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A Review of Recent Progress in GDUFA Research Program on PLGA-Based Drug Products: Three Case Studies

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PURPOSE

- FDA has approved 17 long acting injectable (LAI) new drug products formulated with poly (lactide-co-glycolide) (PLGA) polymers.
- PLGAs are random copolymers, which are available with different molecular weight (MW), lactide/glycolide (L/G) ratio, type of end capping, and polymer structure. These molecular characteristics of PLGA can affect the mechanism and rate of drug release.
- According FDA's regulation 21 CFR 314.94(a)(9)(iii), generic drug products intended for parenteral use, such as PLGA-based LAI drug products, generally must be qualitatively (Q1) and quantitatively (Q2) the same to the corresponding reference listed drug (RLD).
- As a random copolymer, the inherent heterogeneity associated with PLGA makes assessment of Q1 sameness challenging.
- In addition, Q1/Q2 sameness does not necessarily lead to comparable product performance since performance of these products are sensitive to manufacturing conditions.
- Minor differences in manufacturing may result in significant changes in release rates of finished products.
- Due to the complexity of these formulations, to date, none of the marketed PLGA-based products has an approved generic version.
- Recognizing these challenges, since 2012, the Office of Generic Drugs (OGD) at the U.S. Food and Drug Administration (FDA) has established a regulatory science and research program under the Generic Drug User Fee Amendments (GDUFA) to fund research projects to address scientific and regulatory knowledge gaps that will facilitate the development and approval of complex generic drug products.

OBJECTIVE(S)

- The current abstract highlights significant findings on three GDUFA-funded research projects on PLGA-based drug products with different objectives.
- Case I aimed to investigate *in vitro-in vivo* correlations (IVIVCs) of PLGA microspheres.
- Case II focused on improving the current understanding of *in vitro* release testing (IVRT) methods for PLGA-based drug products.
- Case III intended to provide information on suitable reverse engineering of commercial PLGA-based drug products.

METHOD(S)

1 IVIVC of Naltrexone-PLGA microspheres	2 IVRT of Risperidone-PLGA microspheres	3 Reverse Engineering of Lupron Depot® (Leuprolide-PLGA microspheres)
⊙ 2 Manufacturing processes at 4°C: -Stirring (S) -Homogenization (H) ⊙ 3 Solvent systems: -Methylene dichloride (DCM) -Ethyl acetate (EA) -Benzyl alcohol (BA)	⊙ 2 Manufacturing processes: Solvent extraction -1.5 h → (DCM:EA) -24 h → DCM	⊙ 3 Drug Extraction processes: -DCM:pH 6 Na_2HPO_4 buffer -DCM:pH 4 NaAc buffer -Amino acid analysis ⊙ Excipients Extraction: -Gelatin content, Type ⎫ Molecular -PLGA content, L/G ratio ⎭ weight -Mannitol content
⊙ *In vitro* studies: -USP apparatus IV ⊙ *In vivo* studies: -Rabbit model ⊙ Level A IVIVC -Validated for predictability	⊙ IVRT study parameters and their impact on drug release: -Type of apparatus -Shape of vessels -Solid material (glass/PDVB beads) -Sampling volume -Agitation	⊙ Product Attributes Characterization -Particle size distribution (Mastersizer, SEM) -Glass transition (Tg, DSC) -Residual moisture (Karl Fischer titration) -Residual solvent (Gas chromatography) -IVRT (sample-and-separate method)

RESULT(S)

1

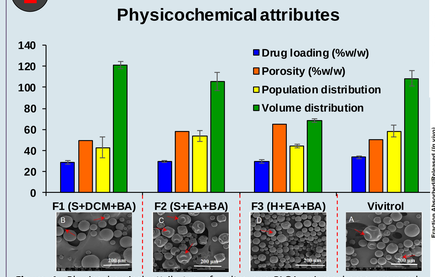

Figure 1: Physicochemical attributes of naltrexone-PLGA microspheres prepared using different manufacturing processes

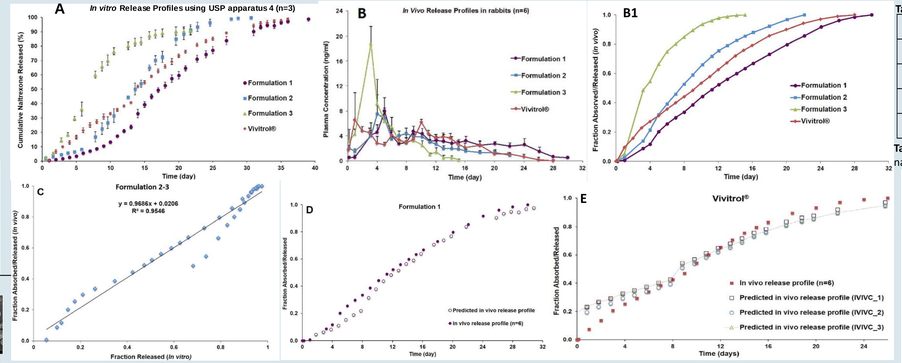

Figure 2: (A) *In vitro* release profiles; **(B)** *In vivo* release profiles; **(B1)** *In vivo* fraction absorbed/released profiles (*i.m.*); **(C,D)** Level A IVIVC using Loo-Reigelman method (time shifting factor: 5.2); and **(E)** Experimental and predicted *in vivo* release profiles of RLD Vivitrol® using developed IVIVCs of naltrexone-PLGA microspheres with manufacturing differences.

Table 1: Pharmacokinetic parameters of naltrexone solution *(i.v.)*

Key Pharmacokinetic parameters of naltrexone solution (*i.v.*)			
A	B	$K_{10}(h^{-1})$	$K_{12}(h^{-1})$
38.44±7.35	1.982±0.820	0.795±0.119	0.280±0.058
$\alpha(h^{-1})$	$\beta(h^{-1})$	$K_{21}(h^{-1})$	
1.124±0.169	0.118±0.047	0.168±0.067	

Table 2: Validation and % predictor error (PE) of the developed IVIVC of naltrexone-PLGA microspheres with manufacturing differences.

	C_{max} (µg/L)			$AUC_{0\text{-}last}$ (µg/L* day)		
	Obs.	Pred.	%PE	Obs.	Pred.	%PE
Internal validation						
Formulation1	7.98	7.84	− 1.68	80.82	70.99	− 12.16
Formulation 3	18.78	14.61	− 22.24	72.17	70.79	− 1.92
Average internal			11.96			7.04
External validation						
Formulation 2	7.49	7.74	3.38	62.78	69.14	10.13
Prediction						
Vivitrol®	7.54	6.84	− 9.27	74.60	81.70	9.53

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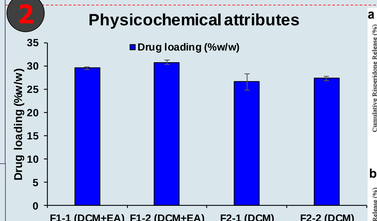

Figure 3: Physicochemical attributes of risperidone-PLGA microspheres prepared using different manufacturing processes

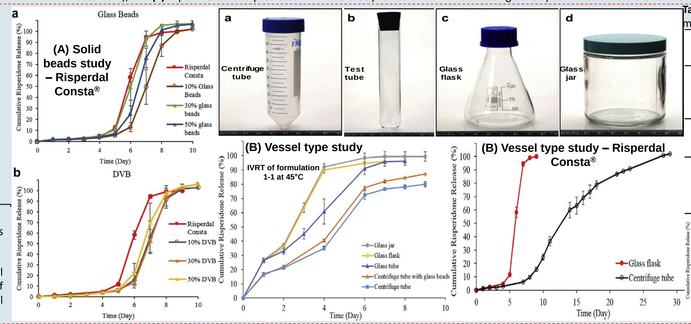

Figure 4: IVRT profiles of risperidone-PLGA microspheres and Risperdal Consta®: **(A)** Effect of solid beads; **(B)** Effect of vessel type; **(C)** Effect of sampling volume; **(D)** Effect of agitation; and **(E)** Effect of experimental parameters on molecular weight of PLGA

Table 3: Molecular weight changes of PLGA in risperidone-PLGA microspheres under various release conditions

Time (Day)	No Agitation		Control	
	Molecular Weight (Da)	PDI	Molecular Weight (Da)	PDI
0	84,832	1.66	84,832	1.66
5	38,553	2.29	42,150	2.84
12	26,523	2.88	30,034	2.27
21	Undetectable	–	24,679	4.06
Time (Day)	Glass Beads		DVB	
	Molecular Weight (Da)	PDI	Molecular Weight (Da)	PDI
0	84,832	1.66	84,832	1.66
5	51,247	1.87	52,873	1.89
12	26,891	3.16	36,508	1.79
21	24,391	4.08	32,707	1.79

Table 4: Risperidone solubility at different pH

Solution	pH	Risperidone Solubility (mg/mL)
0.1% lactic acid	2.85	6.91 ± 0.15
0.5% lactic acid	2.52	19.41 ± 0.22
1.0% lactic acid	2.31	38.16 ± 0.22
0.1% HCl	1.68	12.62 ± 0.23
1.0% HCl	0.80	57.26 ± 0.92
PBST	7.45	0.291 ± 0.001

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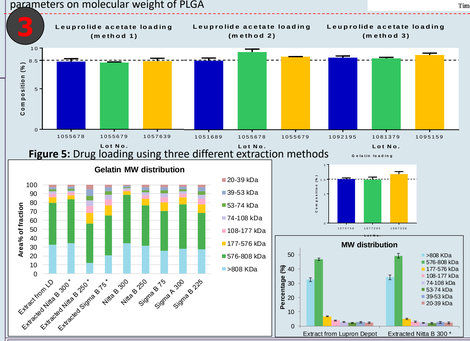

Figure 5: Drug loading using three different extraction methods

Figure 6: Gelatin and PLGA composition, type and molecular weight

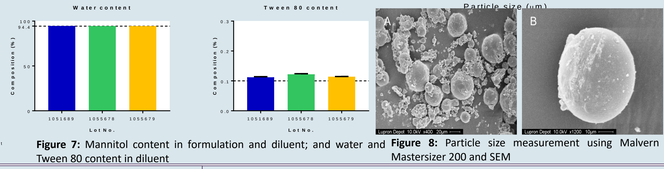

Figure 7: Mannitol content in formulation and diluent; and water and Tween 80 content in diluent

Figure 8: Particle size measurement using Malvern Mastersizer 200 and SEM

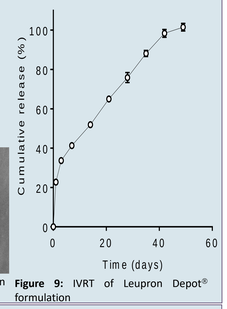

Figure 9: IVRT of Leupron Depot® formulation

CONCLUSION(S)

1) The developed USP apparatus 4 method was able to detect invitro performance changes resulting from manufacturing processes differences and most importantly, predict in vivo performance of the Naltrexone-PLGA microspheres. Although the IVIVC was developed in an animal model, it paves the way for developing IVIVCs in humans.

2) Drug release kinetics of PLGA microspheres could be sensitive to experimental conditions. For the orbital shaking method, agitation speed, vessel dimensions, solid beads and media exchange volume showed an impact on drug release profiles, therefore, these parameters should be evaluated during IVRT method development and validation.

3) Attributes including particle size distribution, residual water and solvent levels, Tg, and invitro release demonstrate the unique features of leuprolide-PLGA microspheres. The reverse engineering study of Lupron Depot will be useful for the development of generic leuprolide-PLGA microspheres and could be applied for reverse engineering analysis of other PLGA-based long acting release products.

FUNDING / GRANTS / ENCORE / REFERENCE OR OTHER USE

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[3] Zhou, J., Hirota, K., Ackermann, R., Walker, J., Wang, Y., Choi, S., Schwendeman, A., & Schwendeman, S.P. (2018). Reverse engineering the one-month Lupron Depot®. AAPS J. (accepted)