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A REVIEW ON MICROSPHERES AS VERSATILE CARRIERS IN CONTROLLED DRUG DELIVERY

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ABSTRACT

The conventional oral or parenteral administration routes for the medications have several drawbacks such as fluctuation of the plasma level of the drug, frequent dosing and decreased compliance. Microspheres - free-flowing particles with the size of 1-1000 µm, wherein the drug can be distributed or entrapped in the polymeric matrix or shell - offer the opportunity to achieve the control of the drug release rate and site. The review presents an overview of the optimal properties, classification (bioadhesive/mucoadhesive, magnetic, floating, radioactive and polymeric microspheres), selection of the appropriate polymers (natural, semi-synthetic and synthetic) as well as drug entrapment methods and fabrication techniques (emulsification–solvent evaporation, spray drying/congealing, coacervation, ionic gelation, polymerization and novel microfluidic techniques). The drug release mechanisms, evaluation parameters and case studies - Quality by Design (QbD)-optimized microspheres with antidiabetic effect, surface engineered PLGA microspheres for intra-articular administration of the corticosteroid, magnetic microspheres for delivery of chemotherapeutic agents, floating gastro retentive tablets and environmentally friendly herbal/colon-targeted microspheres - will be highlighted.

KEYWORDS: Microspheres; drug delivery; polymers; encapsulation efficiency; drug release mechanism.

1. INTRODUCTION

In recent years, drug delivery research has focused more on the optimization of the pharmacokinetic/pharmacodynamic behavior of the medications, rather than discovery of new molecules[6]. The conventional tablets/capsules and injectable dosage forms provide a peak-trough

plasma profile when the sub-therapeutic trough may lead to the failure of the therapy, and the supra-therapeutic peaks to the drug toxicity [6] . Thus, the maintenance of the drug plasma levels within the therapeutic window implies the necessity of repeated dosing which is associated with decreased compliance and increased costs, especially in the cases of chronic diseases requiring long-term pharmacotherapy, such as osteoarthritis, type II diabetes mellitus, inflammatory bowel diseases and solid organ tumors. [1,2]

Microspheres are minute, free-flowing spherical particles, the size of which ranges from 1 to 1000 μm, wherein the drug is distributed or entrapped in the polymeric matrix or shell [4,6]. High surface area-to-volume ratio, small size and ability to entrap small molecules, proteins, peptides and even nucleic acids have made microspheres perspective for the oral, parenteral, nasal, ocular, pulmonary or targeted drug delivery systems providing the prolonged/targeted delivery of the medication, protection of labile drugs, decrease in dosing frequency and enhancement of the compliance [1,4]. The clinical translation is also confirmed since PLGA depot microspheres have been developed for the peptide and hormonal treatments, and Zilretta® - the first FDA-approved extended-release triamcinolone acetonide microsphere suspension for intra-articular administration - was released [1,13] Moreover, the activity in the field of PLGA microspheres is steadily increasing [9,1]. The review discusses current approaches to the microspheres classification, polymer composition, drug loading, manufacturing technologies, drug release mechanism and evaluation and presents recent examples from the literature[2,3].

2. Ideal Characteristics, Advantages and Limitations

The criteria for designing a good sustained-release microsphere formulation include: using a biocompatible and biodegradable non-toxic polymer with biologically compatible degradation products; having high loading capacity and efficient entrapment; ensuring a constant particle size as it controls the rate of drug release, site of drug deposition, and mode of administration; having consistent release rate with ideally zero order kinetics; being physically and chemically stable with an appropriate shelf-life; and being capable of being produced by a simple, economical, reproducible and scalable method which produces free-flowing particles that can be easily handled, packed and administered [4,6]

While there are significant advantages of employing microsphere-based delivery over traditional dosage forms, these are offset by certain process and product limitations as listed in Table 1 [4,6]

Table 1. Key advantages and limitations of microsphere-based drug delivery.[4,6,]

Advantages	Limitations
Sustained, controlled and site-specific release; multiple administration routes (oral, parenteral, nasal, ocular, pulmonary)	Reproducibility is sensitive to process variables (stirring speed, temperature, polymer concentration)
Reduced dosing frequency, improved compliance, and taste-masking/reduced GI irritation	Residual organic-solvent toxicity concerns; higher production cost than conventional forms
Protects labile drugs, proteins, peptides and phytoconstituents from degradation	Parenteral doses cannot be retrieved once administered; risk of dose dumping if matrix integrity fails
Improves dissolution of poorly soluble drugs	Release affected by GI transit time and food effects
No surgical removal required for biodegradable systems	Complex regulatory pathway, especially for herbal/multi-component actives

3. Classification of Microspheres

Depending on the nature of the polymer or the drug release mechanism or functional properties such as bioadhesiveness or responsiveness to stimuli, microspheres may be classified accordingly [4,6] . The different categories are summarized in Fig.1.

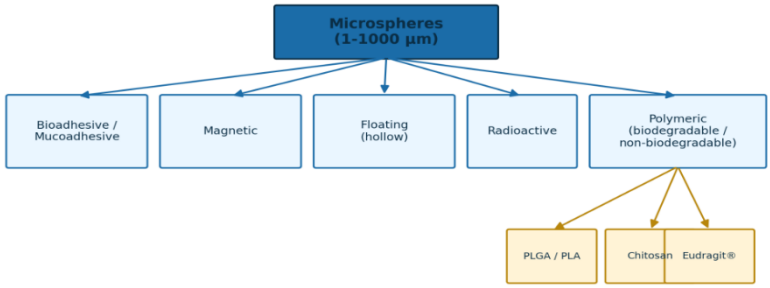


Fig.1. Classification of microsphere based drug delivery systems.

3.1 Bioadhesive and mucoadhesive microspheres

Bioadhesive microspheres bind with the tissue surface to retain the dose of the drug at the absorption site through hydrogen bonding and interpenetration of the network of polymers like chitosan and carbopol. Mucoadhesive microspheres (generally 1-1000 µm) are highly suitable for increasing the bioavailability of poorly absorbable drugs and herbal phytoconstituents and target the oral, nasal, urinary and gastrointestinal mucosae. Chitosan/Sodium Carboxy Methyl Cellulose microspheres produced by ionotropic gelation have a maximum entrapment of 90% with sustained release, thus making them suitable for oral antimicrobials.

3.2 Magnetic microspheres

Magnetic microspheres comprise a magnetic core (magnetite (Fe_3O_4), or maghemite (γ-Fe_2O_3)) surrounded by a polymer matrix (chitosan, dextran, albumin). Exposure to a magnetic field (<1 T) results in targeted transport of the particles to microvessels and pathological tissues (liver tumors) minimizing toxic effects of systemic administration and enhancing the localized concentration of drug; thus, a smaller targeted dose produces the same effect as a much larger systemic dose [3,4] . Magnetic cores are superparamagnetic (no magnetic moment when field is turned off) or ferromagnetic (permanently magnetized). They are usually produced by phase-separation emulsion polymerization and continuous solvent evaporation and are applied for targeted delivery of cytostatics, antibiotics, radioisotopes, and diagnostics/bioseparation purposes (see Section 9.3).

3.3 Floating (hollow, gastroretentive) microspheres

Floating microspheres are characterized by low bulk density (due to a presence of hollow core formed during solvent evaporation or emulsion-solvent diffusion technique) which allows them to float on the surface of gastric fluid for a prolonged period of time. Extending the residence time in the stomach, they increase the bioavailability of drugs with a narrow window of absorption and are suitable for gastroretention; examples of floating-microspheres tablets can be found in Section 9.4 [11] .

3.4 Radioactive microspheres

Radioactive microspheres contain a radioisotope in the matrix and are employed in interventional radiology and oncology for targeted radiotherapy. Being injected directly into the vascular bed feeding the tumor, their small size (tens of nanometers to tens of micrometers) guarantees that they will retain only in the first capillary bed, and will deliver radiation locally without damaging the surrounding tissue. In contrast to other microsphere systems, their therapeutic value is determined by radiation emitted by the isotope and not by the drug-release [3,4,] .

3.5 Polymeric microspheres

The most studied category of microspheres is the polymeric one, comprising biodegradable and non-biodegradable types [4,6] . The former are made of PLGA, chitosan, starch, etc.; they degrade to nontoxic metabolites and are eliminated from the organism through metabolic processes; starch microspheres also swell and gel, extending residence time. The latter are composed of polymethylmethacrylate, acrylonitrile, glycidyl methacrylate/epoxy resin, and serve either for prolonged release or as a diluent/filler; being not degraded, they may migrate from the injection site and have to be surgically removed.

4. Polymers Used in Microsphere Formulation

The choice of the polymer is the single most important factor influencing physicochemical and release properties of microspheres and materials are divided into natural, semi-synthetic, and synthetic one[6,7] Natural polymers are preferred owing to their biocompatibility, biodegradability, lower toxicity and availability. Natural polymers include proteins (albumin, gelatin, collagen), carbohydrates or

polysaccharides (starch, agarose, chitosan, carrageenan, sodium alginate), modified carbohydrates (polystarch, polydextran) and natural gums (xanthan, guar, karaya, acacia, agar) [4] Alginate and chitosan are used extensively in ionic gelation due to their gelling properties in the presence of divalent or trivalent counter ions (calcium chloride; sodium tripolyphosphate); mucoadhesive property of positively charged chitosan is useful for its use in colon-targeted delivery because of susceptibility to colonic microbial enzymes; exploration of chitosan of different origin (such as insect exoskeleton) is in progress in order to develop a sustainable raw material base [7,18] .

Semi-synthetic cellulose derivatives – ethyl cellulose, hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, cellulose acetate phthalate – are desirable owing to film forming abilities that allow the regulation of drug release through degree of substitution and viscosity grade [6] .

The advantage of synthetic polymers lies in better control over the molecular weight, rate of degradation and mechanical properties. Biodegradable synthetic polymers include PLA, PGA, PLGA, polycaprolactone, polyalkyl cyanoacrylates, polyanhydrides; non-degradable polymers include PMMA, polyacrylates and pH sensitive Eudragit® polymers that are used for enteric/colonic coatings [6,20] . PLGA has become the most investigated and regulated parenteral sustained-release polymer because the degradation can be adjusted via the lactide to glycolide ratio, end-cap chemistry and molecular weight; PLGA degrades to lactic and glycolic acid that are eliminated via tricarboxylic acid cycle; regulatory approval has been received for PLGA depots for LHRH-analogue and other peptide/hormone therapies [9,14] . Double wall PLGA microspheres with drug-free outer layer surrounding the drug-containing core represent an additional diffusion barrier which provides reduced initial burst effect and sustained release of water soluble protein drugs such as lysozyme [16] .

Table 2. Representative polymers used in microsphere fabrication [4,7].

Category	Examples	Typical use / property
Natural — proteins & carbohydrates	Albumin, gelatin, collagen, starch, chitosan, alginate, agarose, carrageenan	Biocompatible matrices; ionic gelation; mucoadhesion; colon targeting
Natural — modified carbohydrates & gums	Polystarch, polydextran, xanthan, guar, karaya, acacia	Tunable swelling/erosion; viscosity building
Semi-synthetic	Ethyl cellulose, HPMC, NaCMC, cellulose acetate phthalate	Film-forming; release modulation
Synthetic — biodegradable	PLA, PGA, PLGA, polycaprolactone, polyanhydrides, polyalkyl cyanoacrylate	Long-acting parenteral depots; tunable degradation
Synthetic — non-biodegradable	PMMA, polyacrylates, Eudragit® grades	Prolonged release; pH-dependent enteric/colonic coatings

5. Drug-Loading Strategies

Loading of the drug may take place either during the process of microspheres formation by co-dissolution/co-dispersion of the drug with the polymer or after their formation when the microspheres are incubated in drug solution and surface adsorption/pore penetration takes place [4] .Three major drug incorporation mechanisms are physical entrapment into the matrix, surface adsorption and covalent attachment of the drug or targeting moiety to reactive polymer side chains, which is useful for antibody or biotin/avidin conjugated microspheres (Sections 8 and 9.2) [1,4] . Loading capacity in process depends on the excipient, preparation process, heat generation during polymerisation/solvent evaporation, mixing intensity, which should be balanced with the desired particle size and morphology [4] .

6. Methods of Preparation

Depending on the physicochemical properties of the drug and polymer, the desired size and loading as well as the way of administration the technique for microspheres fabrication is chosen [4,6] . The emulsification – solvent evaporation technique (Figure 2) is widely used for PLGA and other synthetic polymers. It includes dispersion of the drug/polymer solution in a non-miscible phase and removal of volatile solvent under stirring in order to form hard microspheres; for instance, using this method the PLGA microspheres of 0.36 to 0.98 μm size for intra-articular delivery of corticosteroids were formed via changing polyvinyl alcohol concentration and sonication energy [6,8] . Other emulsification based techniques include simple emulsion technique that can be used for natural water soluble polymers such as gelatin and albumin, double or multiple w/o/w emulsion technique that is applicable for water soluble drugs, proteins, peptides and vaccines (for example, PLGA microspheres with triptorelin) [9,24] .There are several other known techniques including spray drying/congealing, coacervation/phase separation, ionic gelation (mild and aqueous, suitable for proteins and peptides, for example, acyclovir-loaded chitosan microspheres), normal/interfacial polymerisation. For magnetic microspheres there are special techniques including phase-separation emulsion polymerisation, emulsion-solvent extraction, hot melt microencapsulation, dispersion copolymerisation, microwave-assisted synthesis. The recently emerged microfluidic, electrospray, supercritical fluid and membrane emulsification techniques produce highly monodispersed particles with controllable morphology and eliminate much of batch to batch variation inherent to traditional emulsification; for example, monodispersed sirolimus-loaded PLGA microspheres have been obtained [9,15] . The comparison of the main techniques is shown in Table 3.

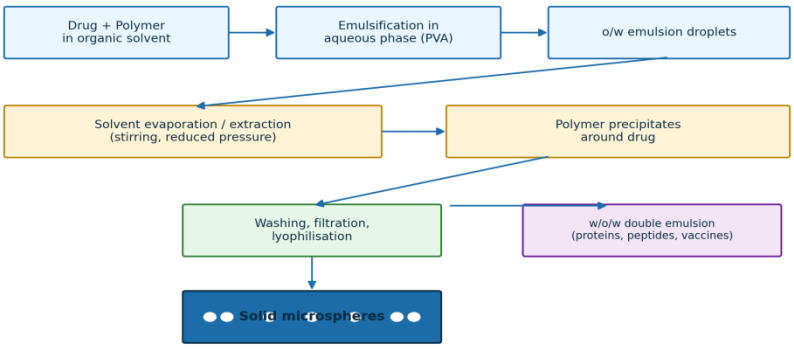


Figure 2. Generalized emulsion-solvent evaporation method.

Table 3. Comparative summary of principal microsphere preparation techniques[4,6] .

Technique	Key principle	Suitability / remarks
Single emulsion	w/o emulsification, then cross-linking or heat hardening	Natural, water-soluble polymers (gelatin, albumin)
Double emulsion	w/o/w multiple emulsion with solvent removal	Water-soluble drugs, proteins, peptides, vaccines
Solvent evaporation	o/w emulsification with evaporation of volatile solvent	Widely used for PLGA and other biodegradable polymers
Spray drying / congealing	Atomisation into hot air, or molten mass into cold air	Rapid, scalable; solvent-free (congealing); heat-sensitive drugs at risk (drying)
Coacervation–phase separation	Phase-induced deposition of polymer coacervate around drug	Classical method; proteins and peptides
Ionic gelation	Cross-linking of polyelectrolyte with counter-ion	Mild, aqueous, solvent-free; biomolecules
Polymerisation (normal/interfacial)	In situ monomer polymerisation around the drug	Precise control of shell molecular weight
Specialised magnetic methods	Phase-separation emulsion polymerisation; emulsion–solvent extraction; hot-melt; dispersion copolymerisation; microwave synthesis	Magnetic/polymer–magnetite microspheres
Microfluidics / step-emulsification	Precisely controlled droplet generation in microchannels	Highly monodisperse particles; controlled internal morphology

7. Mechanisms of Drug Release

Drug delivery from the microspheres can occur via one or more of the following pathways, the significance of which depends upon the type of the polymer, the nature of the drug and its microstructure [6] (Figure 3):

• Diffusion – The dissolved drug molecules diffuse across the polymer network or fluid filled cavities; occurs predominantly for non-degradable matrices.

- Erosion/ Degradation – Hydrolytic and enzymatic degradation of degradable polymer like PLGA releases the encapsulated drugs slowly.
- Swelling and Diffusion - Hydrophilic polymer absorbs the water molecules, thus swelling up the polymer structure.
- Osmotic pumping – osmotic pressure gradient on a semipermeable membrane drives water into and releases the drug solution outward.

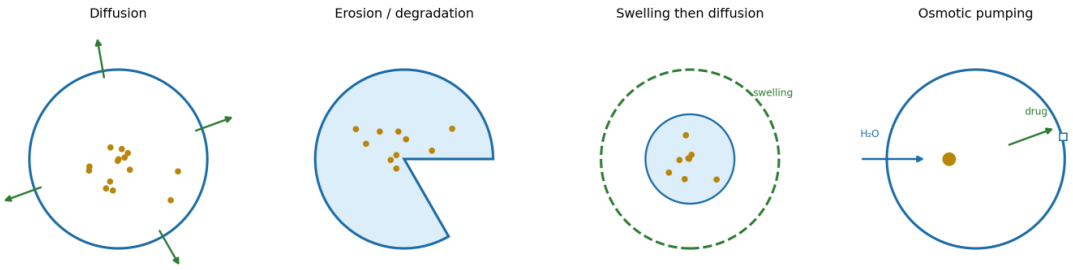


Figure 3. Main methods of drug delivery from microspheres.

In reality, the release process can be biphasic – the first fast phase corresponding to rapid drug release from the surface and then a slower release controlled by diffusion/erosion mechanisms, and described by bi-exponential models, which significantly outperform zero-, first-order, and Higuchi models [1,6] . In one experiment on PLGA microspheres used in bovine cartilage explants, bi-exponential models had very good fitting at a single point (up to R^2=0.999) but poor multi-point validation, which indicated that the transport is size-exclusional rather than Fickian due to the dense collagen network – thus, it is highly relevant for particle size optimization of tissue penetrating microspheres [1] . Double-wall architecture with the outer shell without drug can lower burst effect and increase delivery of water soluble protein drugs [16] .

8. Evaluation Parameters

Comprehensive characterization is important to confirm the quality, reproducibility and performance of a microsphere composition [4,6] ;

- Size/dispersion – optical microscopy, laser diffraction, dynamic light scattering, Coulter counter or SEM; described by mean diameter and polydispersity index.
- Surface morphology – SEM (surface) and TEM (structure).
- Zeta potential - micro-electrophoresis / laser Doppler anemometry; range of values between −30 to +30 mV is considered adequate for colloidal stability.
- Density – true, bulk and tapped – helium pycnometer (true); graduated cylinder pouring (bulk), tapping (tapped).
- Flow properties – angle of repose, Carr's index, Hausner's ratio.
- Hardness – Monsanto type tester; Friability – Roche friabilator.

- Swelling ratio = (swollen – dried mass)/dried mass × 100%.
- Percentage yield/encapsulation efficiency = actual/theoretical mass of drug content using either UV-spectrophotometry or HPLC.
- Floating behavior/gastric retention = buoyancy fraction in simulated gastric fluids using USP dissolution apparatus.
- Release studies in vitro/in vitro kinetics = USP Type I/II apparatus, dialysis/Franz cell and fitted into zero order, first order, Higuchi, Korsmeyer-Peppas, Weibull & bi-exponential models.
- Drug-polymer compatibility = FTIR/DSC.
- Stability and in vitro/in vivo evaluation — storage studies at specific temperature/humidity conditions; in vivo pharmacokinetic (Cmax, Tmax, AUC) and pharmacodynamic (hypoglycaemic response in diabetic rat) correlation [2] .

9. Representative Applications and Case Studies

9.1 Quality by Design (QbD) and the antidiabetic patent landscape

Quality by Design (QbD), supported by ICH Q8–Q11, is a risk-based alternative approach to conventional quality-by-testing development with an intrinsic quality of the product from the very beginning [2] . QbD for antidiabetic microspheres starts with the establishment of a Quality Target Product Profile (for example, a once-a-day oral drug delivery with 1–2 hours delay followed by the sustained delivery of 10–24 hours), critical quality attributes (size, encapsulation efficiency, release profile, morphology, solvent residue), risk assessment (Ishikawa diagrams, failure modes and effects analysis), and DoE (first Plackett–Burman screening followed by Box–Behnken/Central Composite response-surface methodology) to get a validated design space [2] As a specific example of such an optimization strategy, Box-Behnken optimized nateglinide microspheres (drug:polymer ratio, Eudragit® RS100/RL100, stirring speed) were produced with 88.2% encapsulation efficiency, 112 µm mean particle size and 95% drug release during 10 hours together with a pronounced and prolonged hypoglycaemic effect in streptozotocin-induced diabetic rats [2] . Other studied types of drugs include biguanides, sulfonylureas, meglitinides, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 agonists [2] . Patent activity in this area (US 9,950,067 B2; EP 2,845,321 A1; WO 2018/045,123; IN 298,645) demonstrates how more consistent and regulatory ready DoE based optimization is as compared to the one-factor-at-a-time methods [2] .

9.2 Engineered PLGA microspheres for intra-articular corticosteroid delivery

Worldwide about 240 million people suffer from osteoarthritis, and intra-articular corticosteroids provide a temporary relief because of fast joint clearance (halflife varies from hours up to several days) [1] . Recent research is dedicated to the influence of PLGA microsphere size, charge, and functionalization (unmodified, avidinated and palmitic-acid-conjugated, or PEGylated) on cartilage penetration and stability of hydrocortisone-17-butyrate [1]. Unmodified microspheres (0.58–0.98 µm in size, near-neutral zeta-potential, PDI <0.3) penetrated the cartilage much less than avidinated or

PEGylated microspheres, which penetrated two to three times deeper due to electrostatic and steric 'stealth' effects [1] . Functionalization not only decreased the drug release rate (the cumulative release was 7.1% after 14 days for PEGylated, 34.9% for avidinated and 51.0% for unmodified microspheres), but also increased its stability against hydrolysis (96% of active drug remained for PEGylated, 37% for unmodified microspheres after 14 days) [1] , that means that the surface chemistry regulates penetration into the tissue, the drug release, and the chemical stability.

9.3 Magnetic microspheres for site-specific therapy

Magnetic targeting began from Gilchrist's 1956 inductive heating experiments and developed through radiofrequency embolization of Turner and Rand, externally magnet directed iron particles of Meyers, magnetic endocatheters of Hilal and first defined spherical magnetic microspheres made by Widder by the late 1970s [3] . Magnetic microspheres for therapeutic purposes deliver chemotherapeutics (proteins/peptides) to target areas (like liver tumors) and diagnostic microspheres are used for bowel and metastatic tissues visualization; the cores of magnetic microspheres are composed of magnetite, maghemite, and other ferrites, coated with natural and/or synthetic polymers[3] .Some known drug-polymer combinations include: yttrium-90/albumin (radionuclide therapy), oxantrazole/chitosan, and 5-fluorouracil/albumin (hepatic tumor targeting), piperacillin-tazobactam/dextran (antimicrobial), aclarubicin/gelatin (intravascular targeting), and amphotericin B/albumin (visceral leishmaniasis); most of them were prepared by phase separation emulsion polymerization and continuous solvent evaporation [3] .

9.4 Floating microsphere tablet formulations

The floating microspheres incorporated into the compressed

9.5 Herbal and sustainable microsphere systems

Herbal phytoconstituents frequently exhibit poor solubility, poor bioavailability and rapid excretion notwithstanding their good efficacy and safety [7] . However, their entrapment in natural polymers (chitosan, alginate, gelatin, starch, gums) or PLGA using solvent evaporation, spray drying, ionic gelation, emulsion cross-linking or phase separation improves their protection while providing controlled release [7] . Concerning colon-targeted delivery, a sustainable approach uses biodegradable polymers (chitosan, alginate, pectin, guar gum, PLGA/PLA) and environmentally friendly ionotropic gelation (without toxic cross-linkers) taking into account colon's nearly neutral pH, rich microbiome and prolonged transit times via pH-sensitive Eudragit® coating and microbiome-induced polysaccharide matrices [18,22] . For instance, alginate–chitosan microspheres containing icariin showed only about 10% of drug release in simulated gastric fluid versus 60%+ in simulated colonic fluid; this pH- and microbiome-dependent difference in release is employed to treat inflammatory bowel diseases and colorectal cancer [19,22] .The hot-melt extrusion and 3D-printed multiparticulate system with Eudragit® S-100 coating further allows controlling colon-specific release [20].

10. Broader Therapeutic Applications

Apart from the case studies presented above, microspheres are employed in almost all delivery routes. The oral sustained-release microspheres are compressed into tablets or filled into capsules for delivery of antihypertensive, antidiabetic and anti-inflammatory drugs; meanwhile, the PLGA-based depot parenterals can release LHRH-analogue and other peptides and hormones for weeks and months [6,10] . Biodegradable microspheres containing vaccines can act as an adjuvant, affect antigen-release kinetics (including single-dose regimen and prime-boost regimen mimicking) and preserve antigen stability better than the solutions [4] . 'Immune' microspheres, carrying monoclonal antibodies that are covalently coupled, allow extremely selective targeting of cells/tissues; this approach is similar to the avidin/PEG functionalization from Section 9.2 [4] . Bioadhesive microspheres prolong the residence time and bioavailability in the nasal, buccal, sublingual and pulmonary routes (e.g., the microspheres containing venlafaxine based on the linseed mucilage reduce first-pass effect) [4] . In oncology, the cytotoxic microspheres delivered through a catheter allow localized embolization and release; also, the polymethylidene-malonate microspheres with 5-fluorouracil and polymeric films allow treating brain and other tumors with minimal systemic distribution [4]. The porous microspheres are carriers of emollients and fragrances in the topical preparations, and the labeled microspheres can be used for diagnostics in flow cytometry and blood flow/perfusion studies [4,6].

11. Regulatory and Quality Considerations

Regulatory requirements for the controlled-release dosage forms based on particulates follow a risk-based Quality-by-Design approach recommended by ICH Q8–Q11 [2] . Manufacturing in the approved design space allows performing post-approval changes in the manufacturing process without prior regulatory evaluation on condition of having a documented control strategy including critical material attributes, critical process parameters and in-process controls that demonstrate the process understanding [2] . The precise characterization of molecular weight, intrinsic viscosity, lactide:glycolide ratio and end-cap chemistry of long-acting PLGA products, as well as accurate in vitro release testing and in vitro-in vivo correlation are still key scientific and regulatory barriers; that explains the low number of generic products launched after patent expiry of the innovator products and the necessity of strict control considering the risk of dose dumping of the high-loaded and long-acting products [9] .

12. CHALLENGES

The batch-to-batch variability in the herbal extracts and other complex actives makes it hard to reproduce drug loading and release [7] . The use of organic solvents causes the concern regarding residual toxicity, and the process parameters (speed of stirring, concentration of polymer, temperature) greatly affect the size and morphology of particles; thus, reproducibility is still challenging [6,7] . The scaling up from the lab-scale production is rather difficult, particularly in the

cases of special equipment-dependent methods, and drug diffusion from the matrix during formulation is a possible problem in encapsulation efficiency [6,7] . Regulatory approval is often more complicated for herbal and multi-component products due to the lack of standardized quality control guidelines, and human clinical trials are less available compared to laboratory and animal studies [7] , The magnetic systems need special targeting and monitoring equipment and leave the deposits of magnetite in the tissues [3] ; the problems of PLGA characterization and in vitro-in vivo correlation delay the launching of generic products after patent expiry [9] .

13. Recent Advances and Future Prospects

Microfluidics and step emulsification become widely employed to prepare highly monodisperse microspheres with controlled morphology, which reduces the batch-to-batch variability associated with conventional emulsification [6,15] . The stimuli-responsive microspheres releasing drugs in response to the changes in pH, temperature or microorganism activity are gaining attention especially concerning colon-targeted and other site-specific delivery [18,22] . The advances in polymer science (new biodegradable copolymers, double-walled/core-shell structures preventing the burst release, increased understanding of how PLGA composition affects degradation) will increase the clinical utility [14,16] . The integration with nanotechnology (e.g., the microbeads containing the nanospheres with PLGA) becomes a way to combine nanoscale drug loading with microscale release [7,17] . The artificial intelligence-guided formulation design and process analytical technologies will promote the clinical translation in the future when the research and patent activities are increasing [9,14] . The further research and development in the interdisciplinary area of polymer chemistry, pharmaceutical engineering and clinical pharmacology and the establishment of special regulatory framework for particulates will drive innovations [2,9] .

14. CONCLUSION

Microspheres form a well-proven particulate drug-delivery technology, which can help solve problems of most common dosage forms, such as repeated dosing and variable plasma drug concentration. Depending on the choice of the polymer, mode of loading, manufacturing method and process parameters, microspheres can be used for oral, parenteral, nasal, ophthalmic, pulmonary and targeted administration. Case studies discussed — microspheres designed based on the principle of QbD and having patent protection for antidiabetics; surface modified PLGA microspheres for intra-articular delivery of corticosteroids; magnetic microspheres for targeted treatment; floating gastroretentive tablets; sustainable herbal or colon-targeted systems — demonstrate that the size of particles, surface and release characteristics are considered dependent variables. In any case, detailed analysis, including evaluation of the particle size, morphology, entrapment efficiency, release kinetics and stability is of critical importance for the product quality and safety. It can be expected that with further development in polymer technology, process technology, microfabrication and stimuli-

sensitive technology, embedded into a more systematic regulatory environment, controlled drug delivery based on microspheres will become more important.

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