# Amplifying Dual-Drug Microspheres Capacity via Formulation Optimization and Computational Simulation

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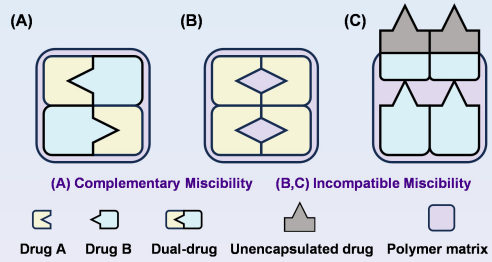
## Abstract and Scheme

Polymeric microspheres can tailor the pharmacokinetic features of encapsulated drugs, thereby prolonging drug therapeutic effects with minimal toxicity. Rational formulation design is essential to enhance the miscibility of drug molecules and polymeric matrix of microspheres. Sufficient miscibility can make sure more drug molecules encapsulated in polymeric microspheres, overcoming the drug-carrier compatibility limitation and amplifying microspheres capacity. Here, the screened dual-drug formulation with **complementary miscibility** was utilized to develop **dual-drug loaded polymeric microspheres**. Under identical drug-to-polymer ratios, it exhibited **improved miscibility** within the polymer matrix compared to single-drug formulations, thereby amplifying microspheres drug loading capacity.




## Highlights of the Research

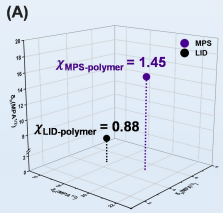
**Better mixing, better loading:** A strategy for enhancing the drug-polymer miscibility for better drug encapsulation of polymeric microspheres.

**Mix to match:** Formulation optimization based on complementary miscibility pairing of dual-drug.

**From model to lab:** Theoretical estimation, computational simulation and experimental verification are used to clarify the principles of formulation screening.

## Theoretical estimation and computational simulation

According to the calculated results of $\chi$drug-polymer (**A**) and $\Delta H_M$ (**B**) of drug-polymer, for optimizing the distribution of methylprednisolone (**MPS**) possessing poor miscibility with the polymer matrix poly(lactic-co-glycolic acid) (PLGA), lidocaine (**LID**) possessing better miscibility with PLGA, was introduced into the dual-drug–polymer system to enhance the overall miscibility of the formulation.




The **Flory–Huggins interaction parameters ($\chi_{drug\text{-}polymer}$)** is used to describe the miscibility between the drug and the polymer matrix, with smaller values indicating better miscibility:

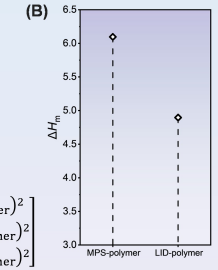
$$\chi_{\mathrm{drug\_polymer}} = \frac{V_{\mathrm{drug}}}{RT} \cdot (\delta_{\mathrm{drug}} - \delta_{\mathrm{polymer}})^2$$

Hansen solubility parameter ($\delta$, HSP) is obtained by partial solubility parameters for dispersion ($\delta_d$), polar ($\delta_p$) and hydrogen bonding interactions ($\delta_h$) calculated based on the additive group contribution method (GCM):

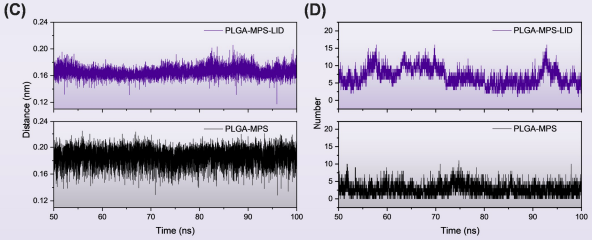
$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \qquad \delta_d = \sum \frac{F_{di}}{V} \quad \delta_p = \frac{\sqrt{\sum F_{pi}^2}}{V} \quad \delta_h = \frac{\sqrt{\sum E_{hi}}}{V}$$

The **enthalpy of mixing ($\Delta H_M$)** is further used to describe the mutual miscibility of the drug and the polymer matrix, with smaller values indicating better miscibility:

$$\Delta H_M = \phi_{\mathrm{drug}}\phi_{\mathrm{polymer}}(\delta_{\mathrm{drug}} - \delta_{\mathrm{polymer}})^2 \quad \Delta H_M = \phi_{\mathrm{drug}}\phi_{\mathrm{polymer}} \begin{bmatrix} (\delta_{d,\mathrm{drug}} - \delta_{d,\mathrm{polymer}})^2 \\ +(\delta_{p,\mathrm{drug}} - \delta_{p,\mathrm{polymer}})^2 \\ +(\delta_{h,\mathrm{drug}} - \delta_{h,\mathrm{polymer}})^2 \end{bmatrix}$$

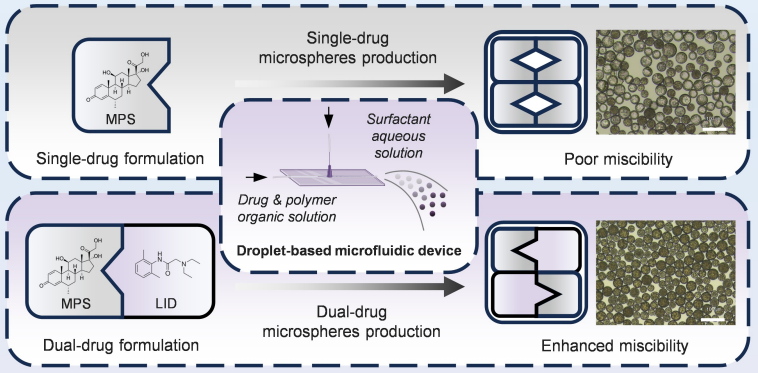



**Molecular dynamics (MD)** simulations were used to analyze the intermolecular distances (**C**) and the number of hydrogen bonds (**D**) between the drugs and the polymer, in order to further demonstrate the improved overall miscibility of the dual-drug–polymer formulation compared to single-drug–polymer formulation:

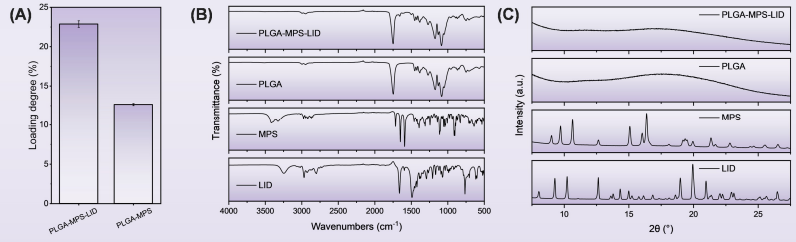



## Microspheres preparation and characterization

Continuous droplets were generated by the mutual shearing of the drug–polymer organic solution and the aqueous solution containing surfactants in a droplet-based microfluidic device. Owing to the better miscibility of the dual-drug formulation compared to the single-drug formulation, the dual-drug droplets formed polymeric microspheres with a more uniform matrix after solidification.




Compared to the single-drug microspheres, the total drug loading capacity of the dual-drug microspheres **increased by 80.80%** under identical drug-to-polymer ratios (**A**). Fourier transform infrared spectroscopy (FTIR) results (**B**) confirmed the encapsulation of both drugs into the microspheres, while X-ray diffraction (XRD) results (**C**) further verified the amorphous distribution of the drug molecules in the dual-drug microspheres, indicating sufficient miscibility within the dual-drug–polymer system.




## Conclusions

1. Drugs possessing high miscibility with the polymer matrix can improve the distribution of poorly miscible drugs within polymeric microspheres, thereby amplifying the drug loading capacity of polymeric microspheres.
2. With the support of computational simulations, the Flory–Huggins interaction parameters ($\chi_{drug\text{-}polymer}$) and the enthalpy of mixing ($\Delta H_M$) can serve as reference criteria for screening dual-drug formulations.
3. A greater difference in miscibility between the two drugs with the polymer matrix leads to a more significant increase in the total drug loading capacity of the dual-drug microspheres.

## References

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