Scientia Pharmaceutica

ÖSTERREICHISCHE PHARMAZEUTISCHE GESELLSCHAFT

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Review

Microparticles, Microspheres, and Microcapsules for Advanced Drug Delivery

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Received: 11 July 2019; Accepted: 1 August 2019; Published: 9 August 2019

Abstract: Microparticles, microspheres, and microcapsules are widely used constituents of multiparticulate drug delivery systems, offering both therapeutic and technological advantages. Microparticles are generally in the 1–1000 μm size range, serve as multiunit drug delivery systems with well-defined physiological and pharmacokinetic benefits in order to improve the effectiveness, tolerability, and patient compliance. This paper reviews their evolution, significance, and formulation factors (excipients and procedures), as well as their most important practical applications (inhaled insulin, liposomal preparations). The article presents the most important structures of microparticles (microspheres, microcapsules, coated pellets, etc.), interpreted with microscopic images too. The most significant production processes (spray drying, extrusion, coacervation, freeze-drying, microfluidics), the drug release mechanisms, and the commonly used excipients, the characterization, and the novel drug delivery systems (microbubbles, microsponges), as well as the preparations used in therapy are discussed in detail.

Keywords: multiparticulate formulations; polymer excipients; processes for microparticles in therapy; structure and drug release; microfluidics; microbubbles; microsponge

1. Introduction

Microparticles, microspheres, and microcapsules are common constituents of multiparticulate drug delivery systems offering numerous advantages based on their structural and functional abilities [1], and their application is suitable for convenient and tolerable drug administration via several routes.

Depending on the formulation, they can be incorporated into different pharmaceutical dosage forms such as solids (capsules, tablets, sachets), semisolids (gels, creams, pastes), or liquids (solutions, suspensions, and even parenterals).

An advantage of microcarriers over nanoparticles is that they do not traverse into the interstitium over the size of 100 nm transported by the lymph, and thus act locally [2]. Possibly toxic substances can be carried encapsulated and liquids can be handled as solids in the form of dried microparticles.

In the case of multiparticulates, the dose is distributed in many small separate particles, which carry and liberate a part of the dose, hence the malfunction of an individual subunit does not cause the failure of the whole dosage.

Multiparticulate drug delivery systems offer outstanding advantages to experts and patients, such as:

- choice of dosage form for the desired drug delivery route (peroral tablets, parenteral injections);
- modified and targeted (even site-specific) drug release and delivery;

- more expectable pharmacokinetics with reduced intra- or inter-subject variability;
- more homogenous distribution in the physiological environment;
- stable fixed-dose combinations of drugs;
- dose titration and less dose-dumping;
- patient centricity through better compliance (e.g., patients with dysphagia) and adherence;
- individual therapy (e.g., for pediatric or geriatric population);
- improving stability of the medicinal preparations;
- isolating the constituents to ensure better compatibility;
- innovative products with a prolonged life cycle through patent protection.

From the viewpoint of technology, microencapsulation provides several advantages: microparticles are formulated in order to protect the core from the environment; masking an unpleasant taste; preserving volatiles or the viability of the cells; separating incompatible substances; protecting the body from the side effects; and optimizing, prolonging, or targeting the effect of a drug.

The polymer excipient protects the active pharmaceutical ingredient (API) from the environment (oxidation, temperature, pH) or the body from the irritative, or mucosa-damaging effect of the drug substance. The lesion (e.g., bisectioning) of the multiparticulate solid dosage form (i.e., micropellets in spansule or compressed) affects only a small number of units, thus does not result in a significant change of the blood level.

However, there are some limitations, such as higher product costs due to the more expensive excipients in the formulations or to the more sophisticated equipment and processes, as well as stricter quality control. In addition, some constituents may not meet the requirements for biocompatibility and biodegradation.

2. Construction and Structure

Microparticles' sizes range from 1 to 1000 μm and the well-known matrix or reservoir structure they exist in have various different structures (Figure 1). Beyond the excipients used, the structure and the shape determines the function as well. Multiparticulate drug delivery systems (micropellets, microgranules, microspheres, microcapsules, microsponges, liposomal preparations) attract attention because of their wide range of favorable technological properties.

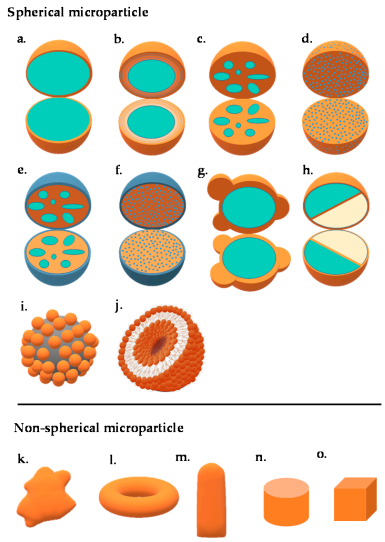

Figure 1. Schematic illustration of the different microparticle structures: (**a**) mononuclear/single core/core-shell, (**b**) multi-wall, (**c**) polynuclear/multiple core, (**d**) matrix, (**e**) coated polynuclear core, (**f**) coated matrix particle, (**g**) patchy microparticle, (**h**) dual-compartment microcapsule, (**i**) colloidosome, (**j**) giant liposome, (**k**) irregular-shaped microparticle, (**l**) torus-shaped microparticle, (**m**) bullet-shaped microparticle, (**n**) microtablet, and (**o**) cubic-shaped microparticle.

Microparticles may be characterized as either a homogenous or heterogenous structure depending on the formulation and processing. Usually the spheroid shape is preferred since it makes the further processing (e.g., coating) easier.

2.1. Microspheres and Microcapsules

Microspheres can be characterized as matrix systems in which the drug is homogeneously dispersed, either dissolved or homogenously suspended [3]. Microcapsules are heterogenous particles where a membrane shell is surrounding the core forming a reservoir (Figure 2) [4].

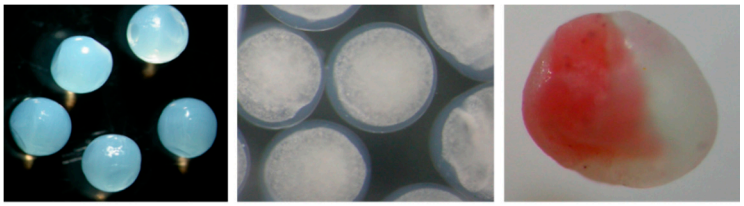

Figure 2. Structures of calcium alginate microparticles: (**a**) microspheres, (**b**) microcapsules W/O/W emulsion in core surrounded by calcium alginate shell, and (**c**) "Janus particle" (the particles were prepared by a Büchi B-390 Microencapsulator).

A classical microsphere structure contains solid or liquid API dispersed or dissolved in a matrix. Microcapsules are reservoirs of microscopic size surrounded by a wall that is able to control the release from the reservoir.

The size plays a role in the gastrointestinal performance: microparticles under 800 μm get through the pylorus without the influence of gastric emptying, thus eliminating the interpersonal and intrapersonal (nutrition-based) differences.

Particles larger than 100 nm stay at the site of administration until the phagosomal clearance. Lymphatic uptake and node accumulation is most significant between 10–80 nm [2]. The foreign body response is decreased by the application of spheres with a diameter of 1.5–2.5 mm compared to that of smaller diameter spheres [5].

The surface charge has a key role in the aggregation of the particles. Aggregation hinders optimal administration and drug delivery (e.g., compromises content uniformity of doses, occludes normal blood flow).

Porosity also has a significance in the in vivo performance in cell transplantation. Porous materials facilitate vascularization relative to non-porous biomaterials. A porosity of 30–40 μm leads to the polarization of macrophages, causing elevated tissue repair [5].

Several unique anisotropic colloidal microstructures have lately been created with special properties.

2.1.1. Janus Particles

These microparticles with a certain shape and phase anisotropy, created by alloying the distinct properties (hydrophilic, hydrophobic) of the separated excipients, are used as multifunctional imaging probes and sensors [6,7]. The anisotropic response to external signals has also been exploited in the preparation of color-changing traffic signals.

2.1.2. Patchy Particles

Spherical geometries with concave, convex, or flat patches on the polystyrene sphere's surface have also been created via colloidal fusion and concomitant shrinking (Figure 1). The patchy particles can form clusters, and by patch-to-patch bonding between oil patches, can build supracolloidal architectures (tetrahedral, hexagonal) that can withstand drying forces and show the ability to reversibly expand

several times their original volume in a swelling agent [8]. Microfluidic techniques give rise to the creation of anisotropic geometries.

Magnetic nanoparticles embedded into nonplanar, bullet-shaped microneedles give access to mild invasive therapy [9].

2.2. Liposomes

Liposomes are lipid vesicles with one or more phospholipid bilayers and their structure comprises small unilamellar vesicles (SUV: 20–100 nm), large unilamellar vesicles (LUV: >100 nm), multilamellar vesicles (MLV: >500 nm), oligolamellar (OLV: 0.1–1 μm), giant unilamellar liposomes (GUV: > 1 μm), and multivesicular vesicles (MVV: > 1 μm).

For ophthalmic delivery, they represent ideal drug delivery systems for both hydrophilic and hydrophobic APIs by performing a cell-membrane like structure. The negative or positive charge can contribute to the bioavailability: cationic liposomes (e.g., fabricated with didodecyldiethylammonium chloride, stearylamine) exhibited better efficacy at the surface of cornea with a negative charge. Liposomes can interact with the cells via several mechanisms: interaction with the cell surface components, fusion with the membrane, endocytosis via phagocytic cells, or swap by bilayer components. The methods of preparation are also versatile: solvent evaporation, double emulsion-evaporation, or reverse-phase evaporation [10].

2.3. Colloidosomes

Colloidosomes are microcapsules that contain a hollow or hydrogel core and their wall is composed of self-assembled colloidal particles. Their sizes range from 10–20 nm to micrometers. It was found that colloidosomes have selective permeability where drugs can diffuse through their shells via size exclusion [11]. They can be stabilized by solid excipients (e.g., Fe_2O_3, $CaCO_3$, colloidal anhydrous silica) forming a Pickering emulsion [12]. Besides the emulsification, depending on the excipient thermal annealing and chemical cross-linking take part in the immobilization of the active ingredient.

3. Types and Mechanism of Drug Release

The process of drug release of microparticulates, produced by special manufacturing technologies and/or possibly containing special excipient(s), is the result of various phenomena and mechanisms (dissolution/diffusion, osmotically driven release, erosion) (Figure 3). Generally, these mechanisms take place side by side and one or the other mechanism provides a greater role during drug release [13]. In the microparticulate, when the active pharmaceutical ingredient is embedded in a polymer matrix (Figure 3), the behavior of the polymer system is crucial during dissolution, but depends on many factors (drug properties, formulation, release medium, etc.) [14].

In the case of a polymer matrix, the diffusion of the active ingredient can be through the intact polymer network or through the pores filled with water. Water-soluble drugs may also dissolve in the aqueous pore networks. Water uptake causes polymer chains to swell, indicating the formation of new pores and/or osmotic pressure. During swelling, the volume increases, the effective diffusion coefficient of the drug is increased, and more pharmacon molecules enter the aqueous part. Erosion of the polymer matrix (bulk/surface) is also possible.

In the case of polymer coated microparticles, the film-forming polymer may dissolve in the medium or act as a water-insoluble, permeable or semipermeable membrane. In the former case, the diffusion is predominantly due to the release of the active ingredient. In the case of a semipermeable coating, the osmotic phenomenon should be taken into account. It is also possible to use water-soluble pore formers, which, by creating pores, accelerate the dissolution profile [15,16].

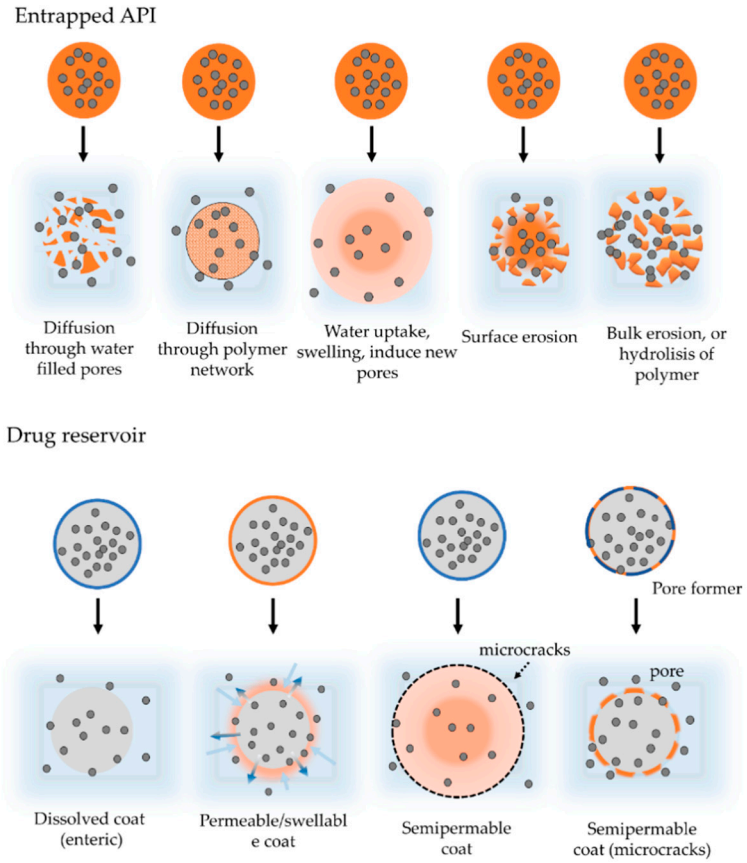

Figure 3. Release mechanisms in microencapsulated products.

In the case of smart drug delivery microparticle systems, the release of the drug occurs via a stimulus. It is possible that one, two, or more (multiple) stimuli are required for dissolution (Figure 4). The stimulus for drug release may be internal or external and be classified as physical, chemical, or even microbiological. Opening and closing signals of these systems are also possible, creating feedback [17].

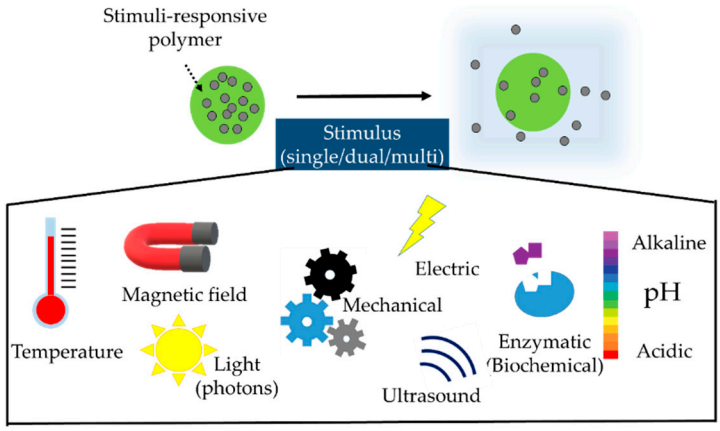

Figure 4. Smart release stimuli via microencapsulation.

Magnetic Microcapsules

Magnetic microspheres are supramolecular particles that circulate through capillaries without causing occlusion in the form of emboly (<4 μm) but show a ferromagnetic character such that they can be dragged into the target tissue with a magnetic field of 0.5–0.8 T [18]. Magnetic microparticles

for medical applications have been developed, such as magnetic resonance imaging (MRI) and drug delivery, and they are a promising choice in tumor therapy accompanied by hyperthermia. The release can be fine-tuned by the strength of the applied magnetic heating: with a gentle magnetic effect, the particles react with shrinkage and slow drug release, and with intense heating, the structure disruption induces the shrinking, which leads to a burst release [19].

Their great advantage lies in the effective method of targeting the drug molecule to the desired site to be treated (i.e., the tumor) with higher therapeutic efficacy and lower toxicity. The reduction of dosing frequency enhances the patient's compliance.

The production involves emulsion methods (multiple and phase separation polymerization, solvent extraction, hot melt microencapsulation, dispersion copolymerization).

4. Formulation and Manufacturing

4.1. Composition and Excipients

The use of plant, animal, or microbial-origin biopolymers are propitious; semi-synthetic cellulose derivatives and biodegradable or non-biodegradable synthetic polymers are used as well. The formulation is usually based on polysaccharides or proteins, but waxes and lipids also play a role in the construction. Nonpolymer excipients play a role in crosslinking the polymer chains ($CaCl_2$, glutaraldehyde, poly-L-lysine, etc.), thus forming and hardening the polymer network of the drug delivery systems. The most commonly used polymers and their important microencapsulation-related properties are summarized in Tables 1–5.

Table 1. Examples of proteins and waxes of plant or animal origin used in microencapsulation.

Excipient	Physicochemical Properties	Application and Benefits	Limitations	Ref.
Gelatine	Amphoteric gelatin A (isoelectric point (IEP) pH: 7–9.4 gelatin B (IEP: pH 4.8–5.5) Swells, then dissolves in water	At low pH coacervation with negatively charged polymers, high potential of crosslinking emulsifier, stabilizer (high viscosity), binder Thermoreversible gelling, implantable pulmonary delivery pH-dependent, swelling, dissolution, erosion	Influence of pH and ionic strength on behavior Need for preservation against possible prion (BSE) contamination	[20,21]
Casein	Hydrophilic, metal binding Insoluble in water at its IEP (pH 4.6)	calcium caseinate –reversible thermal gelation solubility increase (coenzyme Q10)	Anaphylactic reactions	[22]
Whey protein	Insoluble at its IEP (pH 5.2)	Thermal gelation, encapsulation of oils film formation: gas barrier, good tensile strength	Thermally irreversible gel formation above 70 °C Denatures at higher salt conc. Anaphylactic reactions	[23]
Albumin	IEP: 4.7 Freely soluble in water negative charge at pH 7.4	Pulmonary delivery Alginate-albumin	Chemical degradation, denaturation at high salt conc., enzymes, heat	[24]

Table 1. *Cont.*

Excipient	Physicochemical Properties	Application and Benefits	Limitations	Ref.
Zein	α, β, γ, δ, zein with different M_w amphiphilic character IEP: 6.8 hydrophobic	Oral controlled release matrix and wall	Brittle, rigid wall, complex with a gelling component to plasticize	[25,26]
Soy protein	Partly soluble in water, depending on the extraction process; IEP 4.5	Oral controlled release matrix and wall Emulsifier, foaming agent	Sensitivity	[27]
Gluten	Water-insoluble; IEP:7.5	Wall material, good elastic, good thermoplastic properties	Gluten sensitivity	[28]
Bees-wax (Apis mellifera)	mp (melting point): 62–64 °C $HLB_{required}$ = 12	Edible, easy use, smooth surface, hot melt extrusion prolonged release for hydrophilic substances, protection from chemical degradation	Oxidation	[29]
Carnauba wax (Copernica cerifera)	mp: 78–85 °C $HLB_{required}$ = 12	Good compatibility hot melt extrusion, embedding water soluble components, taste masking	Oxidation	[30,31]
Paraffin (hard) (mineral)	mp: 50–61 °C	Embedding water soluble components liquid paraffin in the emulsification process	Sensitivity	[32]

Table 2. Examples of polysaccharides of various origin used in microencapsulation.

Excipient	Physicochemical Properties	Applications and Benefits	Limitations	Ref.
Chitosan (deacylated chitin)	Soluble in weak acids Mucoadhesive reacts with negatively charged surfaces	Antifungal, antibacterial, reduces LDL (low-density lipoprotein), tissue regenerative, pulmonary delivery Ionotropic gelation, coacervation with anions, modified emulsification	pH dependence (insoluble above pH 6.5) Addition of electrolytes precipitates chitosan in solution, hygroscopic	[33–35]
Sodium hyaluronate	Anionic character, soluble in water, high viscosity at low concentration	In microspheres nasal, vaginal, ophthalmic delivery systems	Very hygroscopic, when heated, emits Na_2O	[36,37]
Starch (wheat, corn, potato, rice, tapioca)	Starch from different origins Differ in particle size and shape Soluble in hot water after a time of gelatinization	Spray drying, extrusion, molecular inclusion, coacervation with proteins, hydrocolloid-forming, release via swelling, diffusion, erosion	Hygroscopic	[38]
Guar gum	Water soluble, nonionic, galactomannan forms a thixotropic solution, stable at pH 4–10.5	Controlled-release, colon-targeted release, appetite suppressant, thermoreversible	Needs preservation, borate hinders swelling	[39]

Table 2. *Cont.*

Excipient	Physicochemical Properties	Applications and Benefits	Limitations	Ref.
Locust bean gum (LBG)/carob, ceratonia/	Nonionic, galactomannan, dispersible in hot water, soluble at higher temperature	Controlled release in combination pseudoplastic, gelling with the addition of borate, solubility not affected by pH or ionic concentration	Low water solubility, hypersensitivity	[40]
Konjac gum	Water soluble	Elevation of temperature increases gelation, antioxidant properties	Indigestable	[41,42]
K, ι, λ−, Carrageenan	Anionic polymer, ι−Carrageenan: shear thinning thixotropic gel forming	λ−Carrageenan: highest anionic charge, high solubility, but no gelling, κ, ι−Carrageenan: elastic gel is formed with K^+, Ca^{2+}, thermoreversible gel forming Release by erosion (physical contact-Scentcaps®), effective against HPV (human papilloma virus)	Acid-catalyzed hydrolyses, especially at higher temperature and pH < 3 Administration of >2 g/kg orally Induces intestinal ulcers, not biodegradable	[43,44]
Agarose	Soluble in hot water	swelling, Thermoreversible gelation (at ≈37 °C) with hysteresis	Poor biodegradability	[45]
Sodium alginate	Water soluble, anionic coacervation with ions (Ca^{2+}, Sr^{2+}, Ba^{2+}), polycations (chitosan) or poly-L-lysine disintegrant, binder, viscosity increasing	swelling ability (200–300× of its own weight from water) pH-dependent swelling nontoxic, nonirritant low density (capable of floating in gastric juice) Diffusion, erosion, in situ forming hydrogels	pH dependence (insoluble in acidic medium) heat-sensitivity (hydrolysis) microbial spoilage on storage (depolymerization)	[46]
Tragacanth	Water soluble arabinogalactan and swellable bassorin components, swells quickly in water	Acid-resistance emulsifier, encapsulation of oils, stabilizer in emulsions	Di/trivalent cations cause drop in viscosity because of precipitation	[47]
Gum arabic/ Acacia gummi (Ph. Eur.)	Water soluble, clear solution of pH 4.5, protective colloid	Emulsifier, spray-dry encapsulation of flavor and of essential oils, 30% solution has a relatively low viscosity, Newtonian flow permeable coating dietary fiber	Variation dependent on source pH, ionic strength influences viscosity (max at ≈pH 6–7)	[48–50]
Pectin (low or high methoxylated) (apple, citrus peel, beet)	Negatively charged molecule	Gelation depends on the degree of esterification, cation (Ca,Zn) concentration in solution, temperature and pH In situ gelling, sustained delivery, dietary fiber, drug delivery in colorectal carcinoma (5-FU), antiviral activity	Gelling occurs at low pH (<3.5), presence of sugars necessary for gelation of HM pectin	[51,52]

Table 3. Examples of polysaccharides of microbial fermentation used in microencapsulation.

Excipient	Physicochemical Properties	Applications and Benefits	Limitations	Ref.
Xanthan gum	Soluble in warm and cold water, not affected by pH anionic polyelectrolyte	No gelation at room temp, cryogelation possible, stable viscosity over wide pH range, surface activity, emulsion stabilizer, controlled-release, colon-targeted swelling, diffusion, matrix erosion	Hydrolysis Acceptable daily intake (WHO) 10 mg/kg BW Contains cellulase	[53]
Gellan gum	Anionic polyelectrolyte soluble in water	Thermoreversible gelation with cations sol-gel transition under physiological conditions bioadhesive nasal administration	Poor biodegragability	[54]
Dextran	Neutral polymer, solubility depends on degree of polymerization	Colon-targeted delivery, formation of porous particle pulmonary delivery	At parenteral adiminitration: possible platelet adhesiveness	[55,56]
Pullulan	Neutral polymer underivarized pullulan has high water solubility	Emulsifier sustained-release preparations	Relatively high price	[57,58]

Table 4. Examples of cellulose derivatives applied in microencapsulation.

Excipient	Physicochemical Properties	Applications and Benefits	Limitations	Ref.
Methylcellulose (MC)	Soluble in cold water $T_{sol-gel}$: 80 °C amphiphilic	Emulsifier, pseudoplastic solution, pH-independent gel formation above 50 °C, high variety in M_w	Complexation with surface-active components, laxative	[59]
Carboxymethyl-cellulose sodium (CMC-Na)	Anionic cellulose ether, dispersible in water (forms a colloidal solution)	Injectable thermoreversible gel-forming, mucoadhesive	Microbial instability hygroscopicity	[60,61]
Hydroxypropyl-cellulose (HPC)	Soluble in cold water, compatible with waxes, oils, $T_{sol-gel}$: 55 °C	High surface activity film-forming ability	Incompatible with alkaline substances, substituted phenol derivatives, anionic polymers increase viscosity	[62]
Hydroxypropyl-methylcellulose (HPMC)	Water soluble, nonionic	Reversible thermal gelation surface activity, emulsion stabilizer, film-forming ability	No complex with metallic salts or ionic organics	[63]
Ethylcellulose	Water-insoluble, hydrophobic coating	Film forming ability, membrane-controlled diffusion, modified release, floating, gastroretentive systems	Organic solvent residuals	[64]
Cellulose acetate butyrate	Insoluble in water, soluble in aceton-water blends	Semipermeable coating, extended release formulations, diffusion, matrix erosion	Organic solvent residuals	[65]

Table 5. Synthetic polymers applied in microencapsulations.

Excipient	Physicochemical Properties	Applications and Benefits	Limitations	Ref.
Poly (lactic acid) (PLA)	Insoluble in water degrades to CO_2 and H_2O over 12–24 months	Biodegradability, prolonged-release in im or sc injections, implants, oral solid dispersions	Digestive tract influences degradation, parenteral administration is favorable, initial burst release may occur	[64,65]
Polylactic acid-glycolic acid copolymer (PLGA)	Insoluble in water lactic acid-glycolic acid ratio influences degradation ability to thermoplastic gel forming	Injectable or implantable systems (microparticles, gels) for human and veterinary use, pH- responsive/non-pH -responsive polymer degradation, bone tissue engineering	Degrades into by-products that can induce inflammation	[66–69]
Polyacrylic acid (Carbopol)	Neutralization with alkaline chemicals for gelling	Bioadhesive, targeted delivery, intranasal administration with microencapsulation	Neutralization at preparation, preservative needed	[70]
Polymethacrylates	Soluble in organic solvents, most of them are miscible with water	pH-dependent solubility, permeability gastric or enteric targeted delivery possible	Water insolubility	[71]
Poly-(N-isopropylacrylamide)	LCST: 35–40 °C	Thermoresponsive	Not biodegradable	[72,73]
Polyethylene glycols	Liquid or solid grades depending on the M_w, PEG (polyethylene glycol) 1500 freezing point at 37–41 °C	Plasticizer in wall of compressible microcapsules, oral insulin delivery cell delivery in combination	Not biodegradable	[74]
Fumaryl diketopiperazine (FDKP)	High solubility at pH ≥ 6, no biological activity	Self-assembled highly porous microparticles, Technosphere® carrier	Not biodegradable, excreted via urine	[75]

LCST: lower critical solution temperature.

The combination of polymers of different properties is a common technique to improve the particle characteristics and performance. Because of their opposite charges, alginate and chitosan at low pH form a polyelectrolyte complex [76], thus decreasing the porosity of the polymer network and delay the release of the API (Table 6).

Table 6. Synergistic polymer combinations.

Polymer	Active Ingredient	Particle Size	Physicochemical Mechanisms	Ref
Carbohydrate-Carbohydrate				
Chitosan-alginate	Leydig cells	230–370 µm	Complex coacervation	[77]
Agarose-alginate ($CaCl_2$)	Sertoli cells	250 µm	Microfluidics ionic gelation,	[78]
Gum arabic	Xylitol	100 µm	double emulsion/coacervation	[79]
Cellulose acetate butyrate (CAB)	Sulfopropylated dextran microspheres	40–120 µm	O/W emulsification, solvent evaporation	[65]
Gelatin + gum arabic	Raspberry anthocyanins	150 µm	Emulsification, coacervation	[80]

Table 6. *Cont.*

Polymer	Active Ingredient	Particle Size	Physicochemical Mechanisms	Ref
Carbohydrate-Carbohydrate				
Maltodextrin + gum arabic	Lavender oil	10–20 μm	S/O/W emulsification, spray-drying	[50]
CMC-Na + xanthan gum	Diclofenac sodium	1000–1500 μm	Emulsification, ionic gelation, Interpenetrating network	[81]
LBG + PVA	Buflomedil hydrochloride (BH)	350–750 μm	emulsification, Interpenetrating network	[40]
Chitosan + pectin	Insulin	0.24–2 μm	electrostatic self-assembly	[82]
Carbohydrate-Protein				
Gelatin + gum arabic	Aspartame	100 μm	Double emulsion/complex coacervation	[83]
Gelatin + chitosan	Citronella oil	100 μm	Coacervation	[33]
whey Protein + maltodextrin	Flaxseed oil	≈10 μm	emulsification, spray drying	[84]
Whey protein + alginate	Flaxseed oil	<10 μm	Double layer emulsification spray drying	[85]
Alginate + gelatin	Whey peptides (antihypertensive activity	1000 μm	Dripping, coacervation	[86]
Alginate + zein	Bifidobacterium bifidum	1200–1700 μm	Extrusion coacervation shell-core	[87]
Chitosan-zein	Oral gene delivery	10 μm	Zein-sodium tripolyphosphate W/O emulsion	[88]
Poly-L-lysine	Poly (methyl vinyl ether-*alt*-maleic anhydride) (PMM_0)	400 μm	prilling, coacervation	[89]
Poly (L-ornithine) + alginate + PLA, PLGA	Superoxide dismutase, ketoprofen	500 μm	W/O/W, O/W, solvent evaporation	[90]
Poly (L-ornithine) + ursodeoxycholic acid, Polystyrene sulfonate, polyallilamine	Pancreatic ß-cells	700 μm	Complex coacervation, vibrational jet	[91]
Poly (ethylene glycol) (PEG)-anthracene alginate	Coomassie blue	no data	Coacervation	[92]
Vinyl-sulfone terminated PEG + alginate	Human foreskin fibroblast	550 μm	Simple coacervation	[93]
Alginate + Poly-ε-caprolactone	Theophylline	800 μm	Complex coacervation	[94]
Polypropylene + PMMA + ethylcellulose	Verapamil	150–200 μm	O/W solvent evaporation	[95]
PLGA-alginate	Rifampicin	15–50 μm	Microfluidics	[96]

Funami et al. [97] proved that galactomannans, including guar gum, tara gum, LBG, or konjac gum (glucomannan), influence both the short- and long-term retrogradation process of starch by controlling the gelation, hindering the crystallization, and improving the water-holding capacity of starch.

Farris et al. [88] developed a peroral gene delivery system, where DNA was encapsulated in chitosan nanoparticles and the particles were protected from the gastric environment by embedding the nanoparticles into zein matrix microparticles with a W/O emulsification method. Zein forms a relatively brittle film; however, alginate was successfully administered to decrease the rigidity of the wall [87].

Several studies show that copolymerization between synthetic and natural polymers helps to increase biocompatibility and cell viability (agarose-Carbopol®, hyaluronic acid-polyethyleneglycol) [98]. Hydrophobic excipients (poly-ε-caprolactone) can modify the release of low-solubility drugs from alginate by forming hydrophobic interactions with the drug molecule, thus prolonged release can be reached [94].

Controlled-release, porous, floating microparticles were formulated by combining polypropylene-Eudragit® RS, ethylcellulose polymers [95].

Mahou et al. successfully studied the addition of vinyl-sulfone terminated polyethyleneglycol to alginate and thus eliminated the use of polycations for human foreskin fibroblast cell encapsulation from a cell culture medium [93].

Wells et al. reached prolonged drug release and light-sensitive drug delivery with the chemical modification of PEG and chemical crosslinking with alginate.

Dalpiaz et al. studied the nasal absorption of zidovudine by deoxycholic-acid-conjugated chitosan microparticles and found that the particles could get through the blood–brain barrier, in contrast with active efflux transporters in rats [99].

Alginate microcapsules show shrinking and lower stability in an acidic medium. κ-carrageenan locust bean gum gel beads show lower sensitivity to acidic conditions than alginate beads. A limitation of their use is that the formation of κ-carrageenan locust bean gum beads requires a higher amount of potassium or calcium ions, which in terms of a healthy diet, are not acceptable in high amounts. In cell transplantation, alginate is applied because of its excellent biocompatibility and biodegradability. Alginate, however, has some limitations: uneven porosity, poor mechanical strength, weak wall-formation, and easy rupture on reaction to osmotic change have been reported. To overcome these drawbacks, excipients such as the polyelectrolytes polystyrene sulfonate (PSS) and polyallylamine (PAA) were examined in cell microencapsulation, which improved the physical structure of polyelectrolyte gels and complexes by reducing pore size in the microcapsule membrane. Osmotic or mechanical stress caused lower cell leakage of these microcapsules [91]. The incorporation of PSS and PAA were shown to attract inflammatory cells and to trigger an immune response. The same study showed that ursodeoxycholic acid increased mechanical stability and did not affect cell viability.

Poly-L-ornithine in combination with alginate has been shown to prevent post-transplant inflammatory response and has protected the microcapsules in vivo over the first week after grafting [90].

As artificial cell therapy, an alginate structure strengthened by poly-L-lysine was used for encapsulation [100]. The alkylamino groups of the polyamide chain bonds via electrostatic interactions with alginate, thus the matrix structure has reduced porosity and good immunoprotection.

4.2. Processes for the Particle Formation

From the point of view of the industrial performance, the most important methods for microencapsulation are the air suspension method, spray-drying, and coacervation. Figure 5 summarizes the most important techniques.

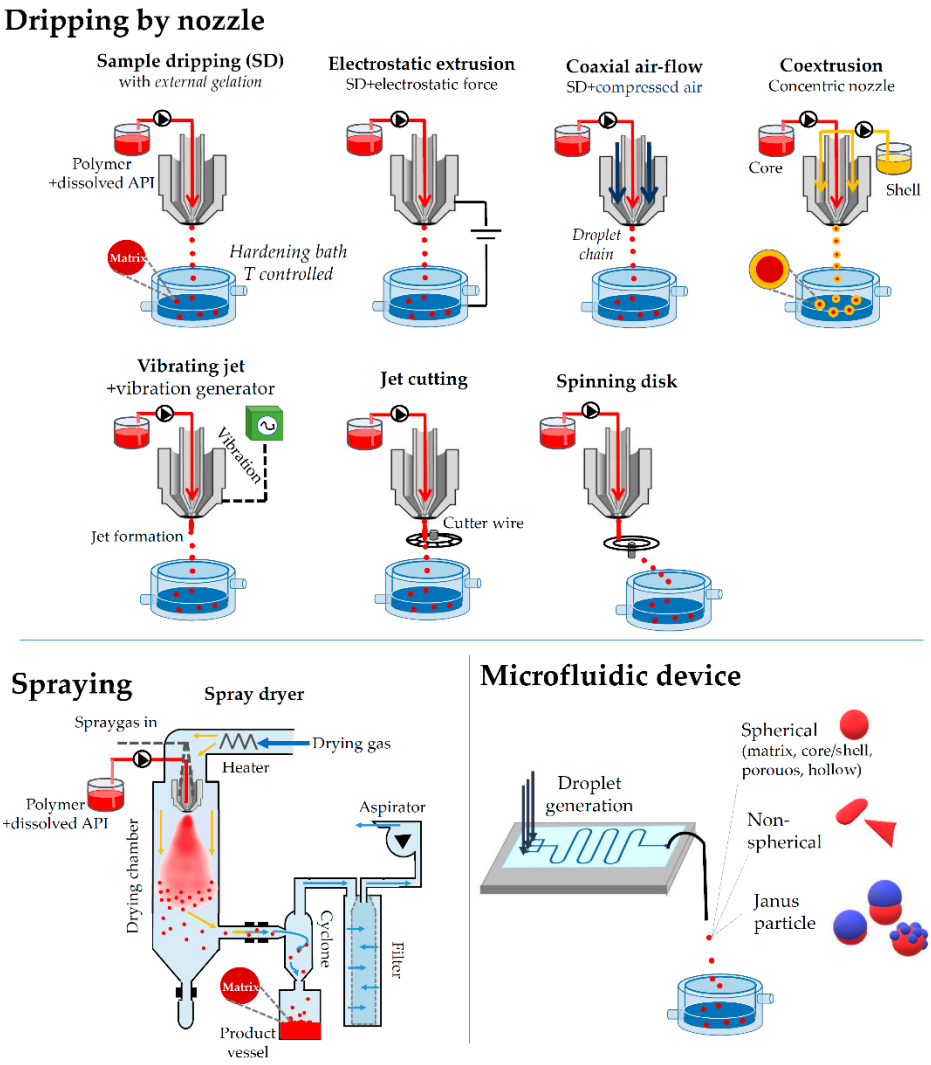

Figure 5. Preparation processes through droplet formation at an orifice.

4.2.1. Coacervation

Coacervation related to the formation of calcium alginate can be considered a classical method for the preparation of microspheres and microcapsules. Calcium-ions form crosslinks between the α-L-guluronic acid and β-D-mannuronic acid units of alginate, thus organizing the polymer chains into an "eggbox-structure." This chemical bonding gives the possibility of forming stable microspheres or core-shell structured microcapsules (Figures 6 and 7).

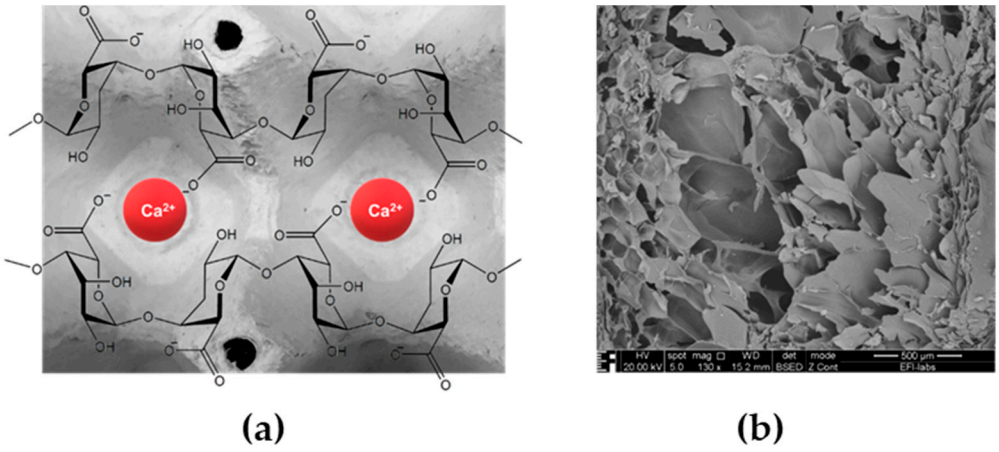

Figure 6. (**a**) Scheme for the interaction between calcium and alginate forming an eggbox-like structure. (**b**) Internal structure of the microsphere using scanning electron microscopy (SEM, magnification: 130×, scale bar indicates 500 µm).

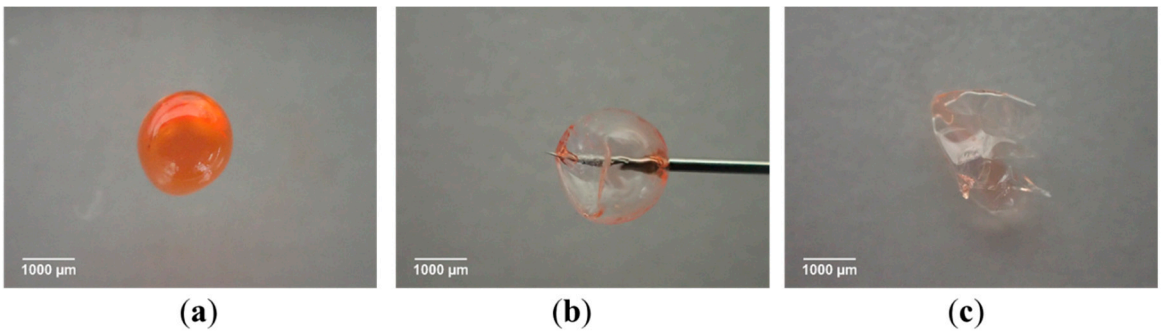

Figure 7. Images of a liquid core calcium alginate microcapsule prepared by vibration nozzle technique (prepared by Büchi B-390 Microencapsulator) followed by coacervation: (**a**) oil-filled hollow particles, (**b**) calcium alginate shell after removal of oil core, and (**c**) calcium alginate shell cut in half (average wall thickness: 8 µm) (Images: Nikon SMZ 1000 Microscope).

Coacervation is defined as the separation of liquid phases in colloidal solutions [101]. During coacervation, the active ingredient can be dispersed in the coating polymer solution and at a specific environmental influence (ionic, pH, thermal change), phase separation occurs, while the core material is encapsulated by the wall-forming polymer. Simple coacervation is based on incompatibilities between the polymers. In most cases, it is caused by salting-out (di- or trivalent cation, as it happens with alginate and Ca^{2+} or Ba^{2+}, pectin and Ca^{2+}). The particle size mainly depends on the excipients' properties (viscosity, surface tension) and stirrer setup [102,103].

During complex coacervation, polyelectrolyte polymers with opposite charges form an insoluble complex and meanwhile encapsulate the active ingredient. pH is important in complex coacervation, as the isoelectric point of the polymers has to be taken into consideration.

Hydrophobic components are often encapsulated with coacervation. In the case of hydrophilic components, a double emulsion process followed by a coacervation proves to be successful way to form a core–shell structure microcapsule [79]. As a result of coacervation, the product contains a high amount of solvent, which needs to be evaporated from the product.

For drying, besides the common processes, lyophilization (freeze-drying) offers a choice. This is an expensive method, but effective for heat-sensitive actives. Shrinking of the particles can be partly avoided; the end product, however, has a high porosity, which is an advantage in fast release preparations to promote the water uptake, but is an obvious drawback in the formulation of sustained-release preparations.

4.2.2. Air Suspension Method/Fluid-Bed Coating

(Wurster (1959)) [104] has successfully administered fluidization in macroencapsulation for the coating of solid particles, but it was also administered to encapsulate small particles in the size range of 74–250 μm by Hinkes et al. [105]. The great advantage is that during the process, the particles are suspended in an air (or inert gas) stream, in constant mixing, relative independently from each other and the wall material solution or dispersion is sprayed on their surface, then dried inside the coating chamber. The particle size can be tuned by the well-controllable process parameters: properties of the core (density, hygroscopicity, surface area, particle size and shape, melting point, wettability, solubility, volatility, compressibility, crystallinity, hardness, cohesiveness, adsorption, friability and flowability of the core material). Concentration and quantity of wall material, inlet, outlet air temperature, and spray settings are also critical for the process.

4.2.3. Extrusion through a Nozzle

Extrusion through a nozzle is a common method in the formation of gel particles. Many factors influence the formation of microgels: the concentration, feeding rate, and surface tension of the polymer solution, solvent, temperature, and nozzle diameter [3,106,107]. The solidification of the formed microgel particles is performed in an additional step. For solidification of the gel, coacervation (either simple or complex) is an optimal choice. The formed particles are collected in a solidification liquid (ionic or polymer solution). The size and shape control of particles is dependent on various factors. The distance, concentration, surface tension of the solidification liquid, and the time of the process have a significance in the particle size and the physical properties of the beads (gel strength, porosity, etc.). The most important limitations of the extrusion are the viscosity of the polymer because of potential blockage of the nozzle; as such, the settings for optimal, narrow particle size distribution, and shape are required. For the scale-up of the process, multiple-nozzle solutions have been presented.

4.2.4. Vibrational Jet/Electrostatic Extrusion

The particle formation via extrusion is completed by various processes: vibrational jet technique means that a changing frequency vibration separates the laminar jet into beads). At the electrostatic extrusion [108] the jet is subjected to an electric field, where having reached a certain voltage (5–6 kV), particles are created, the repulsive forces additionally hinder their aggregation. The applied elevated electric potential does not cause cell death [109].

4.2.5. Spinning Disk and Cutting Wire

These devices mechanically aid the particle formation and disaggregation [110].

4.2.6. Spray Drying

Spray drying is widely used in the industry for microencapsulation of volatiles, probiotics, and viable cells. Besides the obvious drawback (high loss, low yield), the numerous advantages make this technology very popular (uniform particle size, all steps carried out in one apparatus, use of organic solvents, the capability of encapsulating heat-labile materials). The emulsion is sprayed into a chamber, where warm air dries the particles, and as a result, regular shaped, micron-sized, uniform particles are created.

The extruded wax particles can be solidified using congealing, which offers a solution for embedding hydrophilic component to perform sustained release via the slow erosion of the wall in the biological medium.

4.2.7. Supercritical Fluid Precipitation

This technique is capable of constructing very uniform particles, but its use is more significant in nanoencapsulation [111].

4.2.8. Freeze-Drying

Freeze-drying is successfully used in the microencapsulation of protein APIs. The process consists of freezing, sublimation, primary drying, and secondary drying. At the freezing step, the eutectic point of the components is taken into consideration. Lyoprotectants or cryoprotectants (trehalose, dextran) can stabilize API molecules during the process by replacing water, forming a glassy matrix, reducing molecular mobility by establishing hydrogen or van der Waals bonds between the molecules [112]. Despite its high cost, it is an advantageous process for heat-sensitive molecules.

Freeze-drying provides solidification, which then allows particles to be reconstituted in an aqueous medium (Figure 8).

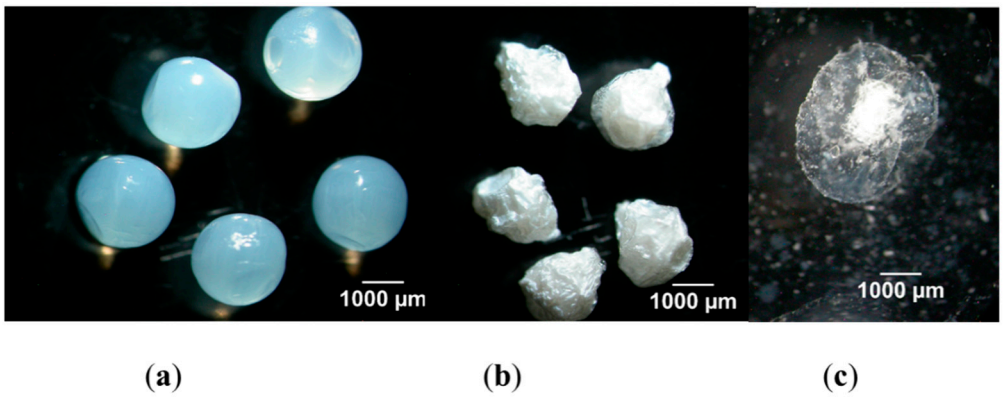

Figure 8. Calcium alginate microparticles: (**a**) initial (prepared using a Büchi B-390 Microencapsulator), (**b**) freeze-dried, and (**c**) reconstituted in a pH 6.8 phosphate buffer (60 min).

Table 7 summarizes the most important methods along with the parameters of the initial and final form of microparticles.

Table 7. Classification of main procedures to prepare microparticles, spheres, and microcapsules.

	Method	Typical Initial Form of the Core	Approximate Size (µm)	Structure		Final State
				Matrix	Core/Shell	
Chemical	Interfacial polymerization	In emulsion or suspension	0.1–500		X	wet (slurry), can be dried
	In situ polymerization	In emulsion or suspension	1–1000		X	wet (slurry), can be dried
Physicochemical	left	In emulsion or suspension	2–5000	X	X	wet, can be dried
	Dripping-(Vibrating nozzle-single; multiple)	Droplet formulation/extrusion; coextrusion	10–5000	X	X	wet, can be dried
	Solvent evaporation	In emulsion or suspension	0.1–5000	X	X	wet, can be dried
	Spray drying (from solution)	Droplet formulation/spraying	1–100	X		dry
	Spray chilling	Droplet formulation/spraying	1–100	X	X	dry
	Fluid bed coating/drum coating	Solid core particle	100–5000		X	dry

4.2.9. Microfluidics in Microparticle Fabrication

Microfluidics also presents promising results regarding microparticle production [113]. A wide range of microfluidic plates have been created concerning their various structure, material, and size [114]. Various methods are used for the engineering of microparticles such as continuous flow-based and electrowetting-based droplet generators.

Microfluidic Droplet Generators (MFDG)

Microfluidic droplet generators (MFDG) with a T-junction, co-flowing junction, and flow-focusing geometries are able to create, depending on the settings, monodisperse spherical or spheroid droplets [114]. The microfluidic-based droplet generation can be implemented using active or passive methods. In the passive method, droplets can be produced in squeezing, dripping, jetting, tip-streaming, and tip-multibreaking modes, depending on the competition between capillary, viscous, and inertial forces [115]. In active control, droplet generation can be manipulated by either applying additional forces from electrical, magnetic, and centrifugal controls, or modifying intrinsic forces via tuning fluid velocity and material properties including viscosity, interfacial tension, channel wettability, and fluid density [115].

Coaxially assembled devices, in combination with emulsification methods, led to the production of monodisperse microcapsules or Janus particles [116]. The polymerization occurs using a concomitant chemical or physical reaction based on the nature of the polymer [117]. Figure 9 presents particle formation through a PDMS (polydimethylsiloxane) hydrodynamic focusing apparatus of a W/O/W alginate system in oil as a carrier liquid. The alginate droplets were solidified via coacervation (own experiments).

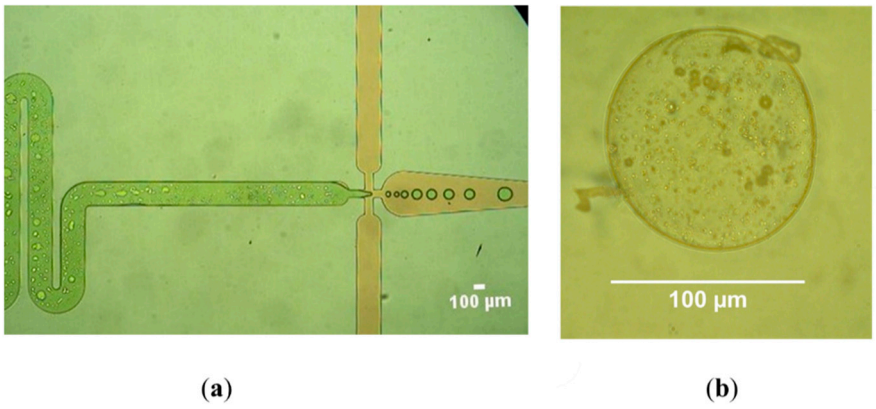

Figure 9. (**a**) Particle generation with microfluidics with a flow-focusing-based microfluidic droplet generator (MFDG). Particle formation was carried out with an own-developed hydrodynamic-focusing-based microfluidic device. (**b**) Emulsion coacervated particle fabricated using microfluidics.

Wu et al. [96] demonstrated that in the case of monodisperse rifampicin-PLGA core-shell microcapsules, the burst-release can be decreased with increased encapsulation efficiency, and the release can be controlled by increasing the wall thickness.

4.2.10. Lithography

Contact lithography was originally developed for the semiconductor industry. It is, however, successfully applied in the replication of nonspherical particles of 500–1000 µm in size. The pattern is transferred from a photomask to a photopolymerizable material (e.g., polyethylene-glycol- diacrylate) using light [118]. Continuous flow lithography has better particle resolution and improved throughput. The monomer solution is pumped through a microfluidic device, where photopolymerization occurs.

The polymer particles (sometimes of extreme shape) are collected after having left the device [9,119] and have been used for the controlled synthesis of bullet-shaped, 12.4-μm long, magnetic and non-magnetic microparticles using stop-flow lithography, which gives the possibility of executing mild invasive drug delivery via microneedles.

5. Characterization

5.1. Morphology

Size plays a crucial role in the in vivo performance of microparticles. Particles larger than 100 nm stay at the site of administration until the phagosomal clearance. Lymphatic uptake and node accumulation is most significant between 10–80 nm [2].

5.1.1. Particle Size Analysis

Particle size analysis of microparticles above the diameter of 3 μm is in most cases carried out based on laser light diffraction (LD) method or using a Coulter counter. In LD, the distribution indicates the span-value, and $d_{0.1}$, $d_{0.5}$, and $d_{0.9}$ are the parameters that can be used to compare the results. Span-value indicates the size distribution and is calculated based on the following equation:

$$\text{Span} = \frac{d_{0.9} - d_{0.1}}{d_{0.5}} \quad (1)$$

where 90% of the particles are under the diameter $d_{0.9}$, 10% of the particles are under the diameter $d_{0.1}$, and 50% are under the diameter $d_{0.5}$.

The polydispersity index (PDI) determined by dynamic laser light scattering indicates the size distribution in the lower size region of microparticles.

5.1.2. AFM (Atomic Force Microscopy)

AFM is a technique providing information about the surface of microparticles in nanoscale by profiling the surface [120].

5.1.3. Coulter Counter

A Coulter counter gives an absolute particle number per volume unit for various size ranges and is very important in the particle analysis of microparticles for intravenous use [121].

5.1.4. Image Analysis

The shape determination can be more accurately achieved using microscopic (light or scanning electron microscopy) image analysis. The shape is characterized by the roundness, aspect ratio (AR), and the Feret-diameter. Roundness (R) is calculated using $R = \frac{P^2}{4\pi A}$, where P is the perimeter, and A is the projection area. The aspect ratio is calculated using $AR = \frac{D_{max}}{D_o}$, where D_o is the longest orthogonal diameter perpendicular to D_{max}.

The aerodynamic size distribution (indicator of the particle deposition during inhalation) can be investigated using cascade impactors (powders, aerosols, and sprays). The deposition is not solely based on the particle size, the flow depends on the particle shape and density as well [120].

5.2. Physicochemical Properties

Zeta-Potential Analysis

The surface charge of the particles influences physical properties (e.g., tendency to aggregation); it also has a tremendous role in their biological performance: negatively charged surfaces (polysaccharide-based natural molecules, e.g., polyalginic acid, hyaluronic acid, polymethacrylic acid, etc.) attract to tissues in inflammations and are hemocompatible. Positively charged microparticles (chitosan, Poly-L-lysine), however, present a mucoadhesive character and are non-hemocompatible [122]. Zeta potential and particle size can be determined using photon correlation spectroscopy. The dynamic light scattering measurement is based on the Brownian movement of the particles. Zeta potential measurements present valuable data concerning the aggregation potential of surface charged microparticles in a suspension (above ±30 mV stable suspended particles because of repulsion), and in indicating whether the surface-charged molecule is encapsulated or adsorbed on the surface [123].

5.3. Physical Properties

5.3.1. Density

The density of particles determines the floating capacity and concomitant disintegration or swelling of the particle. The pycnometric method with helium gas can be used to determine this value [124].

5.3.2. Porosity

The porosity of microparticles has a significant role in the water uptake, swelling, reconstitution, and release mechanisms. This parameter can be measured directly using mercury porosimeters [125].

5.3.3. Microcomputed Tomography

The indirect assessment of porosity can be deducted from a microcomputed tomography assay based on the 3D internal trabecular separation for calcium-alginate microparticles [126].

5.3.4. Flowability and Compressibility Studies

The flowability, Carr's index, Hausner ratio, and angle of repose are significant for particles applied in the dry state. These tests can be executed as it is described in the official pharmacopoeias (e.g., European Pharmacopoeia, Unites States Pharmacopoeia).

5.3.5. Mechanical Test

The tensile strength and the elasticity of microparticles can be tested with a texture analyzer, where the compression force is detected relative to the distance, and the maximum compression force and hardness can be calculated, which indicate the mechanical resistance of the shell or the matrix structure [124].

5.3.6. Swelling

An equilibrium swelling study can be performed to observe the behavior of dry particles under various conditions (Figure 10). The swelling index ($S\%$) can be calculated using the swollen particle diameter (d_s) and the initial particle diameter prior to reconstitution (d_i), as follows:

$$S(\%) = \frac{d_s - d_i}{d_i} \times 100 \quad (2)$$

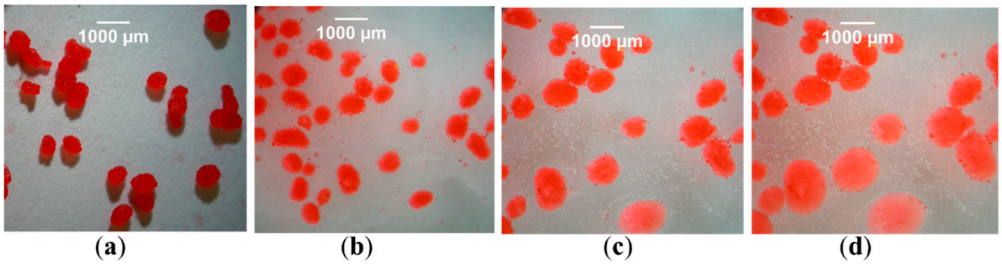

Figure 10. Swelling of air-dried O/W alginate (2%) microparticles (prepared using a Büchi B-390 Microencapsulator) in a pH 6.8 phosphate buffer: (**a**) initial, (**b**) after 5 min, (**c**) after 15 min, and (**d**) after 30 min (the oil phase contained Sudan III. as an indicator). Images: Nikon SMZ 1000 Stereomicroscope.

5.3.7. Wetting Property

The wetting property of the excipients can be determined using contact angle measurements [127,128].

5.4. Drug Entrapment Efficiency

The success of drug loading can be expressed by the actual loading and the entrapment (encapsulation) efficiency:

The actual drug loading is:

$$DL\ (\%) = \frac{drug\ \ (mg)}{(drug\ +\ polymer)\ (mg)} \times 100 \tag{3}$$

The general formula for calculating the entrapment efficiency value is:

$$EE\ (\%) = \frac{entrapped\ drug\ content\ (mg)}{theoretical\ drug\ content\ (mg)} \times 100 \tag{4}$$

The ideal entrapment efficiency (100%) is influenced by various factors such as the type and circumstances of the process [129].

5.5. Drug Release

5.5.1. In Vitro Dissolution Test for Multiparticulates

USP 42-NF 37 suggests different methods for the dissolution of multiparticulate preparations. The apparatus and the volume are chosen based on the dosage form performance in the medium and the volume. Compendial rotating basket (USP Apparatus 1), a reciprocating cylinder (USP Apparatus 3) can be used for nondisintegrating coated beads, or a flow-through cell (USP Apparatus 4) can be used for multiple dosage forms (beaded products), where sink conditions are provided.

Polymers of ionic character perform differently under various pH conditions. The independence or dependence of drug release on the ionic strength of the medium can be proved using distinctive pharmacopoeial methods. The medium ranges between the physiological pH 1.2–7.5 hydrochloric acid or phosphate or acetate buffer with or without enzymes, depending on the route of administration or the behavior of the polymer in the medium (e.g., swelling, ionization (IEP)). The use of surfactants is possible, usually over its CMC value.

As a noncompendial apparatus, a mini-paddle-equipped small-volume apparatus, dialysis tubes, or rotating bottle can be used.

The in vitro release mechanisms (diffusion, erosion, osmotic release, or a combination of the previous) can be interpreted based on the models of Fick, Higuchi, Korsmeyer-Peppas, Weibull, and Kopcha [130,131].

5.5.2. Dissolution Test for Inhaled Particles

Inhaled particles deposit in the tracheobronchial tract depending on the size, density, and shape of the particles. The mucus layer that provides the absorption site for drugs has a small volume and the renewal of the absorption layer is different from that of the gastrointestinal tract; therefore, the development of dissolution methods different from the traditional is used. USP 2, the rotating paddle apparatus, can be used with certain modifications. The drug is set into a special cassette and an apparatus capable of a 150 mL dissolution medium is used, agitated using mini paddles [132].

The dialysis bag method is also useable. The drug is set in the semipermeable dialysis bag, which is immersed in the dissolution medium. The drug diffusion occurs between the two liquid phases, and although both static and sink-conditions are maintained, the method does not simulate the air–liquid transition.

5.5.3. In Vitro Performance of Intramuscular Injections

The in vitro dissolution study of the long-acting intramuscular injection, Risperdal® Consta®, where the small interstitial volume provides an alternative dissolution method, was carried out in a flow-through cell apparatus equipped with glass beads of 1 mm diameter and a pump [133]. The in vitro dissolution data of the accelerated test, performed at a temperature above the glass transition temperature of the polymer, correlated well with the previously published in vivo data.

In both the modified Franz diffusion cell [134] and Transwell® [135] systems, drug powder is poured on a semipermeable membrane, which is located above the acceptor medium and diffuses through the membrane during the test. Small volume, agitation, and regularly withdrawn samples (sink conditions) provide the in vitro simulation of the in vivo performance.

DissolveIt® apparatus [136] presents in vitro dissolution and absorption by mimicking the in vivo performance with a membrane separating the simulated air–blood barrier in the tracheobronchial region of the lung and a flowing blood simulant.

5.5.4. In Vitro Dissolution Test for Topical Microsponge Preparations

A Franz diffusion cell with silastic membranes and a sink condition providing solvents as an acceptor medium has been applied to test benzoyl-peroxid-containing microsponge gel preparations [64].

6. Other Studies

6.1. Spectrometry

Fourier-transform infrared (FT-IR) and powder X-ray diffractometry (PXRD) analysis can be performed to follow the intramolecular changes during microencapsulation [81]. Nuclear magnetic resonance (NMR) studies underline the conformational changes in polymers during complexation [137].

6.2. Thermoanalytical Methods

Thermogravimetry (TG) and differential scanning calorimetry (DSC) give valuable data of the thermal behavior of the polymer. The measurable glass transition temperature plays a significant role in the production and the release mechanisms as well.

In the case of mucoadhesive systems, the tensile strength test, shear strength test, and the peel-off test or in vitro wash-off test can be performed [61].

6.3. Biocompatibility

A tetrazolium-based colorimetric assay, such as an MTT (methylthiazolyldiphenyl-tetrazolium bromide) assay, proved good to screen the cytotoxicity of hydrophylic polymers [138].

7. Applications in the Therapeutical Practice

Several types of multiparticulate sytems and product examples are detailed in Table 8 according their type, dosage form with route of administration, drug and key excipient, and indication for use.

Table 8. Types of multiparticulate systems in use.

Type	Dosage Form	Key Excipient	Drug	Indication	Product Example
Micropellets	Peroral pellets in capsule	HPC	Lansoprazole	Proton pump inhibitor	Lansoprazole®
Enteric-coated microgranules	Delayed-release orally disintegrating tablets	Methacrylic acid, polyacrylate	Lansoprazole	Proton pump inhibitor	Prevacid® SoluTab™
Coated pellets	Compressing pellets into an extended release tablet	HPC, EC	Metoprolol succinate	Cardioselective beta blockers	Betaloc® ZOK
Microtablets	Peroral minitablets in capsule	Methacrylic acid-ethyl acrylate, MCC	Lipase, amylase,	Enzyme supply	Pangrol®
Dry powder (Technospheres®)	inhalation	Fumaryl diketopiperazine	Insulin	Diabetes	Afrezza™
Microspheres	Im suspension injection	Poly-D, L-lactid-co-glycolide	Risperidone	Schizophrenia	Risperdal® consta
Microspheres	Powder for injection	Poly-D, L-lactide-co-glycolide	Bromocriptine	Acromegaly, parkinsonism	Parlodel® LAR
Microspheres	Powder and solvent for suspension and injection	Poly-D, L-lactide-co-glycolide	Octreotide	Acromegaly pancreatic tumors	Sandostatin LAR®
Microspheres	Prolonged-release suspension for injection	Poly-D, L-lactide-co-glycolide	Exenatide	Diabetes type 2	Bydureon®
Lyophilized microspheres	Suspension depot injection	Poly-D, L-lactid-co-glycolide	Leuprolide acetate	Endometriosis	Lupron® depot
Liposomes	Liposome inhalation suspension	Cholesterol, dipalmitoylphosphatidylcholine	Amikacin	Antibacterial	Arikayce®
Liposomes (DepoFoam™)	Powder for suspension for injection	Cholesterol, DOPC, DPPG	Cytarabine	Neoplastic meningitis	Depocyte®
Liposomes (DepoFoam™)	Powder for suspension for injection	Cholesterol, DOPC, DPPG, tricaprylin, triolein	Morphine	Epidural analgesia	DepoDur®
Microbubbles	Intravenous injection	Albumin	Perflutren	Ultrasound contrast agent	Albunex®
Microbubbles	Intravenous injection	PEG 4000, DSPC, DPPG-Na, palmitic acid	Sulfur hexafluoride	Ultrasound contrast agent	Lumason/SonoVue®
Microbubbles	Intravenous injection	DPPA, DPPC, MPEG5000 DPPE	Perflutren	Ultrasound contrast agent	Definity®
Microsponge	Topical gel	Methyl methacrylate/glycol dimethacrylate crosspolymer	Tretinoin	Acne vulgaris	Retin A® micro gel
Microsponge	Topical cream	Methyl methacrylate glycol dimethacrylate crosspolymer, dimethicone.	5-fluorouracil	Multiple acne/solar keratoses	Carac® cream 0.5%

Solid multiparticulates usually involve coated pellets or microtablets in order to ensure gastric resistance (e.g., for acid labile proton pump inhibitor compounds) or to prolong the duration of action and optimize the pharmacokinetic profile. Smart carrier systems react to changing pH, electric impulse, magnetic field, and/or temperature, and have been developed in many platforms (pellets, microgranules, microspheres).

Patient-centric medication involves the development of patient-friendly devices (e.g., DPI—Dry Powder Inhaler) and administration routes. Inhalatives, ODTs, and nasal administration could be an opportunity to reach a systemic effect. There is broad research on this field, however, there is only a limited number of preparations approved by the authorities

Sustained-release injectable depot systems are capable of forming a reservoir at the site of administration and release the API over a longer period. This property is advantageous in the treatment of psychotic patients, or in the medication of children with acute diseases.

7.1. Insulin for Inhalation (Technosphere®)

Afrezza™ is an immediate-release insulin formulation for Type 1 and Type 2 diabetes patients with an optimal bioavailability (25%). The pulmonary applied preparation consists of microparticles (2–3 μm) of self-assembled fumaryl diketopiperazine (FDKP) (M_w = 452.46 Da) molecules. In this preparation, FDKP nanocrystals are formed via a pH-induced crystallization process, and the nanocrystals are self-assembled into a spherical microparticle, like a deck of playing cards. The front and back sides of the "cards" provide the spheres with a high surface area, and the distance between the layers provide the extremely high porosity, low density, and convenient aerodynamic character to deposit into the distant alveolar regions where the API dissolves rapidly at the alveolar surfactant pH. Depending on the API molecular weight, local (>100,000 Da) or systemic absorption is possible. Special inhalers (Dreamboat® or Cricket®) are designed for optimal application [139].

7.2. Depocyte® (Parenteral Suspension)

Depocyte®, a liposomal product, is a pyrogen-free, parenteral suspension containing cytarabine developed for the treatment of neoplastic meningitis (NM) via controlled release. Depocyte® is a slow-release formulation created using DepoFoam™ technology, which includes microscopic spherical particles (3–30 μm) and is suitable for encapsulating hydrophilic compounds in a "honeycomb-like structure" of separated water-containing chambers. Lipid membranes separate each adjacent chamber. Drug release is carried out over an extended time via erosion and/or reorganization of the particles' lipid membranes. The honeycomb architecture of multivesicular DepoFoam™ particles gives allows for a comparatively high drug loading. The injection comprising 96% aqueous foam and 4% biodegradable lipid [140] has to be administered intrathecally every two weeks and it is metabolized by the usual metabolic pathways for triglycerides, phospholipids, and cholesterol.

7.3. DepoDur™

Epidural morphine sulfate sustained-release liposome injection DepoDur™ is a single-dose preparation administered at the lumbar level by the epidural route before operations. The lipid foam contains multivesicular lipid-based particles with aqueous chambers that encapsulate the active drug. The foam releases morphine during a 48-h period via erosion, namely the rupture of the microvesicles (of 17–23 μm in median diameter).

7.4. Microsponge Delivery System (MDS)

Topical delivery of drugs can be achieved with microparticles of very high porosity. These structures (of particle size of 5–300 μm) can entrap and release drugs with a controlled rate as a response to special triggers—skin temperature change, rubbing, moisture, friction, etc.—while they do not penetrate into the skin and perform a local effect. MDSs can achieve a very high embedding

capacity (50–60%), and as their pore size is very small (≈0.25 μm), bacteria cannot penetrate inside, they do not need preservatives to obtain stability. They are usually administered in the form of a gel, and the aforementioned physical and physicochemical tests have to be accomplished with rheological studies (viscoelasticity) [141]. The disadvantage is that by the production only organic solvent technologies proved to be effective.

7.5. Microbubbles

Microbubbles are used as ultrasound contrasting agents, gene delivery vesicles, O_2 carriers, are thrombolytic, and facilitate the transport through the blood–brain barrier without inducing a tissue-damaging effect [142]. Microbubble formulations contain an emulsifier, phospholipids, or protein components, which, following sonication, entrap gases (O_2, perfluorocarbons, or sulfur hexafluoride). The product can be preserved in a lyophilized form. The maximum size may not exceed 10 μm to avoid embolism in vivo [143].

The in vivo performance of microbubbles is influenced by the complement system of the immune system, which is responsible for the removal of drug molecules, bacterial cells, and microbubbles from the circulation. Studies pointed out that PEGylation reduces the immunogenicity of BSA (bovine serum albumin) microbubbles [143].

8. Summary

In the past few decades, numerous microparticulate formulations gained therapeutical and diagnostical significance. A great number of polymers have been tested, of which several have been proved effective.

To accomplish the traditional coacervation, new methods have been developed (freeze-drying, spray drying, microfluidic flow-focusing, lithography, etc.). The various created structures offer a large potential for the fine-tuning of drug release mechanisms and the optimization of the pharmacokinetic profile.

Author Contributions: Formulation, characterization, polymer excipients, and use (M.L.); processes, release mechanisms (N.K.-S.); preparation, samples, and photos (V.A.); microfluidics (A.J.L.); and content, structure, and therapeutical aspects (I.A.).

Funding: This review article received no external funding.

Acknowledgments: The authors thank Ágnes Sárádi-Kesztyűs for technical assistance.

Conflicts of Interest: The authors declare no conflict of interest.

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