poly (lactic-co-glycolic acid) is the most commonly used polymer in microsphere formulations for parenteral applications. Due to their simplicity in fabrication and capacity to release the active component over several weeks to months by adjusting formulation aspects, poly (lactic-co-glycolic acid) microspheres are attracting more and more interest in this field. Due to their vast superiority to conventional formulations, delivery carriers provide numerous intriguing options for management and successful treatment. The most dependable and well-liked delivery technology for parenteral controlled-release depot injections is the microparticulate drug delivery system [61]. The routes of administration for the parenteral microsphere preparations are generally intramuscular and subcutaneous, wherein the tissues are generally used for energy storage (muscle) and release of other tissues (adipose tissue). The tissue is composed of a lipid bilayer, so the drug released in the tissue will likely interact with the existing lipids and fatty acids, affecting the partition of the drug and the speed of drug release [62].

Table 4: Summary of parenteral microspheres drug delivery

No.	Active substance	Polymer	Method	References
1	Leuprolide Acetate	Poly (lactic-co-glycolic acid)	Solvent evaporation	[63]
2	Leuprolide Acetate	Poly (lactic-co-glycolic acid)	Solvent evaporation	[64]
3	Curcumin	Alginate	Emulsification/gelation	[65]
4	Regorafenib	Poly (lactic-co-glycolic acid)	Emulsion-Solvent Evaporation	[66]
5	Celecoxib, Clotrimazole, Erythromycin, Ibuprofen, Indomethacin, Itraconazole, Lopinavir and Ritonavir	Poly (lactic-co-glycolic acid)	Solvent Evaporation	[67]
6	GnRH agonist leuprolide acetate	Poly (lactic-co-glycolic acid)	Double emulsion solvent evaporation	[61]
7	Flurbiprofen, Lidocaine, or Risperidone	Poly (lactic-co-glycolic acid) or Ethylcellulose	Solvent Evaporation	[68]
8	Flurbiprofen, Lidocaine, or Risperidone	Various grades of poly (lactic-co-glycolic acid) or Ethylcellulose	Solvent Evaporation	[62]
9	Aripiprazole	Polycaprolactone	O/W Emulsion Solvent-Evaporation	[69]
10	Bovine serum albumin (BSA)	Poly (lactic-co-glycolic acid)	Double emulsion solvent evaporation	[70]
11	Paliperidone palmitate	Poly (lactic-co-glycolic acid)	Oil in water (O/W) emulsion solvent evaporation	[71]
12	Ivermectin	Polycaprolactone	Solvent Evaporation	[72]
13	Human Chorionic Gonadotropin (hCG) hormone	Poly (lactic-co-glycolic acid)	A modified double emulsion solvent evaporation	[60]
14	Glatiramer acetate	Poly (lactic-co-glycolic acid)	Emulsification	[59]

Ocular microspheres drug delivery system

The primary goal of incorporating microspheres into ocular preparations is to address issues with traditional aqueous eye drop formulations, such as the quick removal of the medication from the eye. There are various techniques for manufacturing pharmaceuticals in microparticulate dosage forms for intraocular and topical delivery. Microspheres are designed to stick to the ocular surface for a lengthy period, improving the bioavailability of the encapsulated drug [73–75]. Erodible microparticulates, swelling mucoadhesive particulates, pH-responsive microparticulates, nanoparticles and latex systems, and ion-exchange resins are a few methods used to formulate medications in microparticulate dose form for intraocular and topical delivery. It has been established that infections of the posterior segment can be treated by injecting bioerodible microparticles into the vitreous humor [76]. However, there are several drawbacks to employing microspheres in ocular medication delivery systems, including the danger of corneal abrasion and injury and inadequate drug release. For instance, the use of microsphere suspensions in the eye may result in partial drug release, and the size of the microparticles should not be greater than 10 μm to avoid irritation and harm to the cornea through ocular abrasion [77].

In the creation of controlled drug delivery systems for ocular preparations, biodegradable polymers are frequently used. As the polymer breaks down at the target spot, these microspheres release the medication. The device eventually vanished, avoiding the need for surgery to remove it. Polymers have been utilized to create injectable particles and ocular implants. One of the most commonly utilized biodegradable polymers in ocularly controlled drug delivery systems is poly (lactic-co-glycolic acid). In an aqueous environment, like the eye, poly (lactic-co-glycolic acid) progressively breaks down and transforms into water-soluble by-products. This characteristic guarantees that the microspheres are evacuated from the implant site and cleansed by the body through metabolic pathways, ensuring their effectiveness and safety. The ability to gradually release medications or therapeutic agents, which eliminates the need for repeated injections or administrations, makes this attribute crucial in ocular microsphere formulations [78–80]. Chitosan microspheres that are loaded with levofloxacin make it a possible platform for prolonged drug release for use in treating eye infections [81].

The synthesis of multi-loaded poly (lactic-co-glycolic acid) microspheres combining two neuroprotectant drugs with a solid-in-oil-in-water (S/O/W) emulsion solvent extraction-evaporation approach demonstrated consistent *in vitro* releases over 91 d [82]. Another study assessed the *in vivo* tolerability of dexamethasone-loaded microspheres (Dx-MS) made by evaporating solvent from an oil-in-water (O/W) emulsion [83]. Dx-MS may offer an alternative to intravitreal injections for long-term back-of-the-eye conditions [83]. MsDexafibro injection of biodegradable poly (lactic-co-glycolic acid) microspheres co-loaded with dexamethasone and fibronectin has been used to develop an animal model for chronic glaucoma [76]. Optical coherence tomography detected increasing neuro-retinal deterioration in both eyes, with higher levels in the injected eye [80]. Semi-interpenetrating polymer microspheres are potential ocular delivery systems for the regulated administration of timolol maleate for the treatment of glaucoma [84].

Topical microspheres drug delivery system

Microsphere systems in topical preparations are indeed not very common. Drugs can be delivered to particular target locations on the skin using microspheres as carriers. The microspheres can be used to encapsulate pharmaceuticals, enabling controlled release and extended pharmacological action. Drugs can be released continuously from microspheres over a long period of time. The therapeutic drug levels in the skin can be maintained and treatment effectiveness can be increased by the controlled release of medications from microspheres. By enhancing drug penetration into the skin and boosting drug bioavailability, microspheres can

improve the therapeutic efficacy of topical therapies. They can also serve as bulking agents or fillers, giving the skin structural support and volume. The stability of active components in topical treatments can be improved via microsphere compositions. Drugs can be shielded from oxidation, deterioration, and other environmental effects by being encapsulated within microspheres, preserving their potency over time [87].

Microspheres can be used to maintain the stability of active substances such as glutathione, which is easily oxidized in its native form. Glutathione microspheres have been previously prepared using alginate by the ionotropic gelation process method. All release patterns were determined to follow Higuchi's diffusion model in kinetic analysis designs [88].

With 20–25% of the world's population affected, dermatophytosis (a topical fungal infection) is the fourth most prevalent disease in the past ten years. To treat this infection in a controlled manner, graphene-ketoconazole nanohybrid (Gn-keto) microspheres using the polymethacrylate derivative Eudragit (ERL100 and ERS100) were created and studied. The formulated Gn-keto microspheres demonstrated synergistic antifungal action against a subset of topical fungal infections, indicating a critical function for graphene in fungi [89]. Microsphere topical preparations have also been used to increase the effectiveness and potency of antibiotics [90–93].

In the current study, a sunscreen cream containing Benzophenone-3 microspheres was created, and an effort was made to administer the sunscreen agent from the cream's microspheres in a continuous release way. The consistency of sunscreen cream is uniform; it applies smoothly, spreads and extrudes well, and is milky white. According to *in vitro* drug release research, cream-containing microspheres at 1% and 2% follow zero-order release kinetics, meaning the release rate is constant [94].

Table 5: Summary of ocular microspheres drug delivery

No.	Active substance	Polymer	Method	References
1	Bevacizumab	Poly(d, l-lactide-co-glycolide)/poly (cyclohexane-1,4-diyl acetone dimethylene ketal)	Solid-In-Oil-In-Water (S/O/W) Emulsification	[73]
2	Dexamethasone (DX), Melatonin (MEL) And Coenzyme Q10 (Coq10)	Poly(lactic-co-glycolic acid)	Oil/Water emulsion solvent extraction-evaporation	[85]
3	Levofloxacin	Chitosan	Spray-drying technique	[81]
4	Sunitinib malate	Poly(lactic-co-glycolic acid)	Emulsification method.	[74]
5	Atorvastatin Calcium-Poly-E-Caprolactone	Methylcellulose (MC) and Polyvinyl Alcohol (PVA)	Solvent evaporation	[75]
6	Glial cell-line-derived neurotrophic factor-GDNF and Tauroursodeoxycholic acid-TUDCA	Poly(lactic-co-glycolic acid)	Solid-in-oil-in-water (S/O/W) emulsion solvent extraction-evaporation technique	[82]
7	Dexamethasone	Poly(lactic-co-glycolic acid)	Oil-in-water (O/W) emulsion solvent evaporation technique	[86]
8	Dexamethasone and fibronectin	Poly(lactic-co-glycolic acid)	Water-in-oil-in-water emulsion method including dexamethasone in the organic phase and fibronectin in the inner aqueous phase	[80]
9	Timolol Maleate	Psyllium (PSY) and polyvinyl alcohol (PVA)	Emulsion cross-linking method	[84]

Table 6: Summary of topical microspheres drug delivery

No.	Active substance	Polymer	Method	References
1	Glutathione	Alginate	Ionotropic gelation method by aerosolization	[88]
2	Graphene–ketoconazole nanohybrid (Gn-keto)	Polymethacrylate derivative Eudragit (ERL100 and ERS 100)	Spray-drying technique	[89]
3	Nisin	Sodium alginate-gelatin	Ionotropic gelation	[90]
4	Usnic Acid	Eudragit	Solvent evaporation	[95]
5	Metronidazole	Chitosan and alginate	Ionotropic-gelation technique,	[91]
6	Acyclovir	Polyvinyl Alcohol (PVA)	Quasi-emulsion diffusion	[92]
7	Benzophenone-3	Gelatin	Emulsion cum thermal gelation technique	[94]
8	Clarithromycin	Ethylcellulose	Quasi-emulsion solvent diffusion	[93]

CONCLUSION

Microspheres can be used in a variety of drug delivery methods, including gastroretentive, colon, nasal and pulmonary, parenteral, ocular, and topical administration. The polymer used is largely dictated by the delivery system to be used, and in general, the preparation of microspheres is highly dependent on the characteristics of the active substance and the type of polymer. Research on microspheres in recent years has focused mostly on the applications of microspheres in nasal and pulmonary delivery systems, with the least attention given to the use of microspheres in topical delivery systems. In the future, deeper studies can be carried out to evaluate the characteristics of the microspheres in each drug delivery system.

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CONFLICT OF INTERESTS

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