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Interfacial tension effects on the properties of PLGA microparticles

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ABSTRACT

Many types of long-acting injectables, including *in situ* forming implants, preformed implants, and polymeric microparticles, have been developed and ultimately benefited numerous patients. The advantages of using long-acting injectables include greater patient compliance and more steady state drug plasma levels for weeks and months. However, the development of long-acting polymeric microparticles has been hampered by the lack of understanding of the microparticle formation process, and thus, control of the process. Of the many parameters critical to the reproducible preparation of microparticles, the interfacial tension (IFT) effect is an important factor throughout the process. It may influence the droplet formation, solvent extraction, and drug distribution in the polymer matrix, and ultimately drug release kinetics from the microparticles. This mini-review is focused on the IFT effects on drug-loaded poly(lactic-co-glycolic acid) (PLGA) microparticles.

1. Introduction

Poly(glycolic acid) (PGA), or polyglycolide, has been known since 1954 as a tough fiber-forming polymer and was developed as the first synthetic absorbable suture in 1962 [1]. The use of poly(L-lactic acid) (PLLA), or poly(L-lactide), in the medical field dates back to 1966 when implanted PLLA powder demonstrated a nontoxic tissue response in guinea pigs and rats [2] and followed with the use of poly(lactic acid) (PLA), or polylactide, as sutures [3] and orthopedic fixation [4] in 1971. The successful development of these materials as surgical sutures and orthopedics led to their expansion as polymeric biomaterials. While PGA suffers from hydrolytic instability and PLA suffers from slow degradation rates, the successful combination of these two has led to poly (lactic-co-glycolic acid) (PLGA), also known as poly(lactide-co-glycolide), being the most widely researched polymer in controlled release drug delivery systems [5].

While PLGA is the most widely used polymer in controlled drug delivery systems, the research efforts to date have led to only three long-acting small molecule PLGA microparticle-based products: Zilretta®, Vivitrol®, and Risperdal Consta®. Arestin® is also a PLGA-based microparticle product approved by the Food and Drug Administration (FDA), but is used for professional subgingival administration into periodontal pockets. The small number of approved long-acting injectable PLGA microparticle products may indicate technical difficulties in their formulation development and subsequent manufacturing.

The basics of PLGA microparticles and implants have been reviewed elsewhere [6–9] and are omitted from this mini-review. The focus of this mini-review is on how understanding the effects of interfacial tension (IFT) during fabrication and drug release may aid in designing better PLGA microparticle drug delivery systems. This mini-review includes the current knowledge about IFT effects on PLGA microparticle drug delivery systems and an overview of strategies for controlling microparticle properties.

2. Emulsion droplet formation

During PLGA microparticle generation, the droplet deformation from the oil phase or discontinuous phase and possible breakup in flow are controlled by a number of dimensionless numbers, including the Reynolds number (*Re*), capillary number (*Ca*), Weber number (*We*), and viscosity ratio (*M*):

$$Re = \frac{Inertial\ force}{Viscous\ force} = \frac{\rho U d}{\eta} \quad (1)$$

$$Ca = \frac{Viscous\ force}{Interfacial\ surface\ tension} = \frac{\dot{\gamma}\eta\alpha}{\sigma}\ or\ \frac{\eta U}{\sigma}$$

$$We = \frac{Inertial\ force}{Interfacial\ surface\ tension} = Re \bullet Ca = \frac{\rho U^2 \alpha}{\sigma} \quad (3)$$

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$$M = \frac{Viscous\ force\ (dispersed\ phase)}{Viscous\ force\ (continuous\ phase)} = \frac{\eta_d}{\eta_c} \quad (4)$$

where ρ is the density of the fluids (kg/m^3); U is the velocity (m/s); d is a characteristic length scale (m); η is the dynamic viscosity (Pa·s); $\dot{\gamma}$ is the shear rate (1/s); α is the droplet size (m); σ is the interfacial surface tension between the droplet and the continuous phase (N/m); and η_d and η_c are the viscosities of the droplet phase and continuous phase (Pa·s), respectively [10].

In the process of droplet formation, the viscous force and IFT between the two phases, i.e., oil and aqueous or continuous, are dominant and the inertial force can be neglected. Therefore, the *Ca* and *M* play the most important roles in different approaches used to generate droplets in techniques such as microfluidics [11–13], membrane emulsification [14], and static mixing [15]. The *Re* is not as important in this area as most of the droplet formation occurs at low Re, where the effect of the inertial force is negligible, relative to other forces. The *We* was shown to be the second most significant dimensionless number in the microfluidics approach. Finally, a high capillary number and/or a low viscosity ratio results in emulsification conditions that favor droplet deformation [16].

While the above equations often describe the droplet formation, as solvent extraction begins, and polymer precipitation occurs, the spreading coefficient may change. Therefore, the spreading coefficient may be used as a rough predictor of the final configuration of the particles post-hardening.

3. Emulsifier type

During microparticle formation using the conventional solvent evaporation/extraction approach, an emulsifier is required to ensure droplet stability until the polymer concentration becomes high enough, i.e., enough solvent has been removed from the oil droplet to maintain the particle conformation. The emulsifier plays a significant role in the emulsification. The emulsifier acts to lower the IFT between the discontinuous oil phase and continuous water phase. In the formation of PLGA microparticles, typically 1% poly(vinyl alcohol) (PVA) is used as an emulsifier in the continuous phase. Other types of emulsifiers include hydroxypropyl methylcellulose (HPMC) [17], poly(N-vinylpyrrolidone) (PVP) [18], poly(ethylene glycol) (PEG) [19], polaxamer [20], vitamin E tocopherol polyethylene glycol succinate (TPGS) [21], and gelatin [22].

PVA at 0.1% was shown to have higher encapsulation efficiencies for ibuprofen in both dichloromethane and ethyl acetate when compared with 1.0% PVA [23]. 0.1 % PVA also resulted in larger particles, potentially altering the drug loading and the drug release kinetics. The encapsulation efficiency of paclitaxel was independent of the PVA concentration (1% vs. 5%), due to the extremely high lipophilicity of the drug [24]. Blue dextran, a hydrophilic dye, was encapsulated in PVA concentrations ranging from 0.5% to 2.5% [25]. The maximum encapsulation efficiency was obtained with a 1.0% PVA concentration and minimal size differences were noted between all samples. The decrease in drug loading was hypothesized to be due to the high surface concentrations of PVA resulting in high wettability of the microparticles. Drug loading into PLGA microparticles is dependent on multiple factors. While the wettability of the microparticles is reduced by decreasing the PVA concentration from 1.0% to 0.5% (due to the increase in the IFT between the water and oil phases) [26], there is a possibility that a PVA concentration of 0.5% was not high enough to create a stable emulsion. This may lead to leakage of the drug before skin formation of the microparticles. A similar behavior was observed by Chitkara and Kumar [27], where they made bovine serum albumin-PLGA nanoparticles using a water/oil/water (w/o/w) double emulsion method. Three different PVA concentrations of 0.5%, 1%, and 2% were used, and the highest encapsulation efficiency obtained was approximately 40% at a 1% PVA concentration.

When plasmid DNA was loaded into PLGA microparticles with 1%, 4%, or 7% PVA as an emulsifier, the average microparticle sizes (volume mean diameters) were 6.6 μm, 3.7 μm, 2.2 μm, and the loading efficiencies were 31.6%, 46.2%, and 18.8%, respectively [28]. While no conclusion was drawn for the drug loading, the 7% PVA concentration did result in the largest amount of degradation of the plasmid DNA. ABT627, a model hydrophobic drug, was encapsulated using 0.05%, 0.1%, and 0.5% PVA [29]. Drug encapsulation efficiency increased from 72% to 82.3% with an increased PVA concentration from 0.05% to 0.1%. Then, a slight decrease was noted as a PVA concentration was further increased from 0.1% to 0.5%. Interestingly, an increase in particle size was noted with an increase in the PVA concentration.

Significant variabilities can be found throughout the literature concerning a number of aspects with regards to PLGA microparticle formulations, including their raw material attributes, manufacturing steps, processing parameters, and characterization. The challenges of manufacturing and enabling comparative evaluation of PLGA formulations are highlighted in a recent study of microparticles containing risperidone [30]. Due to each drug's unique physicochemical properties, potential batch and vendor variability in PLGA, and typical lab-to-lab inconsistencies found in the fabrication process, finding various discrepancies regarding several mechanisms or characteristics of PLGA microparticles is unfortunately common.

4. Interfacial phenomena in W/O/W systems

As there is a shift in new drug development towards large molecules, developing PLGA microparticles using w/o/w emulsions will become ever more critical. Three main types of w/o/w emulsions have been identified based on the size and number of the internal aqueous droplets: (1) microcapsule, (2) multi-vesicular structure, and (3) matrix or monolithic structure (Fig. 1). Microcapsules usually have one large internal aqueous droplet. In multi-vesicular structures, approximately half of the drops include more than one internal droplet (usually less than 50). The matrix or monolithic structures are complex with many more aqueous droplets compared to two other structures [31]. To stabilize the large surface area of the microparticle, a significant amount of surfactant is required.

Unfortunately, many proteins are surface-active molecules resulting in lowering of the IFT of fluid interfaces [32]. Many biological

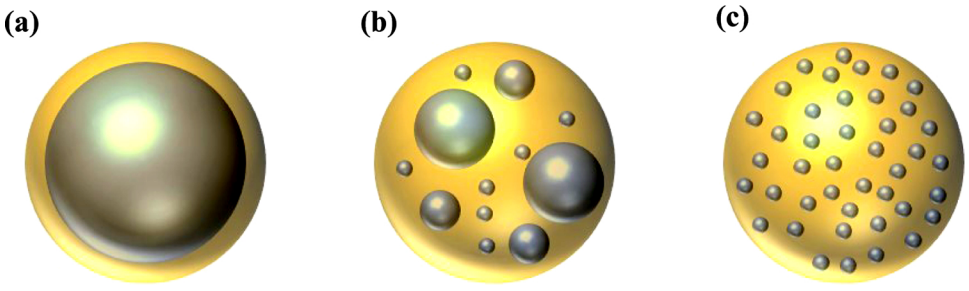

Fig. 1. Three main types of w/o/w emulsions: microcapsule (a), multi-vesicular (b), and matrix or monolithic (c) structures.

molecules become destabilized at the w/o interface during emulsification, including lysozyme [33], tetanus toxoid [34], recombinant human interferon γ [35], α-chymotrypsin [36], nerve growth factor [37], human immunoglobulin G [38], interleukin 1-α [39], and insulin [40]. Furthermore, protein stability can be affected by cavitation, heat, and/or shear during the microparticle process [41]. Additional sources of irreversible inactivation of proteins loaded in the microparticles include elevated levels of moisture, acidic microclimates due to acidic degradation products, and adsorption of the protein to the polymer surface catalyzing unfolding and aggregation [42].

Despite the instability and degradation issues, various attempts have been made to improve stabilization. Due to their markedly different propensity to lower the surface tension, one protein may displace the other from the interface [32]. This technique has been utilized to stabilize the emulsion and protect the protein with molecules such as Pluronic F68 PEG [37], hydroxypropyl-β-cyclodextrin [43], and bovine serum albumin [41].

Several other techniques have been explored to stabilize the w/o interface in double walled emulsions. Lupron Depot® adds gelatin to the water phase with the peptide leuprolide, thereby increasing the viscosity of the inner water phase and adding stability to the w/o emulsion [44]. It has been speculated that the high encapsulation efficiency is produced by the formation of a rigid matrix structure due to rearrangement of the polymer molecules surrounding the drug core [44].

As an alternative method to avoid the instability of biological materials including proteins at the o/w interface, a non-aqueous cryogenic process, ProLease®, was developed. [45]. Lyophilized drug particles were first prepared via micronization with stabilizing excipients followed by making a drug-polymer suspension. The suspension was then atomized into liquid nitrogen, followed by extraction with ethanol, and finally, filtration and vacuum drying. The advantage of this technique is preservation of the protein integrity during the manufacturing process coupled with desirable release kinetics. Additionally, a high protein encapsulation efficiency can be obtained using this technique due to non-aqueous based entrapment in the absence of an o/w interface, which can cause the protein denaturation [46]. Even with all these beneficial properties, Nutropin Depot® made by the ProLease technique with PLGA (L:G ratio of 50:50), was discontinued due to the significant resources required to manufacturing and commercialization [47].

5. Solvent effects

PLGA is an all-encompassing term for an extremely broad class of polymers. Each PLGA may have a different L:G ratio, varying between 50:50 and 100:0, molecular weight, polydispersity index, and end-group chemistry. In addition, the manufacturing process of PLGA polymers can also affect the polymer properties through residual catalyst, solvents, and/or monomer.

One route to alter the IFT between the oil and aqueous phases is to select a different solvent or combination of solvents. However, even with the IFT between the two phases, PLGA dissolution into solvents may be a more important factor, that ultimately depends on the polymer concentration, polymer molecular weight, L:G ratio, and temperature [48,49]. One possible issue in the route of changing the organic solvent would be the possibility of separation and/or refinement of PLGA grades for the mixtures of PLGAs that can occur through the use of semi-solvents exhibiting varying degrees of solubility that depends on the L:G ratio. Separation of different PLGAs used in the Trelstar® formulation using semi-solvents resulted in three different PLGAs with the L:G ratios of 70:30, 75:25, and 85:15 [49]. Since the solubility in different solvents depends on the PLGA L:G ratio, changing the solvent(s) without considering the PLGA solubility is not always the best approach to alter the IFT.

PLGA systems have used a variety of organic solvents that demonstrate a wide range of IFTs with the aqueous phase to form drug-loaded PLGA microparticles. The encapsulation efficiency of rifampicin-PLGA microparticles was compared between four organic solvents, chloroform, dichloromethane, ethyl acetate, and acetonitrile, with IFT values of 31.4, 20.4, 6.78, and 0mN/m, respectively, relative to the aqueous phase [25]. The encapsulation efficiency was improved significantly from 14.7% (acetonitrile) to 68.2% and 90.4% for dichloromethane and chloroform, respectively; due in large part to the difference in IFT between the solvent and aqueous phase. Additionally, the increase of the IFT between organic and aqueous phases reduced the initial burst due to minimal accumulation of the drug near the surface [25]. The solubility of an organic solvent in water and its miscibility can affect the encapsulation efficiency of PLGA formulations and their respective drug release kinetics. Solubility and miscibility are dependent parameters and are strongly related to the IFT, where a higher solubility results in a lower IFT (a zero IFT value means the two phases are miscible) [50]. Ethanol was used as a co-solvent in a dichloromethane-PLGA system to study the impact of the ethanol concentration on the release profile of a hydrophobic molecule – dexamethasone [51]. As the IFT was decreased, drug leached from the core of the particle due to the miscibility of ethanol with water and appeared to crystallize on the surface of the microparticles.

Another commonly used solvent in generating drug-PLGA microparticles is ethyl acetate. It is nearly four times more soluble in water (~8.0% w/w at 25 °C) [52] than dichloromethane (~2.0% w/w at 25 °C) [53]. To account for this difference, the particle fabrication process is typically modified. The IFT between an 85:15 PLGA in ethyl acetate and 1% PVA continuous phase was reduced by ethyl acetate leaching into the continuous phase, leading to a reduction in particle size [54]. Although this effect is diminished as the volume of the continuous phase is increased, larger particles are formed as polymer precipitates faster while ethyl acetate diffuses into the aqueous phase. Therefore, the continuous phase is often pre-saturated to a certain extent with ethyl acetate to: (i) control the size of the microparticles by altering the IFT between the discontinuous and continuous phase; (ii) reduce the diffusion of ethyl acetate (from the dispersed phase) into the water phase by reducing the driving force for the solvent extraction; and (iii) prevent early precipitation of PLGA that results in the formation of undesirable randomly-shaped large clumps of drug-PLGA instead of the formation of spherical microparticles [55–57].

6. Implications on drug release

As previously discussed, the change in IFT between the organic and aqueous phases can affect the organic solvent extraction kinetics from the microparticles and size of the microparticles. These two factors can change the morphology of the microparticles and the drug distribution in the microparticles, both of which play a significant role in the drug release kinetics. The IFT between dichloromethane and water was reduced from approximately 27 mN/m to 5 mN/m when the concentration of ethanol in dichloromethane was increased from 0% (v/v) to 43.75% (v/v) [51]. Then, the dichloromethane/ethanol solution was used to dissolve dexamethasone/PLGA and form drug-loaded PLGA microparticles with different morphologies, such as smooth (0% ethanol) and irregular shapes (43.75% ethanol). As the IFT is reduced due to the increase of the ethanol concentration, the burst release of the drug from the microparticles is increased and a shorter drug release duration was observed. This behavior was due to the existence of drug crystals on the surface of the microparticles during the creation of o/w emulsion at low IFT between the two phases. Different organic solvents with various values of IFT with water were used to generate blue dextran (BLD)-PLGA microparticles. Organic solvents with high IFTs with water had higher encapsulation efficiencies and longer durations of drug release [25]. Similar behavior was also observed for drug-PLGA nanoparticles [58,59]. The IFT between the organic and aqueous phases was modified by mixing different organic solvents. Addition of dichloromethane to dimethyl sulfoxide helped embed doxorubicin deeper into the core of the nanoparticles, thus significantly reducing its release

rate [58]. While some studies consider the impact of IFT, the IFT effects on the properties of the PLGA microparticles, especially drug release kinetics, has not been fully elucidated. Additionally, the approach of altering the IFT has been mainly limited to changing the organic solvent or co-solvent systems at varying ratios. Alternatively, the IFT can also be modified through the use of a single solvent combined with varying chemical functionality and/or concentrations of surfactants [60].

After careful selection of the proper emulsifier and formation of microparticles, residual emulsifier is often present on the surface and/or throughout the microparticle. PVA and Triton X have been shown to increase the hydrophilicity of the microparticles resulting in an increased drug burst release [61]. On the other hand, they may also assist in water sorption and aid in PLGA structural rearrangement during storage at high humidity resulting in lower observed burst release [61]. Although the increase of the emulsifier residual percentage on the surface of the microparticles gives more flexibility for PLGA to rearrange, it is not recommended for microparticles with small molecular weight drugs and high drug loads due to the increased possibility of phase separation between PLGA and the drug, ultimately leading to a high burst and shorter duration of release.

7. Multicomponent systems and block copolymers

In the emulsions and latex fields, it has been recognized for some time that the interfacial properties can dictate the organization of the synthesized particles [62,63]. The IFT between different phases determine the spreading coefficients. The particle morphology is largely determined by the interplay between the spreading coefficients, as different combinations of spreading coefficients may influence the degree of polymer engulfment during the phase separation. The spreading coefficients for different phases can be found based on their IFTs using the Harkin's equation (Eq. (5)). For example, if the emulsion system has two dissimilar phases, dispersed within a third, Harkin's equation can be used to obtain three different polymer engulfment configurations at equilibrium depending on the values of the spreading coefficients (Fig. 2). A positive spreading coefficient means the material will spread, whereas a negative value will result in contraction [62–65].

$$S_i = \sigma_{jk} - (\sigma_{ij} + \sigma_{ik}) \quad (5)$$

where σ is the IFT between the different phases.

The classical equilibrium spreading coefficient theory was applied to generate drug-loaded Janus particles (JPs) with two biodegradable polymers, PLGA and polycaprolactone (PCL) and several drugs, including glibenclamide, tolbutamine, rapamycin, and lidocaine all with different net charges (Fig. 2 (d–g)) [64]. The main factor to obtain different types of engulfment configurations (JP and non-JP) was the IFTs between PLGA/dichloromethane and polycaprolactone/dichloromethane with the water phase. The IFT was also found to be highly dependent on the interfacial charge density corresponding to the drugs and polymer weight ratio.

This theory combined with phase separation provides an approach for preparing double-walled PLGA microparticles, although the number of reports utilizing this technique for PLGA microparticles and microcapsules is relatively limited in scope. PLGA and PLA polymer shell microcapsules were prepared with mononuclear aqueous cores and exhibited sustained release over 7 and 49 days with fluorescein as a model compound [66]. However, the drug loading was only approximately 1–2% w/w depending on the capsule water volume (100–500 µL), which is a relatively low value for a long-acting small molecule delivery system. The same group also used various alcohols, ranging from methanol to octanol, to form mononuclear PLGA microcapsules [67], although the performance, specifically drug loading or release, was not characterized. While the thermodynamics of these ternary systems is fairly well established, kinetic factors can also strongly contribute to the micro- and macro-structure particle morphology and additional studies are needed to obtain greater control and yield over these types of particles.

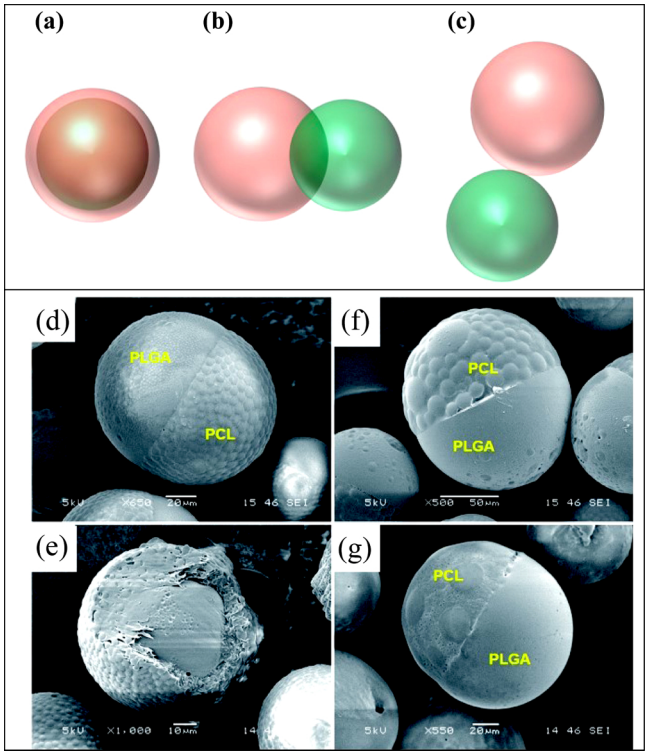

Fig. 2. Potential phase configurations at equilibrium in relation to the spreading coefficient. (a) Full engulfment (i.e., core shell) ($S_1 < 0$, $S_2 < 0$, $S_3 > 0$); (b) Partial engulfment (i.e., Janus) ($S_1 < 0$, $S_2 < 0$, $S_3 < 0$); (c) No engulfment (i.e., individual particles) ($S_1 < 0$, $S_2 > 0$, $S_3 < 0$). Scanning electron microscopy (SEM) images of PLGA/polycaprolactone microparticles formed with the polymer weight ratio of 19:11, (d) without drug; with drugs, i.e. (e) glibenclamide (negatively charged); (f) rapamycin (no charge); and (g) lidocaine (positively charged). Reproduced with permission [64].

Formation of microparticles with block copolymers is significantly influenced by the IFT of the respective block. A PEG-PLA copolymer with a molecular weight of ~33.5 kDa (in a range of 2.6 ~ 218 kDa) had the lowest IFT in a dichloromethane solvent system with water [68]. This balance between hydrophilicity and hydrophobicity resulted in dendritic particles, where the PEG segments drove the deformation of the emulsion droplet, whereas the other molecular weights resulted in spherical, spherical particles with imperfections, or a fiber sphere mixture. While the drug delivery application was not characterized, this study illustrates the importance of the effects of IFT on polymer rearrangement in the microparticle. Small molecular weight changes, emulsifier differences, and drug type could help create the next generation of PLGA microparticle-based products through simple modifications to the processing.

8. Conclusion

As many PLGA microparticle systems are fabricated and explored, it is important to consider understanding the mechanisms of microparticle preparation, as it is essential in controlling the properties of the microparticles, e.g., drug loading capacity, efficiency, and release kinetics. Controlling these properties requires further mechanistic studies using various PLGAs with different molecular weights, L:G ratios, and end groups for a range of drugs with diverse physicochemical properties. The effects of IFT between the organic and aqueous phase and on drug release have been reviewed here. The emulsifier type and concentration in the continuous phase has been shown to be an important factor in altering the emulsion stability, particles size, and encapsulation efficiency. In addition, the solvent can influence the drug locations

in the microparticle, ultimately controlling the initial burst and duration of release. Unfortuantely, many mechanistic studies have been performed with low drug loadings, usually < 5%. As the drug loading is increased, the IFT effects that occur throughout the processing and the final properties of the PLGA microparticles may change. Residual solvent and/or emulsifier can also alter the interfacial phenomenon and lead to entirely different results based on their wetting phenomena. The progress that has been made on the various aspects of PLGA microparticle formation and characterization has provided a foundation for future in-depth studies. The effects of IFT need to be considered in the design and formation of the next generation of long-acting injectable PLGA microparticle products for reproducible properties.

CRediT authorship contribution statement

Andrew Otte: Conceptualization, Writing - review & editing. **Farrokh Sharifi:** Conceptualization, Writing - review & editing. **Kinam Park:** Conceptualization, Writing - review & editing.

Declaration of Competing Interest

The authors report no declarations of interest.

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