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Microspheres and their applications in drug delivery system

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Abstract

This article focuses on microspheres, types, preparation and their applications in drug delivery system. based on recent literatures. The microspheres are used for drug delivery that offers a potent therapeutic substitute for traditional or immediate-release single-unit dose forms. Microspheres are solid objects with diameters ranging from 1 to 1000µ m. The numerous types of microsphere are employed in the delivery of medications. The efficacy and administration strategies of the variously produced microspheres differ from those of standard dose forms. The microsphere is evaluated using a variety of methods that analyse the microsphere's quality. Finally brief summary of the current difficulties in processing these microspheres, which calls for additional study and development, is offered in the end.

Keywords: Microspheres; Types; Preparation; Evaluation; Applications; Drug delivery systems; Polymers

1. Introduction

- Microspheres are naturally biodegradable powders made of proteins or synthetic polymers that flow freely and preferably have a particle size of less than 00 m. This is a crucial strategy for controlled and sustained delivery of medicinal ingredient to the target region.
- Microspheres enable precise delivery of small doses of powerful medication and lower drug concentrations at sites other than the target organ or tissue.
- They preserve unstable drugs both during and after administration, before they are accessible at the site of action.
- They offer details on how to control pharmacological activity in vivo, pharmacokinetic profile, drug distribution in tissues, and cellular interactions. They have the ability to regulate medication release. Drugs, antagonists, and steroid hormones are a few examples [1,2].
- The commonly used materials are polymers. They are divided into two categories
  A. Synthetic polymer
  B. Natural polymer
- Synthetic polymers
- Non-biodegradable polymers**:** polymethyl methacrylate (PMMA), acrolein, glycidol Methacrylate, epoxy polymer
- Biodegradable polymers**:** lactides, their glycosides and their copolymers, polyalkylenes Cyanoacrylate, polyanhydride
- B.Natural polymers It is obtained from different sources such as proteins, carbohydrates and chemically modified products.carbohydrates
- Proteins**:** albumin, gelatin and collagen, carbohydrates: agarose, carrageenan, chitosan, starch, chemicals
- .Modified carbohydrates**:** poly (acrylic acid) dextran, poly (acrylic acid) starch[3].

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Various types of microspheres used for drug delivery are:

- Bio adhesive microspheres
- Magnetic microspheres
- Floating Microspheres
- Radioactive Microspheres
- Polymer microspheres [4].

Various methods used for preparation of microspheres:

- Single emulsion technique
- Double emulsion technique
- Polymerization: A) Normal polymerization B). Interfacial polymerization
- Phase separation/ Coacervation
- Spray drying
- Solvent extraction
- Emulsion Solvent Evaporation [5].

Physical, chemical characteristics and evaluation.

- Particle size and shape: laser microscopy, scanning electron microscopy
- Electron spectroscopy for chemical analysis: determination of surface chemistry
- Attenuated Total Reflection Fourier Transform Infrared Spectroscopy: Determination of Degradation
- Catch rate: % catch = actual content/theoretical content × 100
- Thermal Analysis: Differential Scanning Calorimetry (DSC)
- Swelling index: Characterization of microspheres using the swelling index technique
- METHOD: Take another solution (100ml) such as (distilled water, buffer solution with pH value (1.2,4.5, 7.4) Take alginate microspheres (100mg) and place them in a wire basket. The solution and the swelling allow a weight change between 37oC and the initial weight. The weights of microspheres and aerated are measured by periodic weighing and dipping Filter paper.
- Swelling index=initial weight-final weight/initial weight×100
- Floating behavior: 50 mg of floating microspheres in 100 ml of simulated solution, Gastric fluid. (SGF, pH 2.0) containing 0.02% w/v Tween 20 Shake the mixture at 100 rpm.Use an electromagnetic stirrer to aspirate the layer of live microspheres after 8 hours filtered.The particles in the layer of deposited particles are separated by filtration.
- Driving force (%) = Wf / Wf + Ws where Wf and Ws are the weights of the floating and suspended particles
- Microscopic properties, such as bulk density, bulk density, compressibility index, angle of collapse, etc are also studied.
- Release studies of different types of microspheres have been performed using different appropriate solutions, Media, rotating paddles (USP/BP) Rotation speeds vary between 50 and 100 rpm
- Samples are taken at specific time intervals and replaced with an equal volume of solution medium
- The active ingredients extracted from the samples were analyzed according to the requirements and exemptions of the monograph
- Use the amount of stretch released versus time to determine the profile dialysis and franz
- Diffusion cell technology is also used
- The isoelectric point, surface carboxylic acid residues and surface amino acid residues were also studied [6,7].

2. Applications of microspheres in various drug delivery systems

2.1. Microspheres for colon drug delivery

- Calcium pectate/alginate (PAM) microspheres and their pH-sensitive properties for colon-targeted delivery of encapsulated cisplatin PAM was prepared using the electro spray method The PAM as a core is then coated with Eudragit S100 using polyelectrolyte multilayer coating technology in aqueous solution The morphology of the microspheres was observed under a scanning electron microscope. *In vitro* drug release studies in simulated gastrointestinal fluids showed that approximately 5% of cisplatin was released from Eudragit S100-coated MAP and 51% of cisplatin was released from uncoated MAP within 1 hour. Cisplatin release from Eudragit S100-coated PAM was more persistent in simulated gastric fluid than in simulated intestinal fluid due to the increased

solubility of the coating polymer in media at pH >7.0 Drug release from PAM coated with Eudragit S100 is best described by Higuchi's square root model From these results, it can be concluded that PAMs coated with Eudragit S100 are potential vehicles for the delivery of cisplatin to the colon.[8,9].

- Formulation and optimization of colon-targeting tinidazole microspheres -These microspheres were prepared by emulsion solvent evaporation using Eudragit polymers. A 32-factor design was used in the formulation of the microspheres, with wetting agent concentration (A) and agitation speed (B) as independent variables Percent drug release was considered as the dependent variable The effects of drug-polymer concentration, surfactant concentration, cross-linking agent and agitation speed were evaluated in terms of encapsulation efficiency, particle size, surface properties , crystallite properties, DSC studies and *in vitro* drug release studies It has been found that the particle size and encapsulation efficiency vary depending on different formulation parameters such as surfactant concentration and stirring speed, etc. There is a trace of volatilization of the solvent during the process The release profile of tinidazole from Eudragit microspheres is pH dependent in acidic media, the release rate is much slower; however, the drug is released rapidly at pH 7.4. Eudragit microspheres hold promise as a vehicle for targeted colonic delivery of tinidazole [10].

2.2. Microspheres for opthalmic drug delivery

- Most posterior segment diseases are chronic and multifactorial, requiring long-term intraocular medication Conventional treatment for these conditions involves continuous intraocular injections, which have been associated with side effects Successful therapy requires the development of new drug delivery systems that release active substances for long periods from a single dose. The present work involves the description of a new generation of poly(ester amide) (PEA)-based microspheres, novel polymers with improved biodegradability, process ability, and favorable thermal and mechanical properties the preparation and characterization of PEA polymers, PEA microspheres (PEA Ms). PEA M (~15 μm) were loaded with a lipophilic drug (dexamethasone) (181.0 ± 2.4 μg DX/mg Ms) The *in vitro* release profile of the drug showed sustained release for at least 90 days Based on *in vitro* release study, a kinetic ocular model was developed to predict in vivo drug concentrations in the rabbit vitreous body. According to pharmacokinetic simulations, intravitreal injection of dexamethasone-loaded PEA microspheres provided up to 3 months of drug release in rabbit eyes. Cytotoxicity studies in macrophages and retinal pigment epithelial cells showed that the microsystem was well tolerated *in vitro*. After sterilization, PEA M was administered to male Sprague-Dawley rats by sub-balloon and intravitreal injection, and the location of the microspheres in the rats was monitored and PEA Ms provide an alternative delivery system to control drug delivery to the eye, enabling a new generation of microsphere design[11].
- For evaluating the potential use of chitosan microspheres for ocular delivery of acyclovir Topical application of acyclovir as an ophthalmic ointment remains a problem in the effective management of various ocular viral diseases due to the low ocular bioavailability of the drugs. Chitosan microspheres containing acyclovir as a potential ophthalmic drug delivery system Acyclovir-loaded chitosan microspheres were prepared by ion gelation of chitosan and tripolyphosphate anion. The microspheres were characterized by particle size, zeta potential, surface morphology, differential scanning calorimetry and Fourier transform infrared spectroscopy. All prepared formulations produced micrometric particles (2–12 μm) and exhibited smooth spherical morphologies with zeta potentials (+36.1–+43.6 mV) Encapsulation efficiency and loading were 52% - 78% and 12% - 26%, respectively Acyclovir-loaded chitosan microspheres showed greater crystallinity than acyclovir The *in vitro* diffusion profile of acyclovir from microspheres shows sustained drug release over 24 hours. The kinetic release profile of acyclovir from the microspheres appears to fit better with the first-order Higuchi model, with non-Fickian diffusion phenomena being preferred. Thus, suspensions of chitosan microparticles loaded with acyclovir showed effective control of ocular viral infection [12].

2.3. Microspheres for transdermal drug delivery

- Transdermal drug delivery systems in the form of hydrogel films can deliver drugs through the skin at a predetermined and controlled rate for systemic effects. This system has the advantage of avoiding first-pass metabolic effects. Medication delivery can be easily interrupted when needed by simply removing the device. A hydrogel patch composed of chitosan and cross-linked starch with GA was prepared for the controlled release of the α-hydroxy acids contained in the tamarind pulp extract48. The resulting patch showed good bio adhesive properties, with the amount of tartaric acid released being proportional to the square root of time (Higuchi model). curcuminoid hydrogel patch composed of chitosan and starch has been developed for cosmetic applications. The rapid release of curcumin was observed by the vertical diffusion cell method. A transdermal drug delivery system has been developed for the treatment of cutaneous leishmaniasis by incorporating berberine into a chitosan hydrogel *In vitro* dermal perfusion studies showed that only traces of berberine could penetrate rat skin due to the low oil-water partition coefficient. Surfactants may enhance the transdermal

absorption of berberine. A novel transdermal chitosan patch of lidocaine hydrochloride has been developed using chitosan membranes for rate control and chitosan hydrogels as drug reservoirs. Chitosan with a degree of deacetylation of 95 prolongs drug release *in vitro*[13].

- Domperidone (DMP) is a potent peripheral dopamine D2 receptor antagonist It is commonly used to treat nausea and vomiting caused by Parkinson's disease Oral formulations which are rapidly absorbed after administration and reach peak plasma concentrations within 15-30 minutes are generally used However, due to the "first pass effect" of hepatic metabolism and gut wall metabolism, domperidone has low oral bioavailability and a long duration of action. Therefore, combined spray drying and emulsion solvent evaporation to prepare sustained-release coated microsphere preparations and selected a gel matrix to prepare sustained-release coated microsphere gels for the transdermal administration. The pharmacokinetic results showed that, compared to the oral DMP group, the extended-release transdermal coated microsphere gel effectively improved Tmax, Cmax, T1/2 and AUC ($P<0.05$), and the relative bioavailability was 3. 2 times that of the DMP group the formulation may ameliorate problems associated with traditional oral formulations of DMP. Therefore, they provide a theoretical basis for the transdermal delivery of sustained-release DMP microsphere [14].

2.4. Microspheres for nasal drug delivery

- The nasal mucosa offers a potentially useful site for drug delivery by combining reduced first-pass effects with greater patient acceptability Chitosan hydrogels improve nasal drug absorption because they facilitate paracellular transport of macromolecules at mucosal surfaces by opening tight junctions. Microspheres are synthesized with N-trimethyl chitosan chloride and formulated into a hydrogel containing PEG and GP for nasal administration. Hydrogels containing N-trimethyl chitosan of medium average molecular weight and low degree of quaternization gave an aqueous formulation which underwent a sol-gel transition in 7 minutes at 32.5°C. A heat-sensitive in situ gel system has been prepared by mixing chitosan and polyvinyl alcohol for the nasal delivery of insulin. The prepared hydrogel undergoes a sol-gel transition at 37°C for approximately 12 min. The release of insulin keeps blood sugar levels constant for 6 hours [15].
- Different polymer hydrogels, such as polyvinylpyrrolidone (PVP), chitosan, and carbomer, for nasal delivery of acyclovir the release rate of acyclovir was higher from PVP gels compared to chitosan or Carbopol gels A hepatology study demonstrated that PVP is a safe hydrogel for mucosal administration. A novel heat-sensitive hydrogel system has been prepared for nasal drug delivery by simply mixing quaternate chitosan and PEG with a small amount of α-β-GP. In vivo studies showed that the prepared hydrogel reduced blood glucose concentration (40-50% of initial blood glucose concentration) 4-5 hours after administration Spray-dried microspheres based on methyl pyrrolidone chitosan have been developed for the nasal administration of metoclopramide *In vitro* and in vivo studies suggest that microspheres may be a suitable nasal drug delivery system[16].

2.5. Microspheres for oral drug delivery system

- The use of oral delivery for drug administration is widely accepted. The use of chitosan-based hydrogels as functional biomaterials or controlled release matrices in a variety of therapeutic oral delivery systems has been studied. Drugs have been delivered to specific body parts, including the stomach, colon, small intestine, and oral cavity, using hydrogels based on chitosan. A number of oral diseases, including stomatitis, periodontal disease, fungal and viral infections, and oral cavity cancers, can be treated using site-specific drug delivery to the oral cavity, avoiding the first pass metabolism effect Using spray-drying technology, chlorhexidine buccal tablets were created using drug-loaded chitosan microparticles. The medication showed improved antimicrobial activity against Candida albicans. The formulation displayed a prolonged release of the drug in the buccal cavity, according to an in vivo study. Porphyromonas gingivalis, Prevotella internedia, and Actenobacillus actinomycetem comitans were the periodontal pathogens that the chitosan-based thermosensitive hydrogel was most effective against. The antibacterial process is activated and transported by thermosensitive hydrogel[17].
- For the controlled release of diclofenac sodium (DS), a novel pH-sensitive composite hydrogel containing chitosan-graft-poly (acrylic acid), attapulgite, and sodium alginate was created. At pH 2.1 and 100% at pH 6.8, the cumulative release rate of DS from the composite hydrogel beads was negligible and 24 hours later, respectively. At pH 7.4, the loaded DS was released after two hours. Using nifedine, a brand-new pH-sensitive hydrogel bead made of N-succinyl chitosan and alginate was created. Nifedipine was released *in vitro* from the hydrogel bead at a rate of 11.6% at pH 1.5 and 76% at pH 7.4. For the oral administration of insulin, a superporous hydrogel based on poly (acrylic acid-co-AAm) and N, O-CMCs was created. The oral administration of an insulin-loaded hydrogel produced significant insulin absorption and a hypoglycemic

effect, according to in vivo results. The hydrogel's biocompatibility was verified by a mouse oral acute and subacute toxicity study. Super porous hydrogels were created and tested for their effectiveness in enhancing oral insulin absorption[18].

2.6. Microspheres for vaginal drug delivery system

- Metronidazole is the drug of choice for treating bacterial vaginosis, but oral treatment can cause a variety of side effects The aim of this work was to develop a vaginal multiparticle system loaded with metronidazole that could improve its residence time and achieve complete release of the drug. Different types of Microspheres have been prepared using chitosan dissolved in different organic acids or alginate coated with chitosan Perform FTIR and DSC analysis to study drug-polymer interactions, while light and electron microscopy are used to study Microspheres speciation. All formulations were characterized in terms of drug encapsulation efficiency, mucoadhesion, swelling capacity and drug release behavior, showing the best results for alginate Microspheres coated with chitosan The formulation showed complete rapid release of the drug compared to the commercial form Zidoval®. The best formulation tested for antibacterial activity confirmed the suitability of this new formulation for the vaginal treatment of tropical diseases[19].
- A novel vaginal drug delivery system comprised of clindamycin microspheres embedded in a bioadhesive gel Microspheres were prepared by solvent evaporation using Eudragit RS 100 and Eudragit RL 100 polymers with different drug/polymer ratios The microspheres were found to be discrete, spherical, and had free-flowing properties, and were evaluated for analysis of particle size, shape (scanning electron microscopy), drug encapsulation efficiency, percent drug loading and *in vitro* drug release studies Selected microsphere formulations (F7 and F8, containing drug-to-polymer ratios of 1:1:1 and 1:0.25:1.75, respectively) were incorporated into Carbopol 934P bioadhesive gels. Both gel formulations were evaluated for *in vitro* release studies Stability and antimicrobial activity studies were then carried out on the formulation (F8.CD-MG) which showed a maximum release of 90.12% at 8 hours. The antibacterial activity of F8.CD-MG and placebo gels against Candida albicans j1012 was evaluated using the cup-plate method. CD-MG was able to control the growth of C. albicans for more than 14 hours. The placebo gel showed no zone of inhibition. A 6-month stability study was conducted according to ICH guidelines. Initial and third month studies were conducted and parameters such as pH, drug content, drug content uniformity, extrudability, leveling, viscosity and *in vitro* drug release have been evaluated. CD-MG can be used as a new drug delivery system for the topical treatment of vaginal candidiasis [20].

2.7. Microspheres for pulmonary drug delivery system

- Airgel microspheres based on alginate and hyaluronic acid for potential applications in pulmonary drug delivery were prepared. These two polymers are commonly used in the pharmaceutical and medical fields due to their non-toxic, biodegradable and biocompatible properties. The bio-based microspheres are produced using an emulsion gelation process followed by a supercritical CO2 drying step. The microspheres were characterized by FTIR and SEM In addition, their BET surface, particle size distribution and aerodynamic properties were determined The microspheres have a low density of 0.035 to 0.063 g/cm3 and a high porosity of 97.6 to 98.7%, as well as good aerodynamic properties *in vitro* with a dA value of approximately 5 μm The properties obtained from alginate-hyaluronic acid microspheres suggest that they may be suitable as drug carriers for pulmonary delivery[21].
- Tadalafil is a long-acting PED-5 inhibitor commonly used to treat pulmonary arterial hypertension (PAH) However, its efficacy and clinical application are severely limited by its low water solubility, low bioavailability and a series of adverse effects (such as headache, dyspepsia). tadalafil was prepared and loaded into biodegradable PLGA (poly(lactic-co-glycolic acid)) microspheres (TDF-PLGA-MS) by emulsifying solvent evaporation The microspheres were made into lung inhalers by lyophilization. TDF-PLGA-MS is spherical and uniform with an average particle size of approximately 10.29 μm The encapsulation efficiency and drug loading efficiency of TDF-PLGA-MS were 81.68% and 8.52%, respectively Examination of microscopic indicators showed low water content in TDF-PLGA-MS. The fluidity of the powder is relatively good The aerodynamic diameter and the emptying rate of the microsphere powder are 3.92 μm and 95.41% respectively Therefore, the microsphere powder is easy to atomize and can meet the requirements of pulmonary drug delivery. The *in vitro* release results showed that the release of the microsphere group was slow. The cumulative rejections in 24 hours and 10 days were respectively 46.87% and 84.06%. The *in vitro* release profile of TDF-PLGA-MS was consistent with the Weibull model Pharmacokinetic results showed that tadalafil microspheres were slowly released into the blood after intratracheal instillation The drug residue in the lungs at 0.5 hour was 3.5 times that of the solution group After 10 days, the residual concentration in the lungs was still higher than that of the solution group for 48 hours. t1/2β and MRT0-∞ were 3.10 times and 3.96 times that of the solution group,

respectively the Cmax and AUC of drug residues in the lungs were 3.48 times and 16.36 times, respectively, of the solution group. Tissue distribution results showed that the Re in the lung was 16.358, indicating lung targeting TDF-PLGA-MS for pulmonary administration in this study can significantly improve pulmonary targeting, increase the efficacy of tadalafil, and reduce other non-target organ toxicity[22].

2.8. Microspheres for intestinal drug delivery system

- Most bioactive peptide drugs are administered parenterally, resulting in great pain and risk to patients Oral administration is an acceptable alternative. However, peptide drugs are extremely sensitive to the strongly acidic environment of the stomach after oral administration They are broken down in the digestive tract by pepsin and trypsin. microspheres for oral gut-targeted peptide drug delivery. Sodium alginate reacts with L-cysteine, bringing it into a thiol group. Then the sodium alginate-L-cysteine conjugate is mixed with natural sodium alginate and emulsified by the modified method Ca2+ is used to fix the emulsion in order to obtain microspheres Using bovine serum albumin as a dummy agent, the feasibility of microspheres as an intestinal delivery vehicle was determined. Microspheres have spherical characteristics and a narrow size distribution The drug loading of the microspheres after thiol modification was not affected. the microspheres could maintain structural integrity and keep the drug in the highly acidic environment of the stomach In contrast, the microspheres had the expected sustained gut-targeted drug release capability. the thiol modification further enhanced the adhesion ability of the microspheres to the inner wall of the small intestine, which was beneficial in improving drug permeability thiol-modified sodium alginate microspheres have broad application prospects as intestinal macromolecule-based drug carriers[23].
- Chitosan-based hydrogel systems designed for local drug delivery to the stomach or upper gastrointestinal tract for improved bioavailability an amoxicillin-loaded, pH-sensitive hydrogel composed of chitosan and poly(γ-glutamic acid) for the treatment of Helicobacter pylori (H pylori) infection in peptic ulcer disease Confocal laser scanning microscopy studies revealed that the hydrogel can permeate cell-cell junctions and interact with H pylori infection sites in the intercellular space. Chitosan and polyacrylic acid hydrogels containing amoxicillin and clarithromycin have also been clinically evaluated for the eradication of H pylori39. polyionic hydrogels may be suitable candidates for the site-specific delivery of amoxicillin and clarithromycin into the stomach Modified chitosan hydrogels loaded with metronidazole, tetracycline, and theophylline have been developed for specific administration to the stomach. The modified chitosan hydrogel can bypass the acidic environment of the stomach and release the loaded drug into the intestinal tract [24].

2.9. Microspheres for vaccine drug delivery system

- Adjuvants improve vaccine efficacy by enhancing immunogenicity and maintaining long-term immune responses Lentinan (LNT), a β-1,6-branched β-1,3-glucose hexasaccharide, extracted from the mushroom Lentinus edodes, is a powerful immune activator. the adjuvant activity of calcium carbonate ($CaCO_3$) microspheres and they are used in antigen delivery system. In this study, then loaded with loaded LNT into $CaCO_3$ microspheres and assessed their physicochemical properties prior to ovalbumin adsorption. LNT-$CaCO_3$ significantly enhanced lymphocyte proliferation and increased the frequency of CD69+ B cells and the ratio of CD4+ to CD8+ T cells in small cell, LNT-$CaCO_3$ unexpectedly induced the secretion of IgG- and Th-related cytokines (IL-2, IL-4, IFN-γ and TNF-α) in immunized mice LNT-$CaCO_3$ microspheres can induce strong cellular and humoral immune responses and have potential use as a vaccine delivery system [25].
- Controlled-release strategies for DNA vaccines hold promise for the design of in vivo vaccination platforms, but formulation and sustained delivery still pose significant challenges. a novel dual-particle hybrid delivery system, nanoparticles in microspheres (NIM), to integrate the advantages of nano polymer/DNA complexes and slow-release microspheres for DNA vaccine delivery . Nanoscale cores composed of polyethyleneimine (PEG-g-PEI)/polyethylene glycol-grafted DNA complexes were formulated into PLGA microspheres using a solid oil-in-water emulsion (S/O/W). PEG block is used as a stabilization aid to make DNA soluble and stable in organic solvents to prevent DNA inactivation at the water-organic interface during encapsulation The dry solid-state DNA mode greatly improves the encapsulation efficiency of DNA in the NIM. This new formulation exhibits a burst release of less than 15% followed by sustained release near zero-order kinetics in a physiological environment the microspheres exhibit pH sensitivity and faster degradation in the lysosomal compartment, which contributes to accelerating intracellular DNA release kinetics. Finally, intramuscular injection of NIM encoding HIV proteins elicited significant humoral and cellular immune responses in mice at low doses. Therefore, these may contribute to a broader clinical evaluation of NIM-based vaccination [26].

2.10. Microspheres for protein drug delivery system

- Long-acting injectable depots (LAI) based on polylactide-co-glycolide (PLGA) or polylactic acid (PLA) microspheres have been developed for controlled drug delivery to reduce the dosage frequency and improve the therapeutic effect. Biopharmaceuticals such as proteins and peptides are encapsulated in microspheres to increase their bioavailability and provide a long release period (days or months) at consistent plasma drug concentrations. The biodegradability and biocompatibility of PLGA/PLA polymers, including but not limited to molecular weight, end groups, lactide/glycolide ratio, and minor manufacturing variations, can greatly affect the quality properties of formulations. of microspheres, such as the release profile, size, encapsulation efficiency and bioactivity of the biopharmaceutical. Additionally, encapsulated proteins/peptides are susceptible to harsh processing conditions associated with microsphere fabrication methods, including exposure to organic solvents, shear stresses, and temperature fluctuations LAI microspheres containing proteins/peptides for clinical use are generally prepared by double emulsion, coacervation and spray drying techniques an overview of the formulation characteristics and routine manufacturing techniques of LAI microspheres currently used clinically for proteins/peptides. In addition, the physicochemical properties of the microsphere formulations were taken into account[27].
- Adopting a Quality by Design (QbD) approach in the drug development process has evolved from an "easy to do" step to an essential and required part of development, ensuring the quality of a drug throughout. of its life cycle. the implementation of QbD ideas in the production of long-acting injectable PLGA/PLA microspheres (LAI) for the delivery of therapeutic peptide and protein drugs. Several key elements of the QbD approach, a commercial product of LAI PLGA/PLA microspheres, as a typical example factor affecting the release profile and stability of peptide and protein drugs are studied. The latest manufacturing techniques and associated critical process parameters (CPPs) of LAI PLGA/PLA-based microspheres are then summarized [28].

2.11. Microspheres for targeted drug delivery system

- A reactive oxygen species (ROS)-conjugated iron oxide nanoparticle system responsive to lecithin (LEC) and iron oxide (Fe_3O_4 NP) with potent anti-inflammatory properties.PLGA hybrid is in the "Fe_3O_4@LEC-CUR-PLGA-MMS" magnetic microsphere system. The delivery system responds to ROS, including the H_2O_2 environment, to release the drug payload (CUR). In the presence of Fe_3O_4@LEC-CUR-PLGA-MMS, stronger cytotoxicity was observed against A549 and HeLa S3 cells with IC50 values of 10 and 12 μg/mL and 10 and 20 μg/mL after 24 hours, respectively. The current Fe_3O_4@LEC-CUR-PLGA-MMS system shows better *in vitro* cytotoxicity, cell morphological changes and ability to limit colony formation in A549 and HeLa S3 cancer cell lines than non-cancer cell [29].
- Effective carriers for mitochondria-targeted drug delivery, triphenylphosphine (TPP)-modified ethylene glycol chitosan polymer microspheres, which have a unique chemical structure and a lipophilic benzene base and a cationic phosphine. TPP can easily cross the phospholipid bilayer of mitochondria, resulting in the specific accumulation of bound drug molecules in mitochondria due to the membrane potential between TPP and its membrane Therefore, TPP has been widely used as a mitochondrial targeting fragment. Triphenylphosphine-ethylene glycol chitosan derivatives (GC-TPP and GME-TPP) with two different degrees of substitution (11% and 36%) were prepared by amidation and Michael addition The chemical structures of GC-TPP and GME-TPP were characterized by 1H NMR and Fourier transform infrared spectroscopy, and their dimensions were measured by field emission and dynamic light scattering scanning electron microscopy. Cellular uptake by flow cytometry analysis and confocal microscopy confirmed that GC-TPP and GME-TPP were well incorporated into cells, targeting mitochondria Moreover, cytotoxicity tests performed on the most common cell lines such as HEK293, HeLa, NIH3T3 and HepG2 showed no toxicity of the polymers. the effectiveness of the TPP carrier for drug delivery, doxorubicin (Dox) was used as an anti-cancer drug Confocal microscopy image revealed that Dox-loaded GME-TPP accumulated more intracellularly than Dox-loaded GC-TPP The anti-cancer effect of Dox was also determined by MTT test, apoptosis/necrosis test and three-dimensional spheroid test. GC-TPP and GME-TPP microspheres have great potential as effective drug delivery vehicles[30].

2.12. Microspheres for cancer drug delivery system

- Hybrid magnetite/graphene quantum dot microspheres coated with ternary gelatin (Fe_3O_4/GQDs@GM) as anti-cancer drug carriers. Additionally, pure gelatin (GM) microspheres were prepared to compare the performance of the two preparation systems. The prepared samples were characterized using Fourier transform infrared (FT-IR), X-ray diffraction (XRD) and scanning electron microscopy (SEM) analyses. Photoluminescence (PL) analysis confirmed the PL properties of Fe_3O_4/GQDs@GM, and vibrating sample magnetometer (VSM) revealed its super paramagnetism. The *in vitro* biodegradation behavior of the Fe_3O_4/GQDs@GM ternary in trypsin was studied to confirm its enzymatic degradation capacity. 30.15% and

22.29% curcuminoids (CUR) were loaded into Fe3O4/GQDs@GM and GM, respectively, as a natural anti-cancer agent. Drug release tests at two different pH values (7.4 and 5.0) showed a pH sensitive drug release profile. The biocompatibility of the prepared microspheres was confirmed by calculating the viability of breast cancer cells (MDA-MB 231) after treatment with each microsphere DAPI staining assay showing apoptosis in MDA-MB 231 cancer cells treated with drug-loaded microspheres The biological and drug delivery studies showed that the performance of Fe3O4/GQDs@GM ternary was improved, so that it can be considered as a biodegradable, pH sensitive and non-toxic cancer drug delivery agent. Toxic [31].

3. Conclusion

After the review of various microspheres and their applications in drug delivery systems, different microspheres are prepared and used for drug deliveryThe authors of this review paper study make an effort to give a comprehensive overview of microspheres and their applications in drug delivery systems

Compliance with ethical standards

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Disclosure of conflict of interest

All the authors declare no conflict of interest.

Author's contributions

Authors read and agreed with the final manuscript.

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