4. Summary

Microparticles prepared by the solvent evaporation (cosolvent) method

Initial release, encapsulation efficiency, and scale-up

Adjusting parameters, which affected the PLGA precipitation kinetics, provided efficient ways to increase the encapsulation efficiency and control the initial release. Addition of NaCl at low concentration (0.05 M) to the external aqueous phase increased the encapsulation efficiency and the initial release; in contrast, NaCl at high concentration (0.5 M) delayed polymer precipitation and resulted in non-porous microparticles with a low initial release. The presence of ethanol in the external phase led to porous microparticles with an increased initial release but a decreased encapsulation efficiency. The initial release also decreased with decreasing volume of the external phase and homogenization speed, as well as with covering the preparation apparatus; however, these variations showed no significant effect on the encapsulation efficiency. Scale-up of the formulation by a factor of 5 showed no influence on the encapsulation efficiency and the initial release, a factor of 25 resulted in a slight decrease in the initial release due to a larger particle size.

Tri-phasic release pattern

Varying formulation and processing parameters (e.g., drug loading, volume of the external aqueous phase, using low molecular weight PLGA, different microparticle drying methods) affected the initial release (burst) but did not influence the drug release thereafter. The addition of the hydrophilic polymer polyvinylpyrrolidone (PVP) led to the formation of more porous microparticles. This influenced the initial release but did not change the tri-phasic drug release pattern. The inclusion of medium chain triglycerides successfully shifted the tri-phasic pattern to a continuous release profile. MCT accelerated the leuprolide release in the second, slow release phase and reduced it in the final rapid release phase. MCT led to the formation of microparticles with an irregular surface and a highly porous inner structure. Differential scanning calorimetry (DSC) revealed a high entrapment of MCT in the microparticles and an unchanged glass transition temperature (T_g) of the PLGA.

In situ forming microparticles

Emulsion formation and morphology of resulting microparticles

During emulsification process in ISM systems, the solvent diffuses into the external continuous phase, which leads to an increase in the polymer solution viscosity. The increased surface area as decreased polymer solution droplet size facilitates the solvent diffusion. Therefore, the original low viscosity of the polymer solution and the slow solvent diffusion into the external continuous phase benefit the emulsion formation.

The microstructure of resulting microparticles related to the water miscibility of the polymer solvent. Microparticles prepared with a completely water-miscible solvent presented a highly porous inner structure; in contrast, microparticles from a partial water miscible solvent had a dense inner structure.

Formulation and processing parameters

ISM from RG 503H showed a high initial release (approx. 40%), which could be attributed to the high porosity of microparticles. The initial release could be reduced by increasing the polymer concentration, increasing the volume and viscosity of the oil phase, and decreasing the drug loading. The effect of these parameters on the second release phase (after initial release) was marginal.

ISM from R 202H had a much lower initial release comparing to that from RG 503H, which was followed by a slow and continuous drug release. The initial release could be further reduced by increasing the polymer solution concentration. In comparison to conventional microparticles prepared by the solvent evaporation method, ISM showed a lower initial release and a more linear continuous release.

Cosolvent addition

Introducing a partial water-miscible cosolvent reduced the initial release from ISM, which could be attributed to the formation of less porous in situ forming microparticles. Generally, the initial release decreased with increasing cosolvent concentration and decreasing water miscibility of the cosolvent; however, the cosolvent diffusion rate into the continuous oil phase also affected the initial release.

In vivo study in rabbits showed a suppression of testosterone until day 29 after single administration of ISM prepared with a solvent mixture of 80% w/w NMP and 20% w/w triacetin.

Polymer type

In contrast to microparticles prepared by the classical solvent evaporation method, the use of the lower molecular weight PLGA resulted in ISM with a lower initial release than ISM prepared with the higher molecular weight PLGA. ISM prepared with PLGA combinations showed a decreasing initial release with increasing low molecular weight PLGA content. A slower solvent diffusion from the low molecular weight PLGA solution droplets into the release medium led to a less porous structure of the resulting microparticles, thus explaining the lower initial release. PLGA with free carboxylic acid endgroups led to a lower drug release compared to PLGA with esterified end groups. 6-month controlled release leuprolide ISM could be obtained by blending poly(lactides) (PLA) with different molecular weights.