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Effect of Manufacturing Differences on the Drug Release Characteristics of Peptide Microspheres

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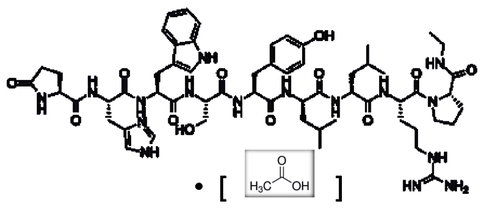
PURPOSE

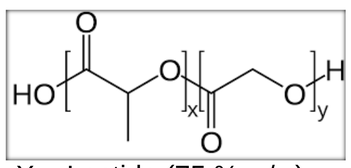
- In order to determine the critical quality attributes of polymer microspheres that may lead to alteration of drug release characteristics, it is important to understand the underlying drug release mechanisms.
- Accordingly, the purpose of the present study was to understand the underlying cause of the effect of manufacturing processes on the *in vitro* release characteristics of prepared leuprolide acetate (LA) microspheres.

METHODS

Model Drug
Leuprolide acetate



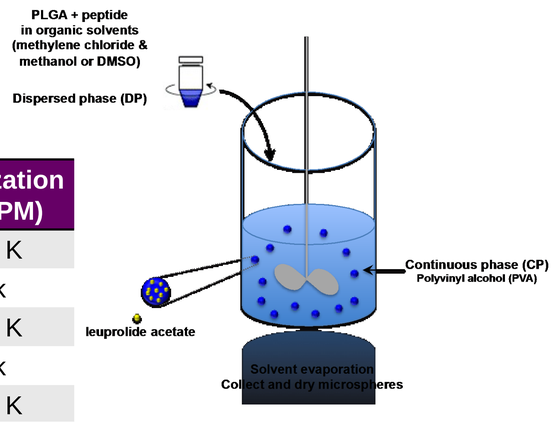
Polymer:
Poly(lactic-go-glycolic acid) (PLGA)



X = Lactide (75 % w/w)
Y = Glycolide (25 % w/w)

Preparation Method

Single emulsion (O/W) solvent evaporation method



Process variables

Formulations	Solvent systems	Homogenization Speed (RPM)
F1	DCM/MeOH	13 to 14 K
F2		8 to 9 k
F3	DCM/DMSO	13 to 14 K
F4		8 to 9 k
F5	DCM/BA	13 to 14 K

Characterization of Microspheres

1. Critical Quality Attributes (CQA):

CQAs	Method of Determination
Drug loading	High performance liquid chromatography
Particle size	Accusizer auto dilution particle sizing system
Porosity	Mercury porosimetry
Morphology	Scanning electron microscopy
Molecular weight	Gel permeation chromatography

2. *In Vitro* Release Testing:

- Sample-and-separate method — Testing conditions: "real-time" (37° C)
- Release medium: 33 mM PBS containing 0.02% (w/v) sodium azide and 0.02% (w/v) Tween 80. Medium was replaced every two-three days.

3. *In Vitro* Degradation Study:

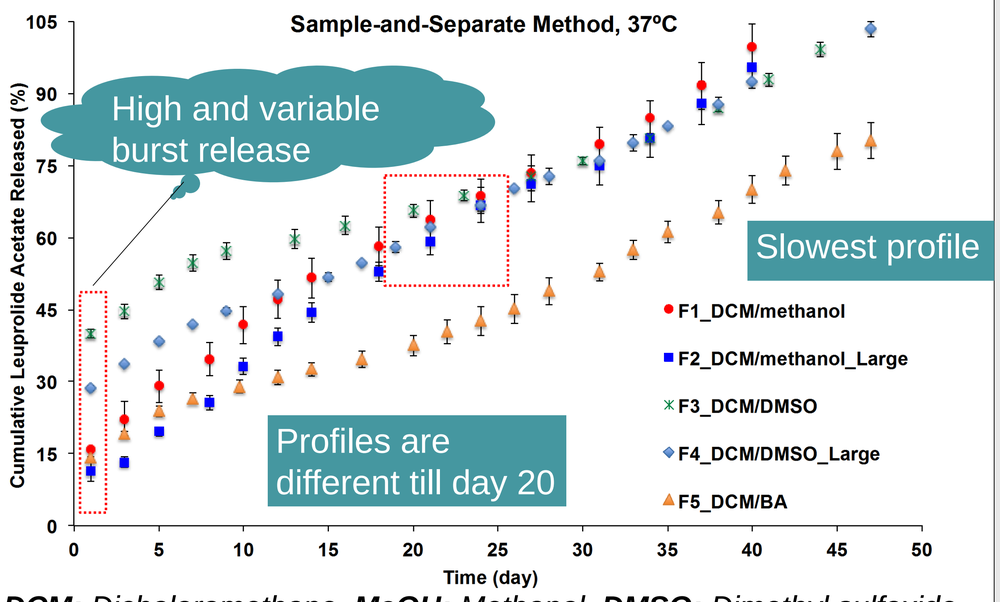
Load samples under above mentioned release condition → Collect samples at predetermined time points, wash, freeze dry → Evaluate for morphology and polymer molecular weight

RESULTS AND DISCUSSION

Table 1: Physicochemical Properties of Microspheres

Formulations	Drug Loading (%W/W)	Particle Size (µm)	Porosity (%)	Pore Daimeter (nm)
F1	~ 8 %	45.52	57.06	814.5
F2		72.69	52.65	712.7
F3	**Q1/Q2**	40.71	61.01	964.0
F4		52.27	56.48	814.1
F5		91.36	62.16	959.8

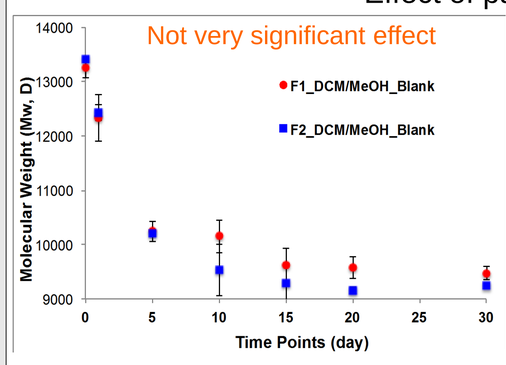
In vitro release profiles

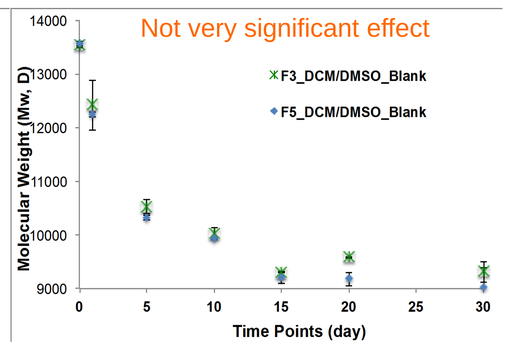


DCM: *Dicholoromethane,* ***MeOH:*** *Methanol,* ***DMSO:*** *Dimethyl sulfoxide,* ***BA:*** *Benzyl Alcohol*

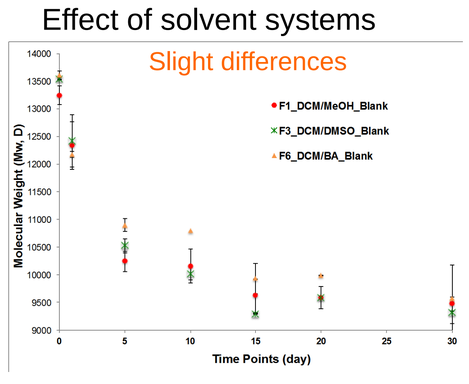
***In vitro* degradation study –** evaluation of polymer degradation rate as release mechanism

Effect of particle size

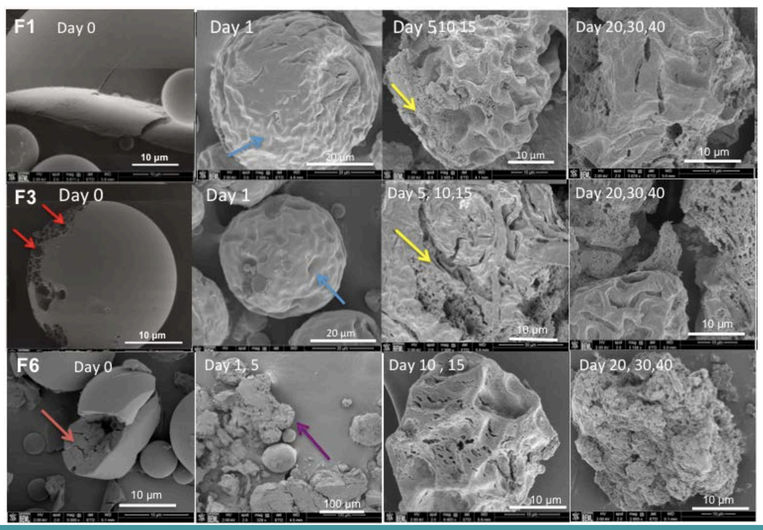




Effect of solvent systems

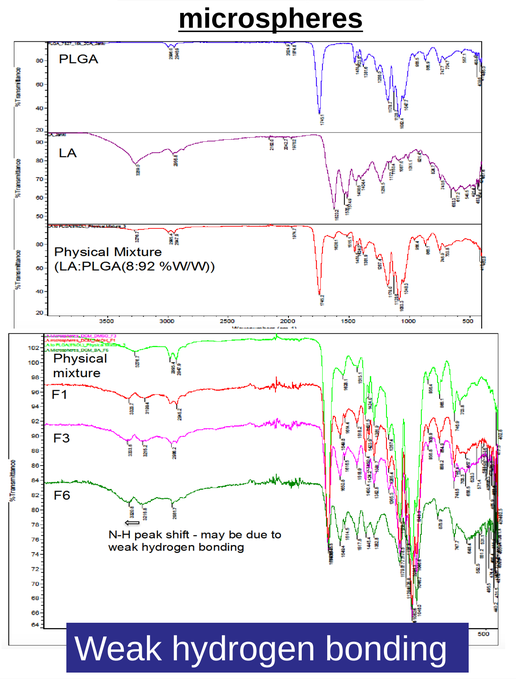


***In vitro* degradation study –** evaluation of morphology to investigate diffusion based release mechanism



Remarkable alteration of microsphere morphology such as formation of channels *vs shape deformation (as shown by arrows) till day 15. After day 20 all samples show similar morphology, which corresponds to the observed* in *vitro* release profiles.

Evaluation of peptide polymer interaction of prepared microspheres



Weak hydrogen bonding

CONCLUSIONS

1. Minor differences in the manufacturing process of compositionally equivalent microspheres resulted in changes in the *in vitro* drug release characteristics
2. Based on the *in vitro degradation study and peptide-polymer interaction study, the observed differences in the drug release profiles* could be attributed to differences in microsphere porosity and hence the drug diffusion rate rather than differences in the particle size or polymer degradation rate.
3. This in turn indicates that the drug release from peptide microspheres is controlled significantly *via the diffusion process.*

REFERENCES

1. Yeo Y., Park K. Arch Pharm Res, 2004, 27(1): 1-12.

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- **Disclaimer**: This poster reflects the views of the authors and should not be construed to represent FDA'S views or policies.