Effects of Process and Formulation Parameters on the Properties of Spray-Dried Microspheres
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Purpose
Spray drying has advantages compared to other methods of manufacturing microspheres: high encapsulation efficiency, high yield, and fast and robust scale-up. Dichloromethane (DCM) has been widely used as a solvent for excipients and APIs intended to be spray dried, and most published process optimization has been performed using this solvent. However, process optimization of spray drying with ethyl acetate (EA), a class III solvent which is much safer than DCM, has not been well studied. Our purpose is to establish a spray drying process that is free of class II solvents, and that could provide spherical sustained release microspheres.

Methods
In this study, methylparaben and its derivatives were used as model compounds and encapsulated into a polylactide polymer (PLA) using EA or DCM as a solvent to study the effects of process/formulation parameters (inlet temperature, solvent, polymer type, molecular weight, polymer concentration etc) on the microsphere properties.

Results
Our study demonstrated that regardless of the inlet temperature, smooth, nonporous and spherical microspheres were obtained with both EA and DCM solvents using one low molecular weight PLA. When standard inlet temperature was employed to spray dry other PLGA/PLA polymer/solvent systems, as report in other literatures, nonporous but doughnut-shaped microspheres were obtained with EA solvent, and porous, spherical structures were obtained with DCM solvent. The change of inlet temperature or solvent did not have a significant effect on methylparaben in vitro release from spray dried microspheres. However, a significant reduction in the model compound’s in vitro release rate was observed when higher polymer concentrations (10-15% w/v) were used. The logP value of the encapsulants played a significant role in affecting the model compounds release rate as well: the higher the logP, the slower the drug release.

Conclusion
Our results, in conjunction with literature reports, indicate that EA can be used as a safe solvent to spray dry microspheres with acceptable residual solvent concentration. Also, formulation variables, such as type of polymer, its molecular weight, logP of the APIs have more profound effects on the particle properties compared to the spray drying process parameters, such as solvents, polymer concentration and spray drying temperature.