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Review article

# Polyester based polymeric nano and microparticles for pharmaceutical purposes: A review on formulation approaches

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ABSTRACT

The novel polymeric particulate systems show high potential in their clinical effectiveness. Nevertheless, many of the drug delivery systems developed in the research laboratories have not found their way to clinics. The lack of therapeutic efficacy and safety, due to the use of some materials unapproved by the FDA, seems to be an important reason behind the unsuitability of the developed polymeric systems for the clinical application. Through specific design, choice of proper approach and excipients, the zero order linear release is highly achievable. The aim of this review was to explain the challenges associated with formulation development for several therapeutic agents in polymeric particulate system by scientific evidences. Growing interest in biotechnology and application of therapeutic proteins and peptides in various pathogenic disorders caused our special focus on their quality and preparation challenges. In this review, all formulation development issues i.e. choice of material, the amount of their use and regulatory policies were discussed. In the rest, other formulation development parameters such as effect of particle size, pH, drug loading as well as production method difficulties, dosage form qualities and route of administration to reach high quality particles were reviewed. Generally, this review tried to address an overview on how to solve the difficulties in the path of development of the polymeric particles for the pharmaceutical purposes.

## 1. Introduction

Advancement in particulate drug delivery systems seems to be not feasible without growth in polymer technology. Over the last decade, a growing number of polymeric materials have been industrialized and introduced for drug delivery. However, many efforts in research laboratory have not found their way to clinics. The lack of therapeutic efficacy and safety, due to the use of some materials unapproved by the FDA, seems to be an important reason behind the unsuitability of the developed polymeric systems for the clinical application. Moreover, many of particulate delivery systems fail in preclinical study, due to in vivo instability. Choosing a suitable method for the fabrication of polymeric drug delivery system is critical to develop a stable drug delivery system, optimal in size, surface charge, shape, drug content, and release profile. Physical encapsulation is the most extensive and successful method for loading drug in polymeric drug delivery systems. Polymeric particulate systems are mainly used for the development of various types of the controlled release dosage forms to lessen the drug

*Abbreviations:* FDA, Food and Drug Administration; PLGA, Poly(lactic-*co*-glycolic acid); CP/DP, Continuous phase to dispersed phase; API, Active pharmaceutical ingredient; IID, Inactive ingredient for approved drug products; LC, Loading capacity; EE, Encapsulation efficiency; MW, Molecular weight; PCL, Poly-Ɛ-caprolactone; PLA, poly(lactic acid); Na-CMC, sodium carboxymethyl cellulose; HPMC, hydroxypropyl methylcellulose; L/G, lactide to glycolide; Tg, glass transition temperature; BCS, Biopharmaceutical classification; log D, partition coefficient; PVA, Polyvinyl alcohol; SLS, Sodium lauryl sulfate; SA, Serum albumin; CMC, Critical micelle concentration; ICH, The International Council for Harmonization; DCM, Methylene chloride; EPA, Environmental Protection Agency; DMSO, Dimethyl sulphoxide; FDA-DM, FDA Drug monograph; PQR, Product quality review; PS, Phase separation; EM, Emulsion method; W/O/W, Water in oil in water; rhGH, Recombinant human growth hormone; MAB, Monoclonal antibody; rhuMAbE25, Recombinant humanized anti-IgE MAB; $T_m$, Midpoint of denaturation; $G_D^\circ$, Gibbs energy change at 25 °C; S/O/W, Solid in oil in water; ME, Membrane emulsification; GMP, Good manufacturing practices; CPP, Critical process parameter; SPG, Shirasu porous glass; HLB, Hydrophilic-lipophilic balance; $T_C$, Critical temperature; TIPS, Thermally induced phase separation; SCF, Supercritical fluid; $SCO_2$, Supercritical carbon dioxide; MF, Microfluidics; ABT627, Endothelin receptor-selective antagonist; BSA, Bovine serum albumin; BBB, Blood brain barrier; PVP, Poly(N-vinyl-2-pyrrolidone); ABC, Accelerated blood clearance; NAB, Nanoparticle albumin-bound; IHNV, Infectious hematopoietic necrosis virus

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**Table 1**
Important advantages of controlled delivery systems in medical applications.

| Advantages | References |
|---|---|
| Improvement patient compliance by reducing the dosing frequency | [4] |
| Provide prolonged and constant therapeutic effect | [5] |
| Reducing local undesirable effects by delaying drug release in stomach | [6] |
| Enhancement of the biological half-life | [7] |
| Improvement the bioavailability and therapeutic effect for short half-life drugs | [8] |
| Protection of drugs against environment conditions | [9] |

administration frequency, resulting in an increase in patient compliance [1,2]. Furthermore, polymeric particles have been widely used for tumor-targeted delivery of anticancer agents to enhance their therapeutic efficacy [3]. The advantages of the controlled delivery systems by polymeric particles are summarized in Table 1.

Most polymers, technologically advanced for drug delivery, are biocompatible and biodegradable. Studies have shown that polymeric particulate system can improve the bioavailability of many problematic drugs. The main advantage of using polymeric systems over the other drug delivery systems, such as lipids, is that the polymers can be customized for specific type of drug in order to achieve a better drug polymer compatibility. In this paper, we reviewed the major challenges and proposed the different strategies with appropriate excipients to reach the promising development.

## 2. Formulation development

The choice of the polymer, the physicochemical properties of the drug and excipients, the ration of continuous phase to dispersed phase (CP/DP) and pH are some of the important attributes in the formulation development. Moreover, some characteristics of the active pharmaceutical ingredient (API), such as aqueous solubility, stability and compatibility during manufacturing are the factors which should be evaluated over the product development [10]. The drug loading capacity (LC), the drug potency and size, the route of administration and dosage form are also formulation requirements, and may be challenging factors to be addressed. The other mostly discussed factor is the solidification time, concerning the encapsulation efficiency (EE) of the API in polymeric particulate system [11,12]. All of the above-mentioned issues will be discussed in following sections.

## 3. Materials used in the polymeric particulate system

The advancement of the polymer technology, as drug delivery carriers, has been considerable over the decades. Poly (lactic-*co*-glycolic acid) (PLGA) is well known, due to its biocompatibility and flexibility to control particulate polymeric system by varying chemical structures and molecular weight (MW). Not all the biocompatible and biodegradable materials are appropriate for medical applications, as they are required to have Food and Drug Administration (FDA) confirmation. The U.S. FDA has approved PLA and its copolymers for clinical use as drug delivery systems and medical devices [13,14]. Searching the inactive ingredient for approved drug products (IID) in the U.S. FDA organization website may be useful for choosing and determining the maximum potency per unit dose in formulation development.

### 3.1. Polymer properties

Biodegradation mechanism, suitable toxicological profile, low immunogenicity, drug-polymer compatibility and proper mechanical properties are basic requirements in polymer selection [15]. Polymers are categorized as natural and synthetic [16]. Natural polymers, such as proteins and polysaccharides e.g. starch [17], gelatin [18], chitosan [19], dextran [20], hyaluronic acid [21] and albumin [22] are well-known for their benefits in degradability and insignificant toxicity. On the other side, customizable degradation rate and mechanism as well as physical and mechanical characteristics such as tensile strength and elastic modulus are benefits of the synthetic polymers in comparison with the natural polymers [23]. Furthermore, possible side effects such as immunogenicity, poisonousness and even infections are least for the pure synthetic polymers with identical monomeric units [24,25].

A wide range of biodegradable polymers, including poly-Ɛ-caprolactone (PCL), polyesters such as poly (lactic acid) (PLA) and its copolymers, polyanhydrides, polyorthoesters, polydioxanones, poly (a-cyanoacrylates), polyoxalates, polyiminocarbonates, polyurethanes and polyphosphazenes have been applied to formulate nano/microparticles [26–28]. PCL has received considerable worldwide attention to use in nano/microparticles, due to its slow ester bond hydrolysis at the neutral physiological pH. Some examples of drug-loaded PEG-PCL based nanoparticles are summarized in mentioned reference [29]. There are both advantages and disadvantages to choose and use some polymers; for example the encapsulation efficiency (EE) for sodium alginate-sodium carboxymethyl cellulose (Na-CMC) was observed higher, in contrast to sodium alginate-carbopol 934P and sodium alginate-hydroxypropyl methylcellulose (HPMC) [30].

PLGA is registered safe by U.S. FDA for clinical use. PLGA is the most successful choice to use in nano/microparticles, attributable to the resultant biodegradable products upon hydrolysis process [31]. Consequently, produced monomers turn to $H_2O$ and $CO_2$ in Kreps cycle. There are three types of PLGA microparticles including neutral, negatively and positively surface charged. Neutral and negatively surface charged microparticles are fabricated by applying capped (steric) and uncapped (carrying free carboxylic groups) end group of PLGA polymer, respectively, while positively surface charged PLGA microparticles are produced by combination of PLGA and PLGA-g-poly(L-lysine) block copolymer as it is drawn in Fig. 1.

Polymer degradation mechanism is a key factor in drug release kinetic. The degradation of polymer chains occurs at the uniform rate all through the PLGA matrix. In contrast, some studies demonstrated the PLGA matrix biodegradation takes place randomly on the swollen polymers [32]. Generally, the duration of PLGA hydrolytic degradation is dependent on lactide to glycolide (L/G) ratio, terminal ester or carboxyl group and MW of the polymer. Since glycolide is less hydrophobic than lactide, a decrease in lactide proportion in PLGA copolymers increases the polymer hydrolytic degradation rate, resulting in a faster drug release. Several L/G molar ratios such as 50/50, 65/35, 75/25 and 85/15 are accessible in the market. Generally, the fastest degradation is for 50/50 L/G PLGA copolymers, approximately 1–2 months, though 65/35, 75/25, and 85/15 L/G copolymers have extended degradation in the biological system [33]. In addition, the end-group of the PLGA influences the hydrophobicity of the polymer. As a general rule, the uncapped end groups of PLGA have higher release rates in comparison with the end-capped species [34]. The uncapped PLGA has kind of hydrophilic structure and can absorb much more water. In addition, as a result of catalyzing the uncapped polymer during biodegradation process, carboxylic end groups increases in number as the separate polymer chains, leading to a fast degradation rate than esterified carboxyl termini [35]. The other results demonstrated that the EE and particle size slightly decreased by polymers with free carboxyl end groups. Moreover, spherical morphology in the end-capped PLGA polymers is remained than the uncapped PLGA microspheres, which lost their spherical shape and merged with each other [36].

PLGA has wide range of MW (ranging from 10,000 to > 100,000 Da), [33] providing suitable potential for formulators to prepare formulations with different characteristics. Low MW of PLGA normally leads to a rapid polymer degradation, faster drug release [37] and as well porous particles, while the high MW formulation results in dense particles with a sigmoidal slow release profile [38,39]. MW and

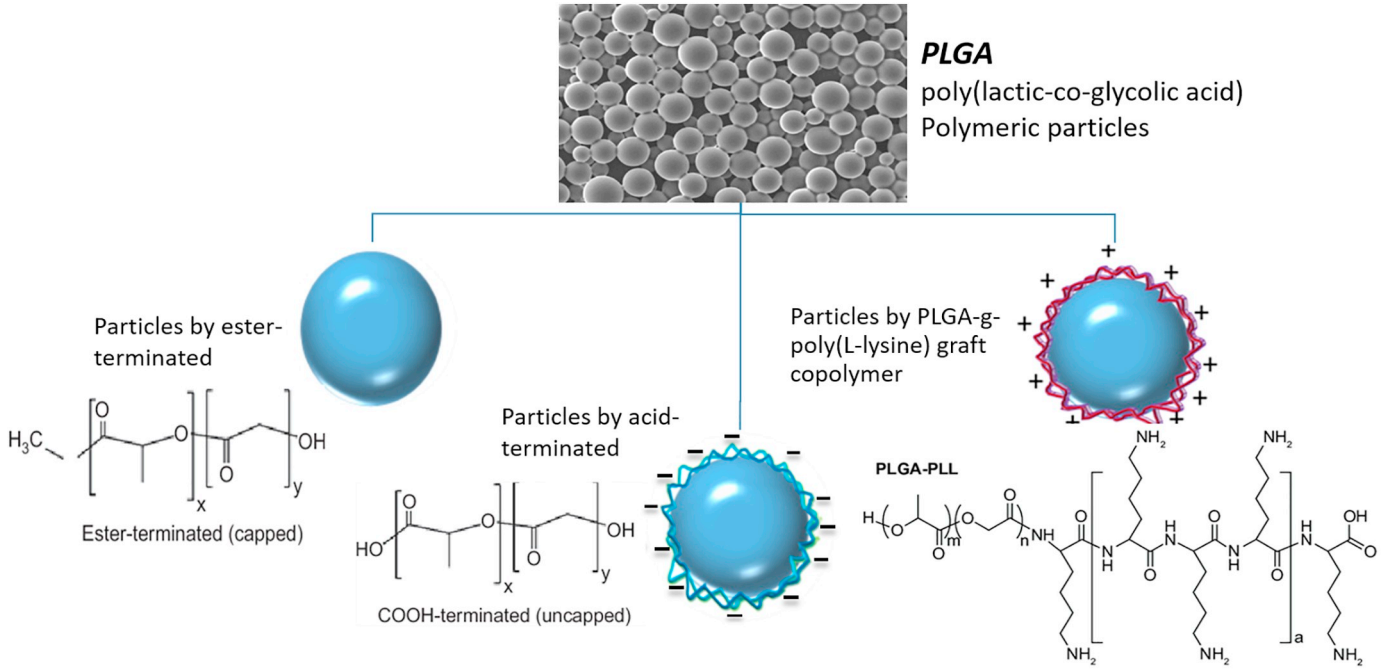


**Fig. 1.** Classification of poly (lactic-*co*-glycolic acid) particles in the point of surface charge.

the concentration of the polymer are obviously correlated to the viscosity of organic phase, in turn correlated to particle size and the drug diffusion rate [12]. High EE, large particle size and slow drug release rate are achieved by high viscosity of organic phase either by using high MW of polymer or high concentrations of it [40].

In addition to end group functionality and MW, other physical characteristics, such as crystallinity and glass transition temperature (Tg), indirectly influence the degradation rate [41]. PLGA is available in two enantiomeric isomers (d-, l- and d, l-isomers), attributable to pendant methyl group on different positions of lactide proportion; in contrast, the lack of methyl group on glycolide proportion makes it crystalline. Therefore, by altering the L/G ratio, the amorphous or crystalline shapes of PLGA is achieved, completely amorphous (PLA) or in relatively crystalline forms. The polymer by < 70% glycolide proportion is completely amorphous [42]. It has been proposed that the degradation of the semi-crystalline polymer increases the degradation rate, due to an increase in hydrophilicity [40]. This logical discussion was not provided for some conflicting observations. Some authors have suggested that microsphere rupture may happen with crystalline form structure during drug release, causing burst release of entrapped hydrophilic drug from microcapsule (not microsphere) structure. Hence, as mentioned above, the characteristics of polymers, such as MW, copolymer composition, end groups functionality, Tg are key factors, affecting the biodegradability of the polymers, should be considered in the formulation development.

### 3.2. Drug properties

Although the release rate parameters do not have strong relationship to the chemical structure of the API, the physicochemical properties of the API, such as ability to react through hydrogen bonds or water solubility, should be considered in explaining the dissolution rate mechanisms using biodegradable polymers [43]. However, the solubility of the drug is important factor in determining the EE in polymeric particulate system. Type I and III small molecules, hydrophilic and amphiphilic, respectively, according to biopharmaceutical classification (BCS), are used as therapeutic agents for various diseases. The fast biodistribution and clearance, requiring frequent administration, can restrict their clinical application [44,45].

By sustaining the release of API by using the encapsulated these drugs in polymeric particles can be change it to more patient-compliances medication regime. Biodegradable polymeric particles, due to numerous applicable features, have good potential to extensive use in the sustained release drug delivery system for a wide range of drugs, especially for short half-life drugs [11].

To achieve high EE in polymeric particles of hydrophilic drugs, using the specific strategies is necessary [46]. In fact, the tendency of these drugs to leak into the external water phase is main problem. One approach to overcome the above-mentioned obstacle is using free base instead of salt form of drug, aiming at achieving high EE [46].

Other approach to increase the EE is adjusting the solubility of hydrophilic peptides in organic phase or mixtures [47]. Ion-pairing hydrophobization by using polyelectrolytes has received lots of attention over the last decades. In an aqueous solution, complexation between proteins carrying partial charge and polyelectrolytes is performed mainly by either electrostatic and/or hydrophobic interactions. In addition, by interaction of polyelectrolytes and proteins, conformational rigidification may be occurred, which can control the protein instabilities during encapsulation process. Conformational rigidification reduces the denaturation amount by preventing the protein adsorption and interactions in the interfacial of organic and aqueous phases and also by preventing the interactions of proteins by the hydrophobic polymer matrix during the emulsion process [48]. Moreover, by addition of several salts such as NaCl, NaSCN, $NaClO_4$, $Ca_3(PO_4)_2$, NaBr and $Na_2SO_4$ to the secondary aqueous phase, the leakage of hydrophilic APIs into the aqueous medium decreases and subsequently causes high EE [49,50].

In addition, the pH of external buffer phase for hydrophilic drugs should be suitable for drugs with high partition coefficient (log D), meaning to have a least aqueous solubility at pH which the drug is in neutral form. Contrary to the external phase, the pH of internal aqueous phase must be adjusted to a point where the drug is charged with a higher aqueous solubility, resulting in the higher EE for hydrophilic drugs. In the case of imatinib (pKa 8.1), adjusting the external phase to the pH upper than pKa, almost completely in neutral form, the loading efficacy is improved about 9 times compared to two points of pH 5.0 and 9.0 [51].

The other approach is preparing the polymeric particles by applying

amphiphilic polymer such as poly (L-lactide) copolymers grafted to water-soluble backbones like poly-a,b-[N-(2-hydroxyethyl)-1-aspartamide] without using any stabilizer or surfactants [52,53].

In some formulations, the low EE is related to the denaturation of the APIs, especially in the case of macromolecules formulations like proteins. A particular approach is the control of interaction of the acidic end group of the polymer with the cationic peptides to prevent the peptide acylation [54]. To block acylation, PEGylation on either α- and/or ε-amino group can cause a considerable polymer-peptide interaction inhibition results. However, PEGylation on the N-terminal and di-PEGylated peptide completely inhibits the acylation reaction. In addition, in the case of octreotide, by applying different divalent cations such as $Mn^{2+}$ and $Ca^{2+}$ into the polymer/octreotide dispersion, the peptide-polymer interaction is strongly inhibited [55].

In general, the neutral and acidic drugs such as methotrexate have low EE and high initial release. The addition of basic amino acids like lysine or arginine to the internal phase is a proper solution for these difficulties. The burst release of methotrexate from PLGA microsphere (PLGA(75/25)-14,000) with 3% lysine is significantly reduced from 85 to 8% [56]. The summary of above-mentioned approaches for improving EE of hydrophilic drugs is depicted in Fig. 2.

In addition, contrary to hydrophilic drugs, the hydrophobic drugs have release difficulties from polymeric particulate system. The solubility of the fenretinide [57] and daidzein [58] is < 0.1 ng/mL and about 16.22 μg/mL, respectively, and the crystalline forms of these drugs possess literally slow release rates from polymeric particles. To improve these release kinetics complications and drug solubility, the simple and well known approach is to increase the wetting of polymeric particles by adding the nonionic surfactants to aqueous media. In these three different following conditions, the incorporation of nonionic surfactants with polymeric particles will improve the release kinetic complications of these drugs: a) the creation of micelles at aqueous resultant pores, b) the decrease of the interfacial tension in the aqueous pores, c) as a plasticizer, the hydrophobic chains of surfactants can be partitioning into the polymeric matrix [57]. In emulsion methods, as an accepted rule, the double emulsion methods are suitable for hydrophilic drugs including macromolecules, while the single emulsion methods are best suited for the hydrophobic drugs [43].

### 3.3. Other excipients

#### 3.3.1. Surfactants

Surfactants are widely used in the formulation development of polymeric particles to improve particle characteristics e.g. size, shape, loading efficacy, surface properties, colloidal stability, and etc. [59–61]. Furthermore, drug release rate (initial burst and then constant release), muco-adhesion [62], bio-distribution, and cellular uptake (bioactivity) [63] of the polymeric particulate system can be affected by the type, concentration and MW of the polymeric surfactants [64].

Polymeric surfactants have an important effect on the other formulation parameters [65] in most approaches [66]. Polyvinyl alcohol (PVA) is well-known among the polymeric surfactants in the formulation of microparticles [67]. Poloxamer (Pluronic®) and carbopol (Carbomer®) could be considered as alternatives for PVA as stabilizer [68]. Low molecular weight surfactants mainly Tween®s, Span®s, sodium lauryl sulfate (SLS), Brij®s and cyclodexterins also are used as modification particles. Interestingly, proteins are utilized as surfactant in the formulation of nano/microspheres. The most widely used protein surfactant is serum albumin (SA), because of its stability, high solubility, and availability. Similar to surfactants, SA is adsorbed at the surface of APIs, especially therapeutic proteins, and prevents their adsorption to the other surfaces. Additionally, SA prevents oxidative degradation reaction of APIs by sacrificing first. The most outstanding advantage of SA is its safety and non-toxicity, which can be used in much more concentrations than other surfactants. However, surfactants are often organic molecules with toxic properties, restricting their application to the predetermined concentrations e.g. as stated in IID FDA webpage or other references. Furthermore, in the case of therapeutic proteins, there is still more limitation in application of organic surfactants, because of the increased solubility of hydrophobic side of

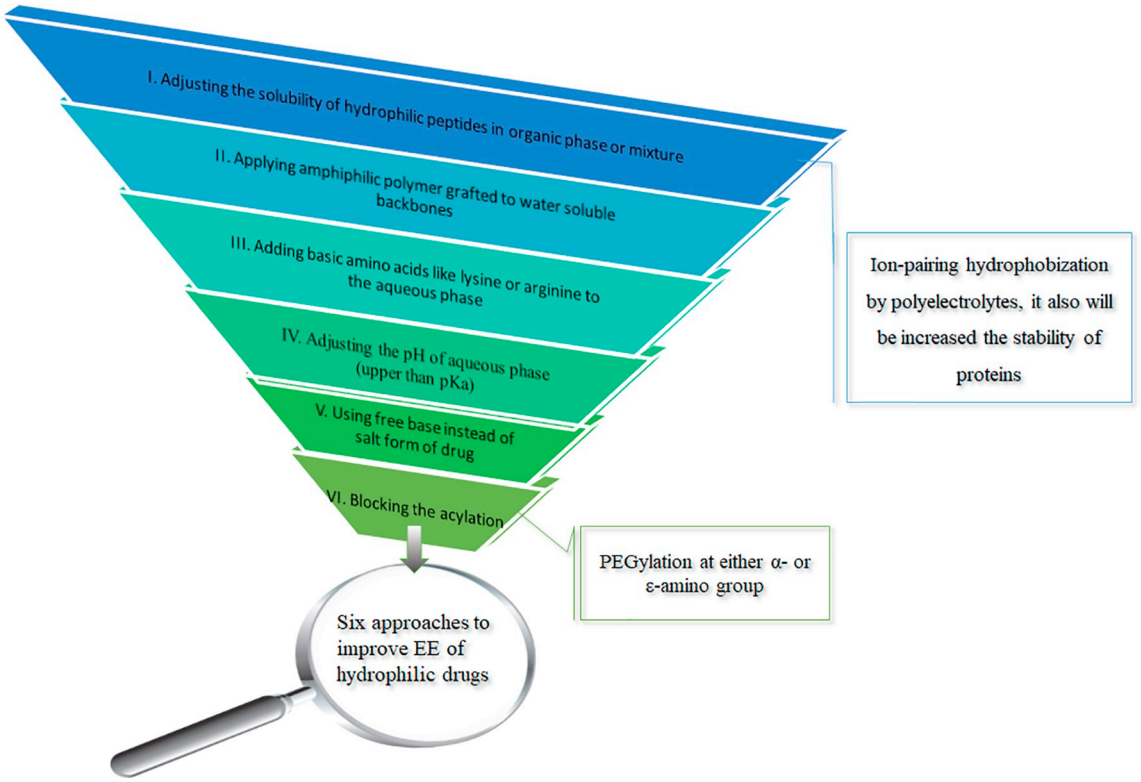


**Fig. 2.** Schematic representation of approaches to improve encapsulation efficiency of hydrophilic drugs into polymeric particles.

proteins and consequently unfolding proteins, which may cause immunogenic reactions. As mentioned above, surfactants in concentrations below the critical micelle concentration (CMC) influence the particle characteristics, mainly by dropping the continuous phase surface tension effects on particle size.

Microparticles containing surfactants have low burst release and ideal constant release rate than those without surfactants, attributable to the enhanced polymer density at the surface of particles and high loading efficacy [57]. Applying Brij 98 in any types of PLGA microspheres results in the improved release profile of fenretinide. The release profile in microspheres with Brij 98 is more consistent than that in porous particles by using PBS in the internal aqueous medium [57]. However, another study demonstrated that the particle size and EE% of all-trans retinoic acids were reduced by high concentration of PVA [69]. These results have been proved by most studies. The influence of three kinds of polymeric surfactant, Tween®40, SLS and various concentrations of PVA on the appearance of hydroxyapatite microparticles has been investigated. It has been shown that the only microspheres formulated by PVA have spherical shape without agglomeration, and by increasing the PVA concentration, the produced particles were become smaller [70].

In addition to enhancing the formulation parameters, polymeric surfactants can improve the API properties in the biological system. By adding poloxamer 407 to the formulation of PLGA microspheres, the bioactivity of urease has enhanced [71,72]. Evaluating the effect of poloxamer 188 on the SA encapsulation demonstrated that the Poloxamer 188 was able to improve SA aggregation 6.2 times, from 31% to 5%; however, it reduced the EE around 20% [73].

In the final dosage form, the addition of SA or other surfactants to the diluent, as reconstitution medium, can considerably prevent the loss by adsorption or any kind of API denaturation. Nevertheless, SA is associated with self-aggregation problems [48]. As a summery, the main effects of surfactants in nano/microparticles preparation are on stability of particles, acceptable appearance, the improvement of drug loading and the modification of the release profile.

### 3.3.2. Salt

Our review literature clarifies the main influences of salts on EE, release kinetic, and the stability of the encapsulated APIs and surface properties of polymeric particulate system. As an example, in the study of blue dextran particles (as a hydrophilic drug model), researchers reported that in double emulsion method, as a result of adding various concentrations of sodium chloride to the external aqueous phase, EE was enhanced from 10 to approximately 90%. Besides, the initial burst release significantly decreased, and was more controlled than that from particles without electrolyte, probably attributed to the location of the drug at the particles core instead of near the surface [74].

Addition of $Ca^{2+}$ in alendronate microparticles preparation (1:2 alendronate/calcium ratio) led to high EE (approximately 18 times than that without using $Ca^{2+}$) [75]. This modification in the EE might be justified considering the followings: API solubility is reduced in the O/W interphase to have a more efficient partitioning into the organic phase [11]. (b) Osmotic pressure between the aqueous phases is increased by salt addition, causing better distribution of API at the microspheres core [74]. In addition to EE enhancement, the drug release kinetics has also improved (reduced initial burst release with constant release rate). Water influx from the aqueous phase to the particles leads to porous and larger microparticles. However, by balancing the osmotic pressure, particles become denser and smaller. Besides, the initial burst release has meaningfully reduced by vanishing of the large pores at the surface of the particles [76]. (c) Addition of salts to the emulsification medium and then adsorption of salt to the organic phase surface causes increased polymer ionization and consequently increased chance of drug ionic coordination with oppositely charged polymer [77]. By the adsorption of methylene blue (positively charged hydrophilic drug model) into carboxyl-functionalized polymer (negatively charged polymer), microparticles reached to approximately 60 mg/g [78]. The same results was observed by adding different salts by different concentrations of NaBr, KSCN/NaSCN, $Na_2SO_4$ and $NaClO_4$ to the aqueous medium for the preparation of quinidine sulfate -loaded D, L-PLA microspheres. The EE increased from about 60% to approximately 75%, 95% and > 90%, respectively, but extraordinarily $Na_2SO_4$ caused a decrease in EE% to about 50% [79].

Studies demonstrated that adding of $Mg(OH)_2$ and sucrose, as buffering salts, could stabilize bovine SA encapsulated in injectable PLGA implants [80,81]. They reported that the aggregation level decreased to < 7% and 51% over the application of 3% $Mg(OH)_2$ and 10% sucrose, respectively, compared to 81% aggregation level without mentioned excipients after 1 month incubation at 37 °C. Consequently, the carriers associated with $Mg(OH)_2$ had least BSA aggregation and almost complete release of BSA,approximately 80%, compared to 20% release from microsphere without the antacid [82].

The enhancement of antigen stability through pH control was also reported as a result of encapsulation of salts by different bases such as $ZnCO_3$, $Mg(OH)_2$ $MgCO_3$, $Ca(OH)_2$ [73,81]. Additionally, the incorporation of $NaHCO_3$ enhanced the lysozyme bioactivity (as a model protein) and reduced the protein burst release; however, it also strangely reduced the EE from 90 to 70% [83]. As a result, the polymer (PLGA) hydrolysis and consequently particle instability decreased obviously because decreased accumulation of resultant monomers and oligomers of lactic and glycolic acid in the PLGA matrix medium. These are some explanations: first, by reacting salts with the products of acidic hydrolysis, the products change to form salts. In fact, by additional reactions, the acidity of the environment decreases, which in turn reduces acid-catalyzed. Second, as a result of ionic reaction between the polymer (PLGA) and oppositely charged ion, the solubility of the PLGA oligomers is reduced, causing the decrease of the hydrolysis. Third, while the use of salts seems to enhance water adsorption, resulting in the increase in the rate of hydrolysis, studies show that salts have only minor effects on polymer degradation, due to the accumulation of absorbed water in just polymer aqueous pores [13,84].

Furthermore salt properties such as relative solubility, concentration and dissociation constant in either polymeric or aqueous phases strongly control the environment pH [85]. The effects of salts on developing the polymeric systems is summarized in Fig. 3.

### 3.3.3. Solvent and cosolvent

The proper selection of solvents plays a vital role to achieve a desirable particle size in all nano/microparticles' fabrication techniques [15]. Generally, the properties of a suitable solvent for this purpose are high polymer solubility, poor miscibility in the aqueous medium, the least toxicity (according to the solvent classification mentioned in ICH Q3C guideline), low boiling point and high volatility. The most commonly used solvents in microparticles preparation with emulsification technique are dichloromethane (methylene chloride (DCM)), ethyl acetate, and ethyl formate, owing to properties mentioned above. DCM has higher solvent evaporation rate compared to other solvents, because of comparatively high saturated vapor pressure. On the other hand, according to the ICH and EPA (Environmental Protection Agency), DCM is classified in the class II with inherent toxicity; therefore, it is essential to evaluate the residual solvent to assure that it is within the accepted limit [52]. In addition, Bodmeier and McGinity (1988) demonstrated that DCM caused higher EE than chloroform or benzene for the PLA microparticles [86].

Furthermore, application of water miscible cosolvent e.g. acetone, methanol and dimethyl sulphoxide (DMSO) in the dispersed phase (mostly polymeric) improves the drug release parameters and EE [52]. As methanol is non-solvent for the PLGA polymer, while being miscible with water, it is expected to participate as dual role in smoothing the polymer precipitation for following reasons: First, it is able to diminish the polymer solubility in the dispersed phase. Second, by miscibility with water, it can facilitate the water diffusion within the dispersed

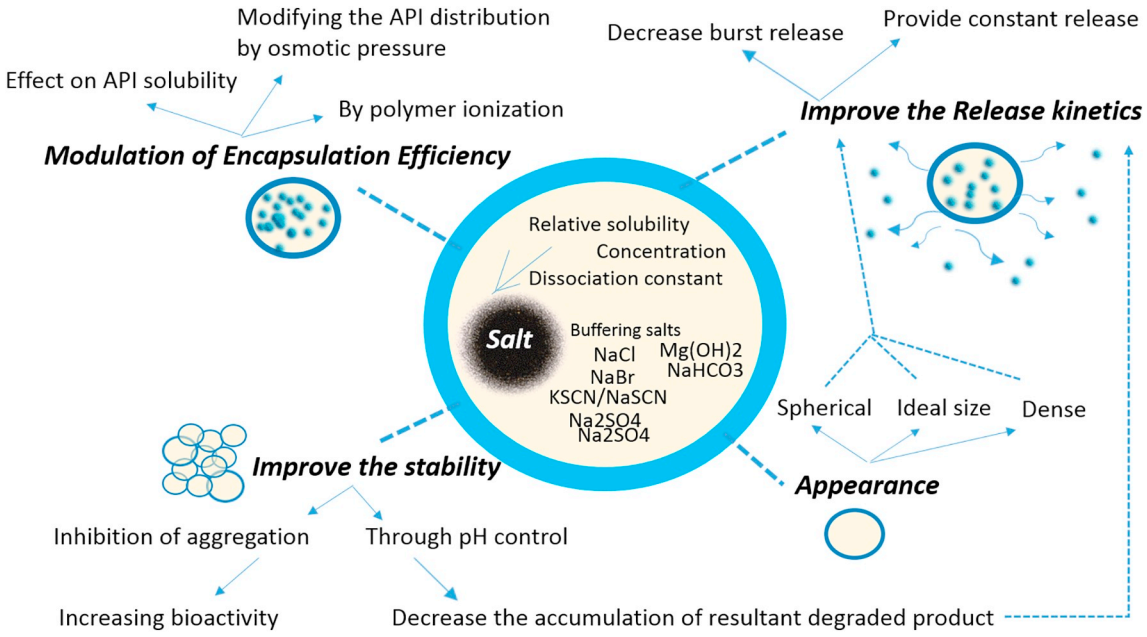


**Fig. 3.** Schematic representation of salt effects on the polymeric systems.

phase [86]. In the case of proteins, for increasing the solubility of protein, the low concentration of cosolvent can be used. However, even the low concentration may denature the protein structure, as given the increased solubility of lipophilic sides of protein, the previous hydrogen-bonds are broken and new hydrogen-bonds are formed, and consequently the effective structure is destroyed.

### 3.3.4. Sugars as osmotic agents and stabilizer

In micro/nanotechnology, carbohydrates (e.g. mannitol and sorbitol) and amino acids inhibit unfolding of proteins, due to which they are frequently used as protein stabilizers during storage in solution or as lyophilized powders [87]. The secondary structure of proteins is stabilized by intra chain hydrogen bonds. By water removal during drying, these hydrogen bonds are destroyed and new hydrogen bonds are formed between inter/intra chain. It is likely that the bonds formed become very strong and cause a permanent change in protein configuration that will cause the original protein structure to be destroyed after rehydration. Osmolytes is substituted for water during drying meaning that during drying, the hydrogen bonds between the peptide and water are substituted by bonds between the peptide and osmolyte. After adding water, the osmolyte is dissolved fast and protein returns to the first state. Protein destabilizing effect of osmolytes may occur by binding or surface adsorption, mainly by hydrophobic and electrostatic interactions, and hydrogen bonding, which are different for various proteins. Consequently, it is critical to inspect the additives separately for each individual protein to evaluate stabilizing effect.

In addition, most medicines with a solid dosage form are reconstituted before use. Prevention of crystal growth or aggregation is essential to maintain particle size. In these cases, sugars are also used as a stabilizer in diluent composition. There are some examples, stated in Table 2, which are stabilized by mannitol via the mentioned mechanism.

To dry the particles, spray drying and freeze drying are the most popular approaches. The common cryoprotectants used in freeze-drying process are mannitol, trehalose, sucrose and glucose [98]. In recombinant human growth hormone (rhGH) PLGA microsphere, trehalose is added as stabilizer, limiting the movement of biomolecules during emulsification with DCM [99]. In another study, the impact of dextran 70 on the thermodynamic stability of RNase A was evaluated. The results proved that by changing $T_m$(midpoint of denaturation) and $G_D^{\circ}$(Gibbs energy change at 25 °C) items in Gibbs–Helmholtz equation, it stabilized the RNase A in dilute solutions [100]. Other study evaluated the stability of the monoclonal antibody (MAB) by using mannitol. The spray-dried finish product of recombinant humanized anti-IgE MAB (rhuMAbE25), containing 10 and 20% *w*/w mannitol, was stable during storage, but formulation with 30% mannitol showed a high reduction over storage at temperatures 5 °C and 30 °C, probably due to mannitol crystallization [101] although some ingredients can delay mannitol crystallization, like $NaPO_4$, associated with mannitol in spray dried formulation. In addition, mannitol has been investigated as a hydrophilic excipient in myoglobin solidification process. They reported that by increasing the porosity in the polymer matrix, the release rate increased and finally the complete release was achieved [102]. As a result, it should be considered that the concentration of sugars for proteins stability should be investigated and optimized for each protein individually. The addition of matrix formers, e.g. mannitol, cellulose and sucrose into the nanodispersion previous to drying process is the other best technique to avoid the instability problems through the solidification procedure [103].

### 3.3.5. Pore-forming agent

The pore closing/opening seems to be one of the most important phenomena, capable of modifying the drug release kinetics from polymeric particles. Pore-forming agents also have a direct effect on the morphology of the particles. Porous particles have received a lot of attentions in the last ten years, thanks to their sufficient applications in numerous areas such as carriers for drug delivery [104], pulmonary drug delivery [105], absorption and desorption of materials [106] and tissue regeneration scaffolds [107].

Among the determining factors in LC and release kinetics are the porosity and properties of porous particles i.e. diameter, amount, and the structure of the pores. The nature of pore-forming agents can be solid or liquid and inorganic or organic. Beside different types of polymers, materials such as $CaCO_3$, $NaHCO_3$, $K_2CO_3$, mesoporous silica, hydroxyapatite, and carbohydrates such as mannitol, sucrose, fructose, glucose, mannose, sorbitol, lactose and biodegradable porous starch foam, showing advantages like biocompatibility, hydrophilicity and porosity, can be used as pore-forming agents. These materials are dispersed in the organic solvents, containing dissolved polymers, and embedded into polymeric microspheres upon the solvent evaporation.

**Table 2**
Formulation parameters of pharmaceuticals made of polymeric microspheres.

| Brand name | Production methods | Size of particles (μm) | Matrix polymer | Formulation (polymer/excipients) | Weight of administered polymer (mg/dose) | Ref. |
|---|---|---|---|---|---|---|
| Zoladex® | [a]EM | 10 to ~ 20 | [c]L/G ratio of [d]PLGA are 1:1 or 1:3 | Different molecular weight of [d]PLGA copolymers/mannitol/ < 2.5% acetic acid and 10–12% goserelin | 12–15 | [e]FDA-DM [88] |
| Octreotide (Sandostatin LAR depot®) | [a]EM | 1 to 10 | 75/25 | 20% [d]PLGA (Atrigel®): both [d]PLGA and [f]PLGH/15% to 20% drug loading/pva18–88/mannitol. Diluent including [g]Na-CMC (14 mg), mannitol (12 mg), poloxamer 188 (4 mg), [h]WFI 2 mL. | For 10, 20 & 30 mg: 188.8, 377.6, 566.4 respectively | [e]FDA-DM [89] |
| Doxycycline (Atridox®) | [b]PS (Solvent exchange) | No data | [f]PLGH | 500 mg of formulation composed of 450 mg of the Atrigel®, which is a polymeric formulation composed of 36.7% [f]PLGH dissolved in 63.3% [i]NMP and 10% of doxycycline | 183.5 of [f]PLGH | [e]FDA-DM [90] |
| Minocycline HCl (Arestin®) | [b]PS | 30 to ~120 | [d]PL GA ~50/50 | [j]API (containing 1 mg minocycline free base) and [d]PLGA | 95–60%/dose | [91] |
| Risperidone (Risperdal Consta®) | [a]EM | 25 to150 (80–90) | [d]PLGA 75:25 | Diluent including [g]Na-CMC, citric acid, dibasic sodium phosphate dehydrate, polysorbate 20, [i]NaCl, NaOH, [h]WFI. | Drug loading about 38% *w*/w | [92] |
| Risperidone (Perseris®) | [a]EM | 75–125 or < 38 | 80/20 | [f]PLGH dissolved in [i]NMP | For 90 & 120 mg: 228, 304 respectively | [k]PQR 210655Orig1s000 |
| Naltrexone (Vivitrol®) | [a]EM | No data | 75\25 | [j]API and [d]PLGA. The diluent containing of [g]Na-CMC, polysorbate 20, [i]NaCl, and, [h]WFI | 6.63% *w*/w polymer/dose | [e]FDA-DM [93] |
| Leuprolide Lupron Depot® and Lupron Depot- PED® and lupaneta pack® | [a]EM | No data | 75/25 | [j]API, [d]PLGA, purified gelatin and D-mannitol. For pediatric Leuprolide acetate (7.5/11.25/15 mg), gelatin (1.3/1.95/2.6 mg), PLGA and D-mannitol (13.2/19.8/26.4 mg). Diluent including D-mannitol (50 mg), [g]Na-CMC (5 mg), polysorbate 80 (1 mg), [h]WFI, and acetic acid (for pH adjustment). | For 3.75, 7.5, 11.25, 15, 22.5, 30 & 40 mg: 33.1, 62.5, 99.3, 132.4, 198.6, 264.8, 169.9 respectively | DM and [56] |
| Leuprolide acetate Eligard® | [b]PS (Solvent exchange) | No data | [f]PLGH For 7.5, 22.5, 30 and 40 mg: 50/50, 75/25, 75/25, 85/15 respectively | [d]PLGA dissolved in [i]NMP 45:55 (polymer: [i]NMP ratio) | For 7.5, 22.5, 30 and 40 mg: 82.5, 158.6, 211.5, 165 respectively | [e]FDA-DM [90] |
| Ozurdex® (Dexamethasone) | Double extrusion process | < 20 | [d]PLGA 502H and 502 in 3:1 w/w ratio | 0.7 mg [j]API, [d]PLGA (Novadur®) without a preservative | No data, but the diameter and length of rod shape implant are about 0.46 and 6 mm. | [94] |
| Triptorelin (Trelstar®) | [b]PS | No data | For 3.75, 11.25 & 22.5 mg: [d]PLGA 57/43, [f]PLGH 78/22, [f]PLGH 80/20 respectively | Triptorelin pamoate (base units), [d]PLGA, mannitol, [g]Na-CMC, polysorbate 80. The diluent contains [h]WFI. | For 3.75, 11.25 & 22.5 mg: 138, 120, 183 respectively | Allergen DM, [95] |
| Triptorelin Triptodur®) | No data | No data | No data | [j]API, PLGA, mannitol (74 mg), [g]Na-CMC (26 mg), polysorbate 80 (1.7 mg) and 2 mL [h]WFI. | 183 | Arbor DM |
| Triptorelin Pamorelin® | [a]EM | < 180 ~ 55 | at least 75% of lactic acid | [j]API, [d]PLGA, mannitol, [g]Na-CMC, polysorbate 80. The diluent contains [h]WFI. | No data | [96, 97] |
| Exenatide (Bydureon®) | [a]EM | No data | 50/50 | Formulation containing [j]API, [d]PLGA and sucrose (0.8 mg/dose). The diluent composed of [g]Na-CMC (19 mg), polysorbate 20 (0.63 mg), monobasic sodium phosphate (0.61 mg), dibasic sodium phosphate (0.51 mg), [i]NaCl (4.1 mg), [h]WFI and NaOH (for pH adjustment). | 37.2 | [e]FDA-DM |

(*continued on next page*)

**Table 2** (*continued*)

| Brand name | Production methods | Size of particles (μm) | Matrix polymer | Formulation (polymer/excipients) | Weight of administered polymer (mg/dose) | Ref. |
|---|---|---|---|---|---|---|
| Triamcinolone (Zilretta®) | No data | No data | 75/25 | [j]API and [f]PLGH. Diluent containing of NaCl 0.9%, [g]Na-CMC 0.5% and polysorbate 80 0.1% (5 mL sterile suspension). | 120 | [c]FDA-DM |
| Pasireotide (Signifor LAR®) | [a]EM | No data | A mixture of two [d]PLGA [50–60:40–50], [50:50] | [j]API, [d]PLGA. Diluent containing of mannitol (90 mg) [g]Na-CMC (14 mg), Poloxamer 188 (4 mg), [h]WFI add to 2 mL | For 20, 40 and 60 mg: PLGA [50–60:40–50]: 26.29, 52.58, 78.87 and for [50:50]: 26.29, 52.58, 78.87 | DM |
| Buprenorphine (RBP-6000®) | No data | No data | [f]PLGH | [j]API and [f]PLGH dissolved in [i]NMP. | For 100 & 300 mg: | [c]FDA-DM |

[a] Emulsion method.
[b] Phase separation.
[c] Lactide/glycolide.
[d] Poly(lactic-co-glycolic acid).
[e] U.S. FDA drug monograph.
[f] PLGA Polymer with acid end group.
[g] Sodium-carboxymethyl cellulose.
[h] Water for injection.
[i] N-methyl-2-pyrrolidone.
[j] Active pharmaceutical ingredient.
[k] Product quality review.
[l] Sodium chloride.

Other examples of pore-forming excipients are sodium chloride, gelatin, polyethylene glycol, ammonium bicarbonate, and pluronic F127 [52].

The solvent evaporation method is the best suited method to fabricate porous nano/microspheres. Due to the efflux of organic phase between the aqueous phases during multi-emulsion solvent evaporation, pores easily are formed by diffusion mechanism. If drug is added into the polymeric solution, drug will be entrapped or embedded by the polymer. Using the organic solvents and totally removing them is the main problem of these methods to use in the clinical applications as commercial product. Furthermore, to achieve an optimum porosity, beside the volatile solvent, pore-forming agents should be employed to adjust the diameter and amount of the pores. Additionally, stirring rate and time can modify the pore size and porous layer properties [108]. It has been demonstrated that in solid in oil in water (S/O/W) emulsion method, the high solid dispersion in S/O phase (polymer solution) is the key factor to achieve stable ideal S/O/W emulsion.

Other pore-forming mechanism is the reaction between the pore-forming agent and acidic solution to release $CO_2$. When the amount of $NaHCO_3$, as pore-forming agent decreases, the concentration of produced $CO_2$ is reduced and the formed particles are less porous. In comparison with $NaHCO_3$ and $K_2CO_3$, as pore-forming agents, the weight of the particles prepared using $NaHCO_3$ was about 70% smaller than those prepared by $K_2CO_3$, while the density of these particles was comparatively low. These results are attributable to the amount of produced $CO_2$ [109]. Generally, the ratio of pore-forming agent to the polymer is 1:1, 1:2, 1:3, and 1:4 to achieve an optimum pore size and amount.

## 4. Preparation methods

The selection of preparation method in aqueous/oily core- systems mainly depends on the solubility and stability of the therapeutics agents. Several techniques are used for preparing these drug delivery systems, including chemical processes e.g., polymerization methods [110,111], physicochemical processes e.g., solvent evaporation methods [112], phase separation method [113] and self-healing encapsulation technique [114] and mechanical processes e.g., membrane emulsification (ME) [115], spray drying [116], supercritical fluid [117] and microfluidic methods [118]. All the preparation steps should be performed under the controlled conditions i.e. constant mixing rate, constant solidification time, and in the case of industrial purposes, they should be done according to the good manufacturing practices (GMP)s rules.

### *4.1. Polymerization method*

The methods for the synthesis of polymeric particles are roughly divided into two different types: producing from linear pre-existing polymer chains or starting polymerization from a monomer solution and radical polymerization. The suspension and emulsion are the most common approaches [119]. The drug loading of particles can be achieved via two basic approaches; the drug can be added during the synthesis of particles or can be saturated after production [120].

In the suspension approach, also known as phase-separation polymerization, in order to initiate the polymerization, the monomers or a mixture of monomers and API in the continuous aqueous phase are heated and nano/microspheres are obtained [121]. Generally, the size range of produced particles is from 50 to 500 μm [119]. During polymerization, the phase separation from the continuous phase happens through enthalpic or entropic sedimentation by providing some conditions like adding poor solvent (less than a θ solvent) or salt or decreasing the temperature [122]. To obtain nano-scaled particles, emulsion polymerization or polymerization-induced self-assembly process are applied [123,124]. In fact, both particle size and size distribution are dependent on the reaction conditions; by increasing monomer and initiator concentration the particle sizes increased

[125,126].

### 4.2. Solvent evaporation method

The solvent evaporation is the most commonly used approach in the preparation of polymeric particles and polymeric coating of particulate systems [127,128]. Simplicity, reproducibility, fast processing and least critical process parameters (CPP) are its important advantages at the industrial scale. In most emulsion processes, choice of solvents, stirring rate, CP/DP ratio and solidification time mainly affect the EE and final particle size.

In O/W single emulsion method, by adding the drug into the polymeric medium, the drug-polymer solution is prepared. Then, it is emulsified in large [197] amount of water in the presence of emulsifier. While, in W/O/W double emulsion method, first drug solution is added into polymeric organic phase to prepare a primary emulsion and then, the prepared primary emulsion is added to aqueous solution in the presence of PVA, to prepare a secondary emulsion. Similar to all of the emulsion methods, the evaporation or extraction of organic solvent is done to harden the droplets under valid conditions. In the case of the S/O/W method, the powder of API is dispersed in the polymeric organic solution. In this approach, the mechanical milling is essential to guarantee that the crystalline drug is uniform and less than specific size [57,11].

Generally, the costly large-scale production, narrow and uniform size distributions of the particles and the use of large amounts of organic solvent are critical problems in this process. In fact, applying organic solvent in the process may cause the risk of denaturation of drugs or proteins, which can cause some unpredictable adverse effects such as immunogenicity and/or other toxicity.

### 4.3. Membrane emulsification procedures

ME process is a recent advancement in the nano/microparticles manufacturing technology to prepare monodisperse polymeric drug delivery system [66]. In this method, monodisperse emulsion is obtained by pumping the disperse phase or pre-emulsion through a membrane with specific cut off into immiscible continuous phase, flowing in a narrow path [129]. As an example, the monodisperse lysozyme-PLA microcapsules is prepared by the shirasu porous glass (SPG) ME technique through solvent evaporation method [130], harvesting uniform particles with 92.20% EE. In another study, rapamycin-PEG-PLGA microsphere was prepared using Iris-20 Microsieves technology [115] the uniform particles with higher EE were obtained (7 times more than the traditional emulsification methods). The membranes can be compatible with different kind of emulsions by adjusting the hydrophilic-lipophilic balance (HLB) of the membrane surface by altering surface chemistry [131].

### 4.4. Phase separation technique

Phase separation or coacervation techniques are among the oldest and applicable microencapsulation techniques [132]. The basic mechanism of these processes is decreasing the solubility of the wall material, e.g., polymer in organic phase, and generating the wall material rich phase to wrap the API, as core-shell structure [133]. In the case of hydrophobic drugs, they can be added in solubilized form or in dispersion in the polymeric solution (O/W emulsion). The different alternative approaches applied for phase separation are coacervation by lowering the temperature less than critical temperature (TC), adding non-solvent, adding electrolytes (salting out method), adding incompatible polymer (Dobry theory) and complex coacervation [134] upon which two oppositely charged polymer solutions are mixed [135].

In addition, thermally induced phase separation (TIPS) has achieved significant attention as a scientific and practical approach. In fact, the recent application of the TIPS technique, beside drug delivery carrier, is the fabrication of microporous and microcellular membranes and scaffolds for tissue engineering [52]. The CPPs of this technique includes polymer concentration, the aqueous phase/organic phase volume ratio, reducing temperature, stirring rate and solvent composition. When the concentration of polymers is higher, salting out approach is desirable; nevertheless, due to the difficulty of purification process, the application of this method is limited [15]. The size of droplets and agglomeration can be controlled by using a suitable speed stirrer and controlling the temperature of the system.

### 4.5. Spray drying

Spray drying is a relatively simple approach to encapsulate all kinds of drugs, peptides and proteins with the minimum API loss. In addition, fast and feasible manufacturing procedure with few CPPs make it suitable for industrial scale processing [136].

This mechanism of this method is based on the atomizing and drying the dispersion of the particle solution (S/O dispersion or W/O emulsion) in an air flow. Depending on whether it is dried by elimination of the solvent or by the cooling methods, the process is called spray drying and spray congealing, respectively. The CPPs of this technique include the choice of solvent and machinery conditions e.g., feeding amount and orientation of jets, affecting the morphology of the particles i.e. uniform, double-walled and controllable shell thickness. Operation under aseptic conditions is the main advantage of this process. However, adhering particles to the inner wall of the spray-dryer is the major drawback. Nevertheless, development of the novel spray nozzle can solve this problem [137].

### 4.6. Supercritical fluid method

The supercritical fluid (SCF) method has also been applied to prepare nano/microparticles in recent years [138]. Here, the formation of polymeric particles is based on the rapid expansion SCF solvent. Generally, it is a single-step process, whose significant benefit is that there is no need for the drug or polymer to be dissolved in the organic solvents. In fact, supercritical carbon dioxide ($SCO_2$) is the main used solvent, which is recyclable, risk-free, non-inflammable, and cost-effective. However, if the drug is insoluble in $CO_2$, it is accomplished by the anti-solvent techniques. In general, in these approaches, a condensed gas is applied to precipitate a solute from the organic solution [139]. Nevertheless, it may be complicated by the problem of residual solvent, for which washing the produced particles by SCF is the main solution.

In this technique, by changing CPPs i.e. temperature and pressure (above critical point), polymer amount and adding cosolvent (in the case of drug solubility problems), the particles with certain size, shape or porosity will be prepared. Monodisperse particles can be obtained under conditions i.e. low polymer (< 1%) amount in formulation, setting high pressure and high $CO_2$ flow rate [200].

### 4.7. Microfluidic approach

Despite all advancement in the production of polymeric drug delivery systems, still producing uniformly sized particles is an important challenge. In the microfluidics (MF) or micro-reactor technology, the fluid flow is under control on a microscopic scale, aiming at producing the monodisperse nano/microparticles by emulsification process [140]. Here, dispersed phases or pre-emulsion is pumped into the continuous phase through a micro scale path on a micronized chip. Batch-to-batch reproducibility, fabrication of uniform particles with high EE%, and porous structures are main advantages of this process, entitling it as ideal carriers aimed at 3D cell cultures, tissue engineering, drug delivery and even cosmetics proposes. In the preparation of PLGA-Rapamycin, the two-phase microfluidic device was designed. The particles size was averagely 65 μm with 98% EE [141]. In a recent study, the

PLGA nanoparticles of ribavirin were prepared by microfluidic-assisted nanoprecipitation technique. The particles' diameter was 50–200 nm with 74% EE [142]. In the study of development of CNS-targeted polymeric nanoparticles by MF technology, the size of particles was 73 nm, and EE was reported to be 81% [143]. On the other hand, the dramatically prolonged fabrication time is the main disadvantage of this process. Further, the production of porous particles is sometimes considered as a disadvantage. However, the porosity degree is controllable by gradual variation of flow rates [144].

### 4.8. Self-healing encapsulation

Self-healing encapsulation technique is a new spontaneous method, leading to load the aqueous large molecules deep into the produced PLGA nano/microspheres, to shut down the initial burst release [145]. Studies on the effect of temperature on the protein release have shown the pore closing could occur later during incubation at 37 °C or at elevated temperatures. In contrast, these previous pores can be opened to release the drug into blood by physiological phenomena like osmotic mediated events [146].

There is a model for self-healing microencapsulation systems through self-assembly of the polymer chains to rebuild defects in three steps [147]. First, drug-free particles, containing a penetrating pore network, are created. Using high amounts of osmotic agents such as trehalose or sucrose, pore network can be created. Second, the produced porous particles are located in the aqueous drug solution under slight agitation at the temperatures below the Tg of the polymer. This condition leads to influx of the drug to the polymeric matrix. Finally, the self-healing process is started by increasing the temperature above the Tg of polymer, resulting in closing the pores at the polymer surface and arranging them inside the polymeric matrix.

In this approach, drug loading can be done either passively or actively. Passively means without any further inducement to enter the drug into the polymeric pores, and actively means employing a number of agents at the first step (drug-free polymeric matrix) to enter the drug into the polymeric pores. The $Al(OH)_3$ adjuvant can be reversibly attached and even stabilized the macromolecules [148]. $Al(OH)_3$ and $CaHPO_4$ adjuvant gels are typically incorporated with polymeric particles (as a protein-trapping agent) to improve the EE of large molecules. The schematic drawing of the self-healing process is depicted in Fig. 4. Low uptake rate of the dextran tetramethyl rhodamine (as a fluorescent pore marker) during the initial release confirms the blocking of diffusion pathway by closing pores, resulting in the minimum burst release [13,149,150]. By this method, the problems of protein instability during manufacturing process have been minimized [200,200].

## 5. Methods parameters

The factors concerning the preparation of aqueous/oily core- systems are mainly CP/DP ratio, the adjustment of pH environments, the drug loading capacity, solidification time, designing the dosage form and particle size and as well as selection of route of administration according to medication schedule.

### 5.1. CP/DP ratio in emulsification methods

Most of these production techniques are based on emulsion-based methods. As a rule, when the volume of one phase is smaller than that of the other phase, the phase is considered as the dispersed phase. CP/DP ratio is an important factor in formulating the polymeric particle by emulsion method. The manipulations of the CP/DP ratio have shown conflicting results [151]. Generally, the CP/DP ratio is about 2 to 20, but between 3 and 10 is more suitable. In the most studies, with increasing CP/DP ratio, the internal porosity of the particles decreased, while the surface of microspheres is smoothed, probably due to the faster solidification rate. Nevertheless, by increasing CP/DP ratio, the drug LC and EE increased remarkably. Similar result was reported for the progesterone-loaded PLGA microsphere preparation [152].

In addition, drug release depends on CP/DP ratio i.e. by increasing CP/DP ratio, both the burst release and constant rate decrease. In the low CP/DP ratio, organic solvent will diffuse slowly to aqueous phase and mainly the evaporation rate is determinant. In the case of hydrophobic drugs, with high solubility in the organic solvent, the API by the solvent will move to the surface and subsequently the burst release is observed. In high CP/DP ratio, organic solvent diffuse to the aqueous medium immediately and simultaneously API is fixed in the matrix/core of the polymer. In fact, it depends on the evaporation and polymer precipitation rate [153]. Therefore, evaporation rate affects the porosity, which in turn affects the drug release parameters, especially initial burst effect [154]. As an example, the CP/DP ratio in risperidone Consta® is 5:1 (*v*/v) [155].

### 5.2. The role of pH environment

One of the CPPs in most of preparation methods is the pH of aqueous phase, particularly when solubility of API is pH dependent. When API is hydrophilic, drug tends to partition to continuous phase, causing low drug encapsulation [40,156]. It is obvious that polymer degradation/hydrolysis is in the maximum amount in alkaline or strong acidic media; however, polymer degradation/hydrolysis occurs in the slightly acidic and even in neutral media, because of auto catalysation by the carboxylic end groups [43]. There is no significant difference in auto catalysation rate between the slightly acidic and neutral media. ABT627 (an endothelin receptor-selective antagonist used against

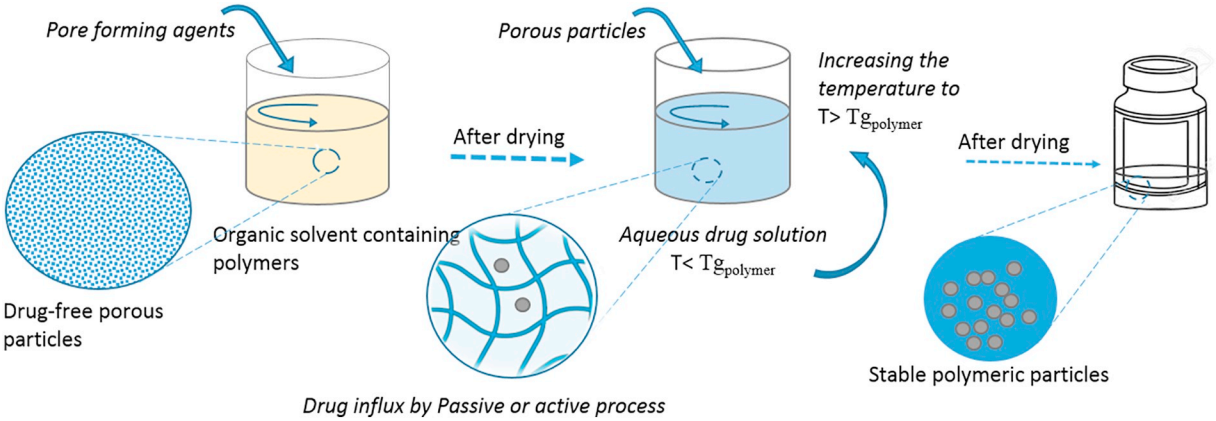


**Fig. 4.** Schematic drawing of the self-healing encapsulation process.

prostate cancer) is a pH-dependent molecule. Although in the pH = 1.5, by increasing drug solubility, the LC increases, the low pH of the internal phase leads to polymer autocatalysis and accelerated degradation. The image of polymeric particle in 17th day of release, as an evidence for auto catalysation, shows that the degradation process has started inside the particles [40].

This approach has been used in various studies to enhance drug release rate [197]. As an example, the duration of dexamethasone release from PLGA microparticles considerably decreased when the pH value was diminished from 7.4 to 2.4 [157]. Acidic microclimate resulted from the accumulation of acidic oligomers and monomers produced during hydrolysis, caused drug instability, particularly peptide and protein drugs [84,158]. To improve the stability of peptide and protein drugs and to inhibit the release of sequestered acidic moieties, some researchers have used magnesium hydroxide, as antacid to increase the microclimate pH. This strategy was applied to the particles [38]. In some polymers, e.g. PCL, degradation process is not affected by acidic microclimate. PCL matrix is eroded from the surface layers and the inner of matrix can be maintained in neutral pH. In fact, the acidic hydrolytic products releases only from the surface of polymer to the external medium and particles' inner environment is not affected [159].

### 5.3. Drug loading

The amount of drug loading as well as the number of final polymeric particles in the reconstituted medium, and the final volume for the parenteral administration determine the dose of the drug delivered. On the other hand, the drug solubility and the degree of polymer biodegradability determine the drug LC. Generally, the upper limit of drug loading for the hydrophilic drugs, such as peptides, is about 20% in sustained release polymeric products [46]. Furthermore, it is important to first make sure the drug is in the correct form and then make sure the drug is accessible all over the duration of action in the in vivo study.

The quantity of drug loading in the drug delivery carriers is known as one of the key modulators for the drug release kinetic parameters. Although there are different opinions on the relationship between the amount of drug loading and release kinetics, many reports showed that by increasing drug content in the carrier, the initial burst release becomes higher, because of low polymer to drug ratio. In contrast, surprisingly, in some studies, the initial burst release became smaller at high drug LC [40].

These conflicting results were attributed to the type and chemical functionalities of the drug. By incorporation of nucleophilic and basic drugs like risperidone and olanzapine into the PLGA (polyester type polymer) microsphere, the study showed significantly high polymer degradation, while the release profile of risperidone was biphasic and in contrast, the MW (as degradation parameter) of the placebo microspheres was completely unchanged. Furthermore, the observed results and rapid initial release were ascribed to the reaction of weak basic drug and the acidic polymer. These reactions by neutralization of basic drugs with produced acidic monomers through hydrolysis is reached to plateau. At the high risperidone and olanzapine loadings (15–30%), the degradation of polymer (by measuring MW) after 2 days were the maximum, proving that finding. Incorporating these types of drugs by weakly acidic polymers would be problematic upon controlling the release kinetics even in low amounts of drug loading [1].

However, drug-polymer interactions e.g. hydrogen bonding and polar interactions caused high EE, attributed to the stabilization of the primary emulsion [86]. At the highest loadings (40%) of fenretinide (hydrophobic drug), the minimum initial burst release was reported. In Fig. 5, the influence of drug loading on the initial burst release is reviewed.

The other approach to achieve high EE is the use of star-shaped PLGA. Using this kind of polymer for loading BSA by double emulsion method demonstrated that the loading capacity and EE% were superior than linear PLGA, the values of which were 67.51 μg/(mg microparticles) and 78.39%, respectively i.e. 5.88 times higher than those of linear PLGA [160].

### 5.4. Solidification time

To dry the particles, spray drying and freeze drying are the most popular solidification processes in polymeric particulate systems [161,162]. Particle agglomeration, crystal growth and sedimentation may occur during these processes. Extraction and then evaporation are two main steps of the solidification process of polymeric particles. By increasing the rate of polymer precipitation, the drug loss, due to the leakage into the continuous phase (mostly aqueous phase), is prevented. Therefore, both EE of hydrophilic and amphiphilic drugs are improved [163]. High organic phase viscosity and high CP/DP ratio are factors causing high solvent extraction and/or evaporation rate as well as high drug EE [11].

### 5.5. Route of administration

The routes of administration are commonly classified as noninvasive and invasive routes. Non-invasive routes e.g. oral, rectal and skin are painless and easily performed; however, invasive routes e.g., parenteral (e.g. IV, IM, SC, IP, intracerebral and more) cause possible pain or discomfort and need trained staff for administration. However, numerous routes can be considered for administration of medicines, either locally to the target site or injections into the blood stream. While choosing the route of administration, various factors e.g. physical and chemical characteristics of the medicine, target site, pharmacokinetic parameters (e.g. absorption, distribution, and the first pass effect metabolism), the type of barriers, patients and their disorders should be considered. The oral route is the most desired one, due to comfortable administration route, patient compliance and cost-effectiveness [164,165]. However, considerable pharmacokinetic difficulties i.e. short half-lives are engaged with large molecule drugs delivery [166]. For example, patients with chronic treatment require daily injections.

Numerous approaches have been developed to overcome the traditional parenteral administration. The embolism or local perfusions within the capillaries between the arterial and venous systems is one of the partly traditional approaches [200]. A controlled release polymeric particulate system, inclusion of targeting moieties [167], designing long circulating particles by PEGylation modification of the peptide/protein molecules [168], or coating liposome/nanocarriers with other materials such as poly (hydroxyethyl L-glutamine), poly(N-vinyl-2-pyrrolidone) (PVP), poly(4-acryloylmorpholine), poly(*N*,*N*-dimethylacrylamide) and polyglycerol-derived lipid to extent circulation time [169,170], and surfactant-surface decorated nano/micro particles [171,172] are the appropriate alternatives to increase patient compliance, convenience, and safety.

However, in the PEGylated particles, an unwanted immunogenic response, known as the accelerated blood clearance (ABC), results in an increased clearance. Therefore, it requires repeated administration, bringing about great weaknesses in the clinical application. In contrary, some investigations have indicated that by modifying some properties of PEGylated nanoparticles, such as size [198,173], polymer/drug ratio [174], molecular weight of polymer [198] and by modulation of injection intervals [198] and route of administration [198] the ABC phenomenon can be reduced or even eliminated.

In order to design a targeted therapy against various diseases, applying novel tools to reach the target site should be considered. Numerous targeting biomolecules, for example transferrin, insulin, folic acid for cancer-targeting and Apo lipoproteins like Apo-E, Apo-A1, and Apo-B100 for blood brain barrier (BBB)-targeting could functionalize nanoparticles to the target site [175]. However, the targeted nanoparticles associated with Apo E are evidently penetrated through the cerebral endothelial cells, whereas PEGylated nanoparticles were not seen in brain tissue after 30 min administration [176]. The adsorption

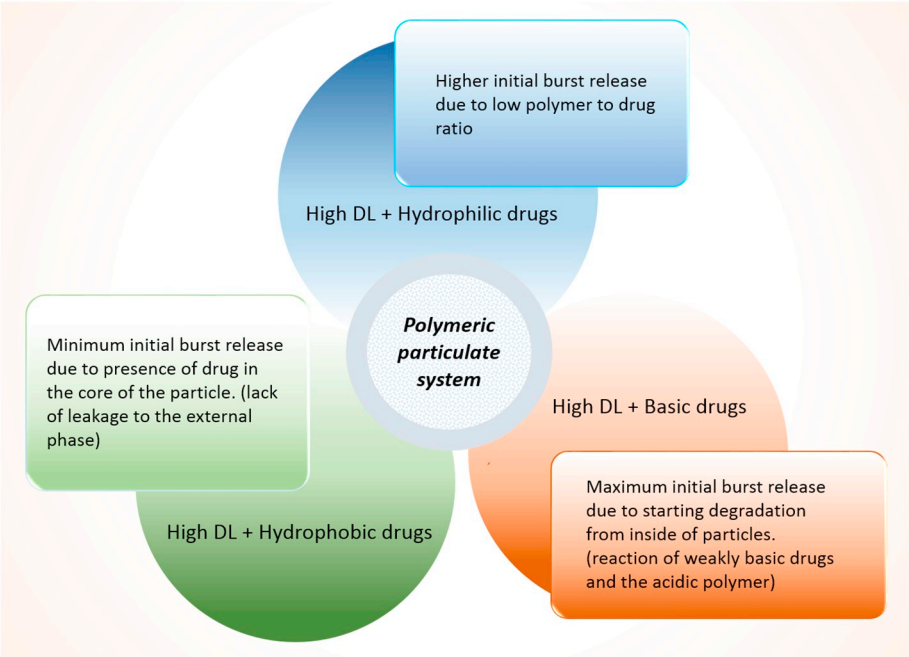


**Fig. 5.** The influence of drug loading on the initial burst release.

of the biological proteins, e.g., albumin, fibrinogen, and immunoglobulin, on the particles called as protein corona can change the properties of particles and alter the biological responses such as particle opsonization, targeting efficiency and circulation time. Protein corona is happened differently to each individual particle and is formed as soon as it is administered into the biological fluid [177].

Surfactant-surface decorated nano/micro particles enhance the resistance to protein corona event, improving specific targeting [178]. Among them, the nanoparticle albumin-bound (NAB) technology and polysorbate coated-targeted nanoparticles meaningfully amplified drug delivery into the target site [200]. Although these methods increase the target up-taking, they do not completely inhibit the effect by protein corona. Zwitterionic polymers e.g. poly (carboxybetaine), concerning their higher stability and high ability upon protein adsorption, are known as covering polymers.

Polymeric-vaccines delivery systems by parenteral route may tackle the conventional vaccines delivery drawbacks. The advantages of the parenteral carriers are high antigenicity by adjuvant action, stabilization of the antigen and adjusting of antigen release [179,180]. In particular, polymeric particles of plasmid DNA or RNA therapeutic agents can be administrated [181] with various routes. The shield against nuclease effect [182], passive targeting, and extended effect and gene expression [183] are some of these benefits. The PLGA-based nanoparticles to encapsulate DNA-based vaccines for infectious hematopoietic necrosis virus (IHNV) were developed through oral administration route. An enhanced survival for 6 weeks in fish confirmed the effectiveness of post vaccination through the high dose of oral vaccine [184]. In the last two decades, different delivery routes and technologies have been investigated in order to overcome these problems, among which polymeric particles, particularly PLGA particles and novel injection devices, were more successful [185].

### 5.6. Dosage form challenges

Size, weight or amount of drug, drug release rate and possess of stimuli response (such as enzymatic-related response or pH), pharmacokinetics parameters and the site of action are essential factors in choosing the drug dosage form. Polymeric microspheres are widely used via different dosages form mainly parenteral and implants. Syringeability, injectability, ability of resuspending or re-dispersion, viscosity and clogging are critical characteristics which should be evaluated for the pharmaceutical regulation. The ease of discharge, blockage, bubbling tendencies, qualities and consistency of flow and precise drug delivery are factors which should be assessed for the injectable drugs. Any little difficulty in above-mentioned factors may cause a considerable effect on the patient discomfort and the percentage of doses delivered [13].

In addition, it should be considered that the nano/microparticles must be reconstituted in the minimum volume of injectable liquid to administrate. The more important problems for particulate systems are viscosity-related ones, caking upon the rest and the merging of the deflocculated particles. Because of these syringe-ability and injectability problems, the concentration of final polymeric particles in the reconstituted suspension typically must not surpass 20% *w/v*, thus high potent drug microspheres are more appropriate with the minimum total drug dose requirement [46].

The high level of syringe-ability, injectability and reconstitution of microspheres are the key advantages for the microspheres, especially viscous polymeric gels or implants as injectable drug delivery system. Moreover, a comparison between the implant and injectable microsphere with good dispersibility shows that the injectable one is more acceptable by patients because of discomfort upon implantation [186].

The diluent chosen should enable rapid dissolution of the freeze-dried cake and be compatible with the freeze-dried powder and does not have a negative effect on the physicochemical stability of the reconstituted product. Typical diluents range from simple systems, such as water for injection to water containing tonicity-modifying agents or preservatives, mentioned in Table 2. For example, the diluent of leuprolide consists of CMC, mannitol and polysorbate 80.

Further efforts have been made to make oral dosage forms with good effectiveness. Now Oramed's oral insulin is in clinical trials phase under the US FDA inspection for two types of diabetes. The drug dosage form of the marketed microsphere products are summarized in the Table 3, considering dose, dosing frequency, administration route, and injection volume.

**Table 3**
Summary of micro-particulate drug products in the market.

| Drug/Brand name | Manufactured company/FDA approval year[a] | Dose/Dosing frequency/Administration route | Drug category | Indication category |
|---|---|---|---|---|
| Goserelin/Zoladex® | Tersera Therapeutics LLC/1989 and 1996 (AstraZeneca) | 3.6, 10.8 mg/vial<br>Every 2, 3 months/Implant (SC) | Deca-peptide | Antineoplastic agent/Prostate cancer |
| Octreotide/Sandostatin LAR depot® | Novartis pharmaceuticals corp./1998 | 10, 20, 30 mg/vial<br>Every 4 weeks/intragluteally (IM) | Octa-peptide | Endocrinology and Metabolism/ Acromegaly |
| Doxycycline/Atridox® | Tolmar Inc./1998 | 50 mg/subgingival single dose (in situ forming gel) | Small molecule | Infectious Diseases/Periodontitis |
| Minocycline HCl/Arestin® | Orapharma Inc./2001 | 1 mg powder/3-month intervals/ Subgingival | Small molecule | Infectious Diseases/Periodontitis |
| Risperidone/Risperdal Consta®, Perseris® | Janssen pharmaceuticals Inc./2003 Indivior Inc./2018 | For Consta®: 12.5, 25, 37.5, 50 mg/vial IM/Every 2 weeks<br>For Perseris®: 90, 120 mg/SC/Every 4 weeks | Small molecule | Neurologic Disorders/ antipsychotic |
| Naltrexone/Vivitrol® | Alkermes Inc./2006 | 380 mg/vial<br>Every 4 weeks/IM | Small molecule | opioid antagonist |
| Leuprolide/Lupron Depot® Eligard® | Abbvie endocrine Inc./1989 until 2011 Tolmar Therapeutics Inc./2002 | 7.5, 11.25, 22.5, 30, 45 mg/vial<br>1, 3, 4, 6 months/IM<br>For Eligard® SC | Nona-peptide | Antineoplastic agent/Prostate cancer |
| Leuprolide/lupaneta pack® | Abbvie Endocrine Inc./2012 | 3.75, 11.25 mg/vial, 5 mg/every 4 weeks and daily/IM and oral | Nona-peptide | Antineoplastic agent/Prostate cancer |
| Ozurdex®/Dexamethasone | Allergan Inc./2009 | 0.7 mg/implant Intravitreal | Small molecule | corticosteroid |
| Triptorelin/Trelstar® Triptodur® | Allergan sales LLC/2000 until 2010 Arbor pharmaceuticals LLC/2017 | 3.75, 11.25, 22.5 mg/vial<br>Every 1,2, 6 months/IM | Deca-peptide | Antineoplastic agent/Prostate cancer |
| Exenatide/Bydureon® | Astrazeneca AB/2012 until 2017 | 2 mg/vial, 2 mg/0.85 mL<br>Every 1 week/SC | 39-amino acid | Diabetes Mellitus, and Metabolic Syndrome |
| Triamcinolone/Zilretta® | Flexion therapeutics Inc./2017 | 32 mg/vial<br>Every 4 weeks/IM, dermal lesional, or intra-articular injection | Small molecule | Osteoarthritis and other corticosteroid trapy |
| Pasireotide/Signifor LAR® | Novartis pharmaceuticals corp./2014 until 2018 | 10, 20, 30, 40, 60 mg/vial<br>Every 4 weeks/IM | Cyclohexa-peptide | Endocrinology and Metabolism |

[a] This data collected by Orange Book and drug monograph.

### 5.7. Effect of size

Drug loading, product syringe-ability/injectability, drug release kinetics, distribution and targeting ability, cellular and phagocytic uptakes are all affected by the particle size [120,187]. The micromeritics characteristics such as particle size, size distribution, and surface area are critical factors for monitoring the microparticles' functionality and some important issues such as water penetration, drug diffusion, polymer degradation, and release kinetics of therapeutic substance. Water penetration in small particles is faster than that in larger ones, due to short distance between surface and center. However, there is a conflicting report. In many cases with the decrease of the particle size, the diffusion of drug from the polymeric particles or erosion rate of polymers will be faster, attributable to the high surface area-to-volume ratio. In the case of PLGA, studies show that bulk degradation is higher than surface degradation, resulting in faster drug release [43]. Nevertheless, in lornoxicam-loaded ethyl cellulose microspheres, drug release rate surprisingly is reduced in smaller microspheres, because of a reduction in water penetration [188,189].

The effect of particle size is literally challenging issue. In small (< 20 μm diameter) and uniform microspheres, the diffusion-controlled release occurs (rhodamine and piroxicam microspheres); while in large (> 50 μm) and uniform microspheres, polymer degradation plays a major role. To achieve zero order linear release, having a certain size, between around 10 and 50 μm, is necessary. The production of the monodisperse nano/microspheres with an accurate and reproducible control over the uniformity of the particles, aided by the recent advancements in nano/microspheres manufacturing technology, can cause improved batch-to-batch reproducibility and consequently improve the performance and therapeutic efficacy, ranging from syringe-ability to target tissue accumulation.

The key factor in determining the potential candidate for any targeting therapy is the size of particles. To pulmonary drug delivery, the particles, over 10 μm, are not able to penetrate the tracheobronchial tree [190-192]. In order to do parenteral vaccination, the size of microparticles should be < 100 μm, enabling them to pass syringe-ability/injectability tests. For targeting to the antigen-presenting cells or mucosal immunization after parenteral injection, a size < 10 μm is required [193]. Additionally, the size distribution is a determinant factor in the biological fate of the particles. Small microparticles (~5 μm) can be phagocytosed, whereas large microparticles (~30 μm) are not affected [198].

The dosage form properties i.e. good appearance, high quality, flow properties of particles, syringe-ability/injectability are also burden to the shoulder of particle size and size distribution. Moreover, particle size and size distribution specifications should be justified by processing parameters i.e. stirring speed or extruder to guarantee that particles have similar size to clinical batch and then to commercial batch [198]. A 10% size distribution is considered ideal lower limit dispersion range and a 25% distribution is approximately the maximum acceptable practical extent. The manufacturing and therapeutic limitations on the degree of distribution depend on the route of administration, particle stability, free drug solubility and the relative potency of the drug either as a free in solution or as the nano/microparticles dispersion.

In addition, aggregation or deformation of particles may occur under storage conditions of high temperature and humidity, resulting in polymer plasticization, degradation, and/or crystallization. However, it was reported that at storage temperatures lower than polymers' Tg, the aggregation of particles was not observed even upon a period of 12 months [194,195]. Following accelerated stability studies for the vancomycin microparticles, at 40 °C/75% relative humidity through 3 months, both physical aggregation and shape deformation were reported [196].

## 6. Summary

Increasing the number of approved polymeric particles, and clinical trials have revealed the important role of these drug delivery systems.

The first and key step to become commercial product is to consider the formulation parameters from lab to up to industrial scales. Biodegradability, biocompatibility, stability and safety evaluations are essential for designing suitable formulations. To achieve appropriate stable products, considering the optimum conditions for the encapsulation efficiency and release profile, according to the route of administration and the target site of disorder, can minimize the failures in the clinical trials. Polymeric particulate systems have been very successful among other drug delivery systems; however, some unsatisfactory properties have been reported for them, including toxicity, unknown side effects as local or systemic ones, which have been evidenced in several studies. Therefore, formulation designing has a main role in determining the product biocompatibility with physiological and pathological condition. Considering some critical parameters in formulation designing guides us to remove almost all the current barriers. The development of novel methods of fabricating polymeric particles, using the maximum amount of drug in the minority of polymers, and the assessment of release behavior in the biological systems are considered as valuable works in the pharmaceutical science.

In this paper, we tried to discuss formulation parameters in polymeric particulate system. Studying appropriate choice of ingredients and also method limits are the main challenging parts in the formulation of polymeric particles. It was confirmed that polymeric particles containing surfactants have low burst release and ideal constant release rate. In addition, when SA is used as surfactant, by sacrificing first, prevents the degradation oxidation reaction in the protein formulation. Spherical morphology and having control over size and size distribution and even improved bioactivity are other undeniable advantages of surfactants. On the other hand, surfactants mainly show toxic properties such as immunogenic reactions by denaturation of proteins, as either API or blood proteins, limiting their application up to concentrations stated in IID FDA webpage or other valid references. In the case of adding salts, they especially improve the rate of EE. In addition, adding buffering salts to the protein formulation can stabilize them via inhibition of agglomeration and improving the bioactivity. Besides, carbohydrates, mainly mannitol, are capable of improving the protein instabilities during storage in solution by changing thermodynamic parameters and as lyophilized powders contributing to the rigidification and inhibition of proteins' unfolding. Furthermore, to bypass the incomplete release rate, increasing the porosity in the polymer matrix is the best solution. The pore closing/opening phenomenon helps to optimize the kinetics of drug release from polymeric particles. Specific type of polymers, polyethylene glycol, pluronic F127, NaCl, $CaCO_3$, $NaHCO_3$, $K_2CO_3$, ammonium bicarbonate, mesoporous silica, hydroxyapatite, and carbohydrates, such as mannitol and gelatin with advantages like biocompatibility and hydrophilicity, can be used as pore forming agents. Another main formulation parameter is the choice of solvent. In general, the properties of a suitable solvent are high polymer solubility, poor miscibility in the aqueous medium, least toxicity, low boiling point and high volatility. Along with the mentioned solutions, applying pure components is vital to evade potential biological responses.

In addition to considering the choice of material by scientific support, the methods and method parameters have to be evaluated to achieve ideal formulation. The physical encapsulation is the most extensive and successful method for loading drug in polymeric drug delivery systems. Among the encapsulation techniques, the emulsification has received additional attention. In this method, CP/DP ratio is more important issues. The studies reported that by increasing CP/DP ratio, the internal porosity of the particles is reduced, due to faster solidification rate resulting in the remarkable increase of the drug loading and EE and consequently better release kinetic. Solidification rate is a determining factor in particle agglomeration, crystal growth and sedimentation during fabricating processes. Generally, the upper limit of drug loading for the hydrophilic drugs, such as peptides, is approximately 20% in constant release polymeric product. Totally, the high drug loading leads to high burst release. But polymer-drug interactions e.g. hydrogen bonding and polar interactions may alter this general rule. High loadings of hydrophobic drug result in the minimum burst release. However, extra interaction also may not be favorable. Mainly, incorporating basic drugs by weakly acidic polymers would be problematic in controlling the release kinetics even in low amounts of drug loading. The modification of the pH of aqueous medium is the main modulator for mentioned reactions. Depending on the pKa or log D of the drugs, changes in the pH of the environment lead to high drug loading, complete and linear release, and avoid of protein instability.

Optimizing the formulation limitations for polymeric particulate system is a fundamental step to achieve more effective medications. In the rest, designing formulation without considering the route of administration seems to be not feasible. Obviously, a complicated biological system is required to be considered in a broad-spectrum lookout. Polymeric particles are widely used via different dosage forms, mainly parenteral and implants. Syringeability, injectability, ability for resuspending, viscosity and clogging are critical characteristics, which should be evaluated for the pharmaceutical regulation. Of course, further studies are required to be focused on inspecting the formulation parameters separately for each individual medicine to achieve optimized product in research and clinical phases for an intended purposes.

## 7. Conclusion

The novel drug delivery systems, such as microspheres, nanoparticles, liposomes, and other innovative drug delivery systems, are studied. Overcoming the disadvantages of the conventional drug delivery systems, such as patient discomfort about frequent administration, low solubility and permeability, poor pharmacokinetics parameters, and toxicity is the main requirement of these drug delivery carriers. In addition, the greatest advantage of particulate systems, especially nanoparticles, is having a potential ability to target drug delivery systems. Besides, the controlled release of medications from these systems is achievable. This review was focused on challenges regarding the formulation development of polymeric particles. The presented discussions in this manuscript may guide a formulator to choose a correct way in adjusting formulation parameters, consequently leading to the goal sooner with the least possibility of wasting the expensive polymers and proteins. Moreover, choosing the reasonable strategies in the formulation of drug-loaded nano/microspheres will bring about successful results for the stability tests, maintaining the therapeutic performance of drug during shelf life of dosage form and passing the clinical trial phases, finally resulting in the achievement of international approvals.

## Declaration of Competing Interest

The authors confirm that this article has no conflict of interest.

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## Appendix A. Supplementary data

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