

Session II:

Characterization of Complex Excipients and Formulations

Yan Wang
Division of Therapeutic Performance
Office of Research and Standards
Office of Generic Drugs



Goals of Section II

- Introduction: challenges to develop generic complex formulations
- Introduce GDUFA research priorities
- Research update

Complex Formulations/Dosage Forms

- Complex formulations/dosage forms
 - Long-acting (LAI) parenteral drug products
 - Microparticles
 - Implants/inserts
 - Multivesicular liposomes
 - suspensions
 - Injectable drug products with nanotechnology
 - Nano size liposomes
 - Iron complex
 - Nano-suspensions
 - Semi-solids
 - Lotion
 - Ointments
 - Cream
 - Emulsions
 - Abuse deterrent formulations

Challenges to Develop Generic Complex Formulations



- Demonstration of qualitative (Q1) and quantitative (Q2) sameness of excipients prior to conduct of bioequivalence (BE) studies of parenteral drug products

21 CFR 314.94 (a)(9)(iii) – *Inactive ingredient changes permitted in drug products intended for parenteral use.*

Generally, a drug product intended for parenteral use shall contain the same inactive ingredients (qualitatively the same – “Q1”) and in the same concentration (quantitatively the same – “Q2”) as the reference listed drug.

An applicant may seek approval of a drug product that differs from the reference listed drug in **preservative, buffer, or antioxidant** provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

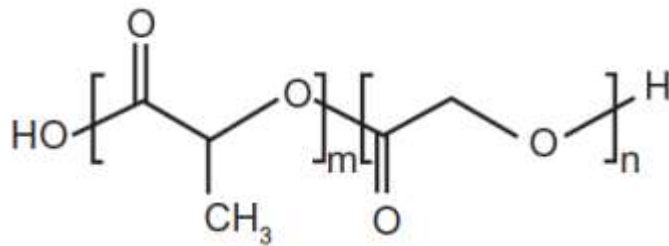
A formulation which contains an excipient not contained in the RLD and not considered to be an “exception excipient” cannot be submitted as an ANDA.

Challenges to Develop Generic Complex Formulations (Cont.)



- Complex inactive ingredients

- Poly(lactic-co-glycolic acid) (PLGA) copolymer

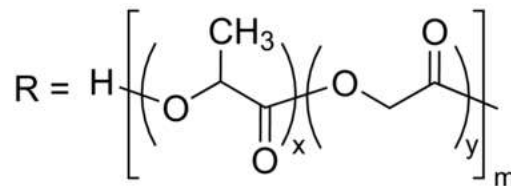
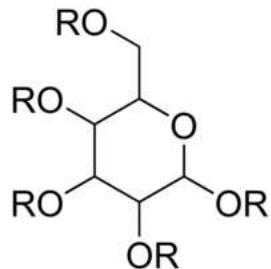


PLGA

m = number of units of lactic acid
n = number of units of glycolic acid

- Ratio of lactic acid to glycolic acid
- Molecular weight ~5kDa -100kDa

- Glucose star polymer, D,L-lactic and glycolic acids copolymer

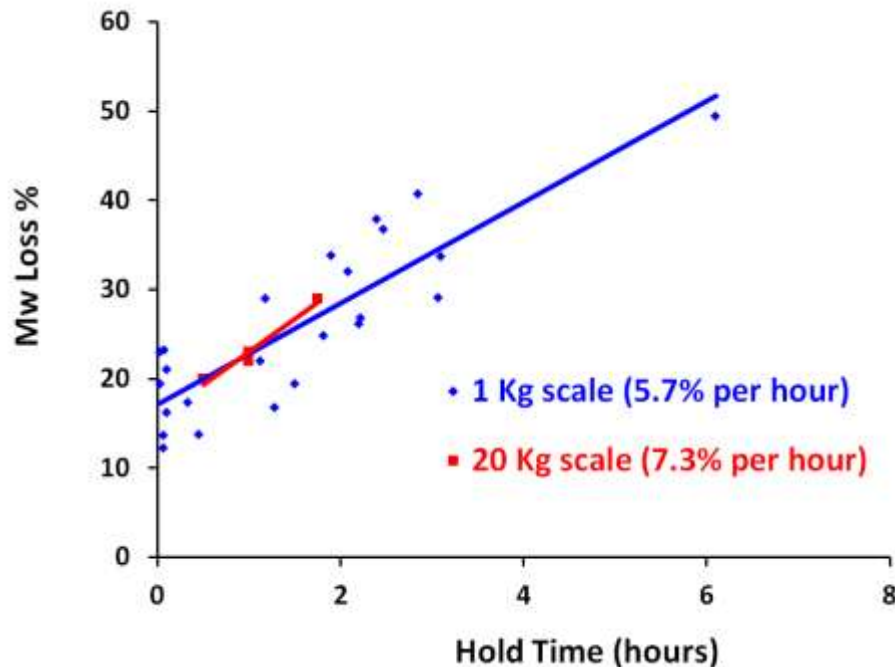


Sandostatin LAR depot
(octreotide acetate microsphere)

Challenges to Develop Generic Complex Formulations (Cont.)



- Impact of manufacturing conditions on complex inactive ingredients (complex reverse engineering)



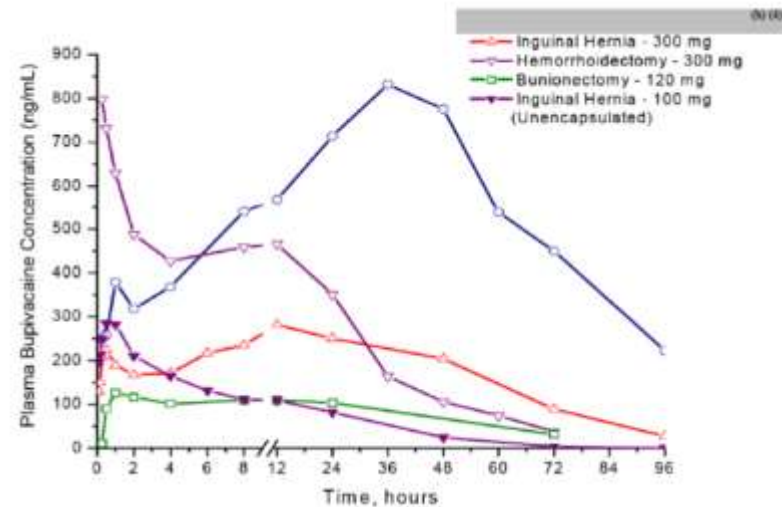
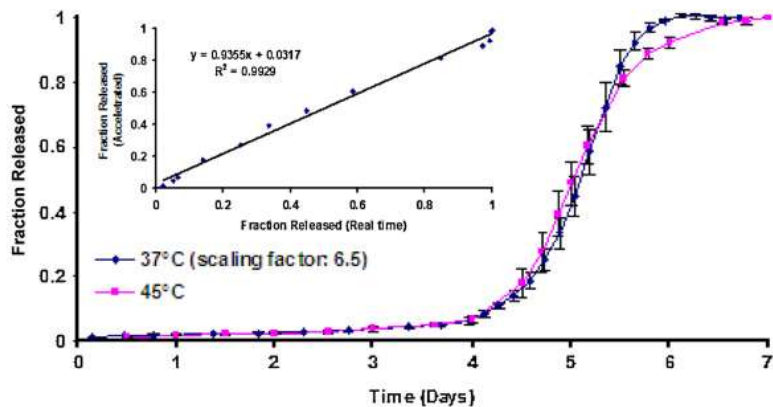
PLGA degradation during manufacturing of risperidone-PLGA microspheres

Alkermes, US 6,264,987 B1, 2001

Challenges to Develop Generic Complex Formulation (Cont.)



- Complicated multi-phasic in vitro drug release profiles and in vivo pharmacokinetics profiles



In vitro release profiles of Risperdal Consta 25 mg in 0.05 M PBS pH 7.4 at 37 °C and 45 °C

A. Rawat, U. Bhardwaj, D.J. Burgess. Comparison of in vitro–in vivo release of Risperdal® Consta® microspheres. (2012) Int J Pharm, 434(1-2), pp 115-121.

<http://dx.doi.org/10.1016/j.ijpharm.2012.05.006>

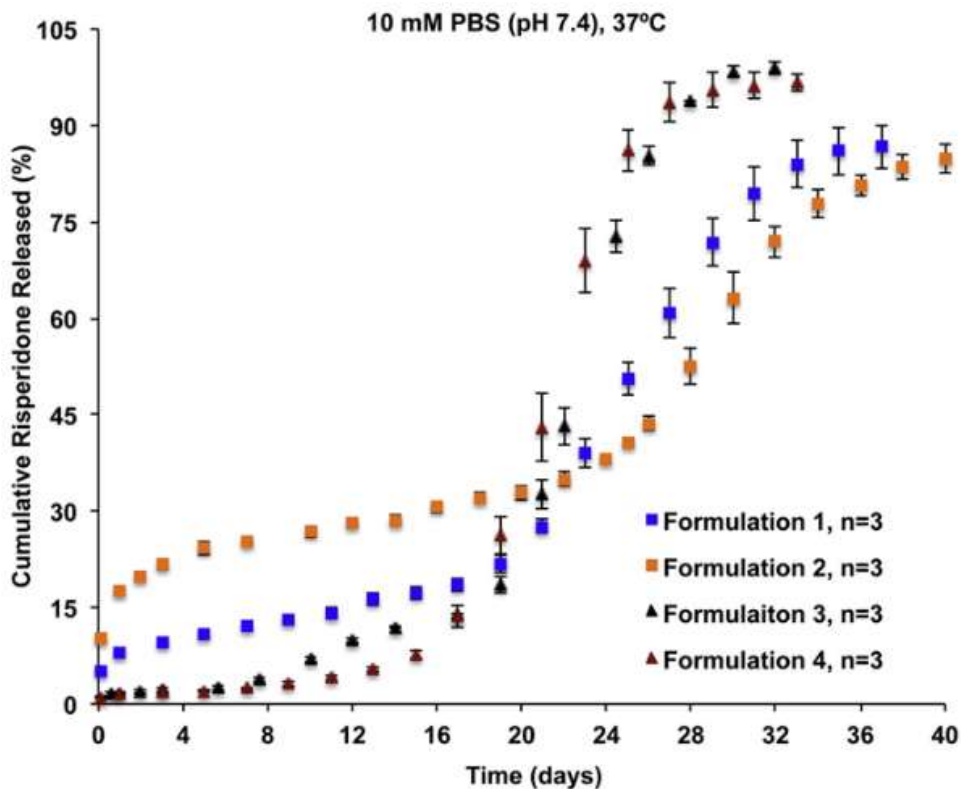
Mean plasma concentrations of bupivacaine after administration of single doses of Experal and Bupivacaine HCl (Un-encapsulated)

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022496Orig1s000ClinPharmR.pdf

Challenges to Develop Generic Complex Formulations (Cont.)



- In vitro and in vivo drug release profiles are sensitive to manufacturing differences



In vitro release profiles of the formulation composition equivalent risperidone microspheres with manufacturing differences obtained using USP apparatus 4 method at 37 °C in 10 mM PBS (pH 7.4)

J. Shen, S. Choi, W. Qu, Y. Wang, D.J. Burgess. In vitro-in vivo correlation of parenteral risperidone polymeric microspheres. (2015) Journal of Controlled Release. 218, pp. 2-12
<http://dx.doi.org/10.1016/j.jconrel.2015.09.051>

Challenges to Develop Generic Complex Formulations (Cont.)

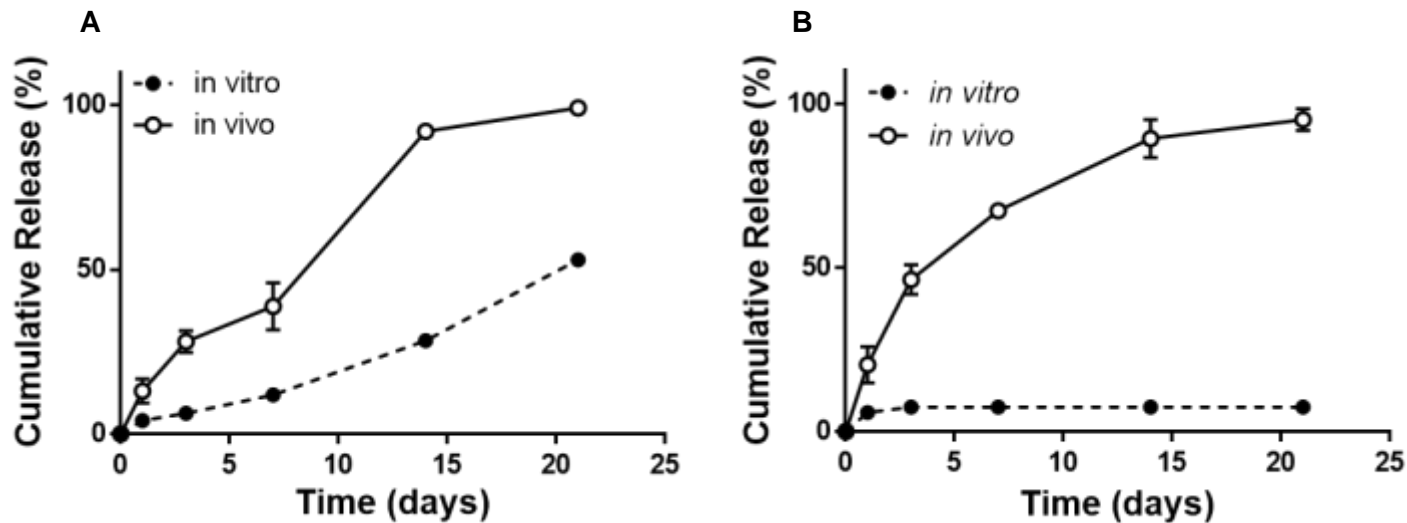


- Complex bioequivalence study design, such as combination of in vitro and in vivo studies, or partial AUCs
 - Risperidone intramuscular injectable microspheres
 - In vitro drug release + In vivo, two period, crossover steady state in patients
(<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201272.pdf>)
 - Doxorubicin hydrochloride injectable liposome
 - Single dose, two way crossover in vivo + liposome size distribution and additional characterization
(<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf>)

Challenges to Develop Generic Complex Formulations (Cont.)



- Lack of compendial in vitro drug release testing methods, in vitro in vivo correlation, and complete understanding of drug release mechanisms



Contrasting in vitro and in vivo release from triamcinolone acetonide_1 (A) and triamcinolone acetonide_2 (B) microspheres.

Doty, A. C., Hirota, K., Olsen, K. F., Sakamoto, N., Wang, Y., Choi, S., Qu, W., Schwendeman, A. S. and Schwendeman, S. P., Validation of a cage implant for assessing in vivo performance of long-acting release microspheres, *Biomaterials*, 109, 88-96 (2016). http://ac.els-cdn.com/S0142961216303787/1-s2.0-S0142961216303787-main.pdf?_tid=9e506490-9caa-11e7-b96e-00000aab0f26&acdnat=1505764407_767d6cbf46bd78acfbdd0a00c9a8c685

Challenges to Develop Generic Complex Formulations (Cont.)



- Duration of BE studies is much long compared to conventional dosage forms, which results in potential high drop out rate
- Different strengths may require separate BE studies due to difference in formulation composition and release characteristics

Role of GDUFA Research



The GDUFA research priorities identified from 2012-2017:

- New analytical tools for characterizing complex excipients and formulations
- Investigation of drug release mechanisms from various complex formulations and development of discriminatory in vitro drug release methods
- Development of IVIVC
- Investigation on how manufacturing affects the critical quality attributes of complex formulations
- Development of new methods to measure PK of complex formulations

Role of GDUFA Research (Cont.)



- GDUFA funded research on long acting drug products (15 grants/contracts):
 - 1) To obtain a better understanding of the impact of properties of PLGA polymers on product performance;
 - 2) To explore biorelevant IVIVCs for biodegradable injectable PLGA microspheres;
 - 3) To investigate dissolution methods for PLGA microsphere and implant drug products that can discriminate formulations with manufacturing differences;
 - 4) To investigate potential peptide PLGA interactions during product manufacturing and use;
 - 5) To develop modeling tools to facilitate development of generic LAI formulation development as well as bioequivalence guidances for LAI formulations;
 - 6) To develop discriminatory and predictive real time and accelerated drug release methods for IUS;
 - 7) To explore IVIVCs of long-acting periodontal drug products,
 - 8) To investigate release mechanisms of multivesicular liposomes.

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Session II Speakers



10:30 – 11:00 am

“Characterization of PLGA polymers”

Kinam Park, Ph.D

Showalter Distinguished Professor of Biomedical Engineering & Professor of Pharmaceutics
Purdue University

11:00 – 11:30 am

“In vitro release from complex parenterals and development of IVIVCs”

Diane. J. Burgess, Ph.D

Board of Trustees Distinguished Professor & Professor of Pharmaceutics
University of Connecticut

11:30 – 12:00 pm

“Mechanisms of release from PLGA microspheres”

Steven Schewendeman, PhD

Chair and Ara G. Paul Professor of Pharmaceutical Sciences & Professor of Biomedical Engineering
University of Michigan