In Vivo Relevance of Dissolution

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Disclaimer: This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Outline

- Background
- Investigation of drug dissolution failure and its vivo relevance
- Development of an innovative chewing method with in vivo relevance for abuse deterrent opioid products
- Conclusions

Industry's View on Dissolution

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Perspective

Industry's View on Using Quality Control, Biorelevant, and Clinically Relevant Dissolution Tests for Pharmaceutical Development, Registration, and Commercialization

Haiyan Grady [1,*], David Elder [2], Gregory K. Webster [3], Yun Mao [4], Yiqing Lin [5], Talia Flanagan [6], James Mann [6], Andy Blanchard [7], Michael J. Cohen [7], Judy Lin [8], Filippos Kesisoglou [4], Andre Hermans [4], Andreas Abend [4], Limin Zhang [9], David Curran [10]

- Quality control (QC) dissolution acceptable for routine batch release and stability studies
- Clinically relevant dissolution supporting biowaiver and other post-approval changes

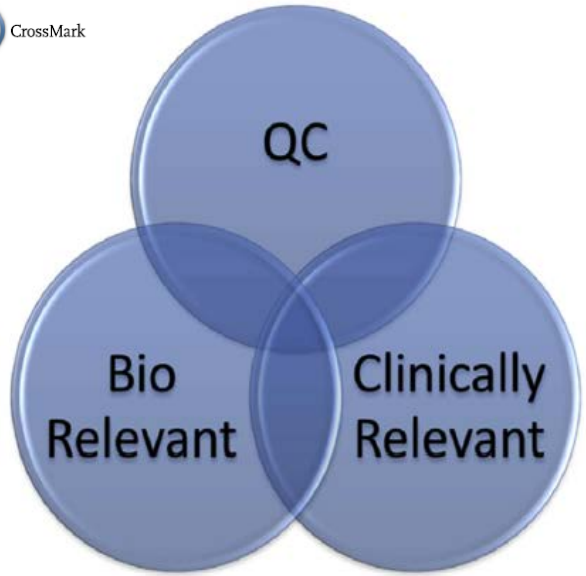


Figure 1. Illustration of the relationship between quality control, biorelevant, and clinically relevant dissolution methods (not to scale).

FDA's Guidance on Dissolution

- Guidance for Industry. Dissolution Testing of Immediate Release Solid Oral Dosage Forms. 1997

- Guidance for Industry. Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlation. 1997

- Draft Guidance for Industry. Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs. 2015

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064964.htm

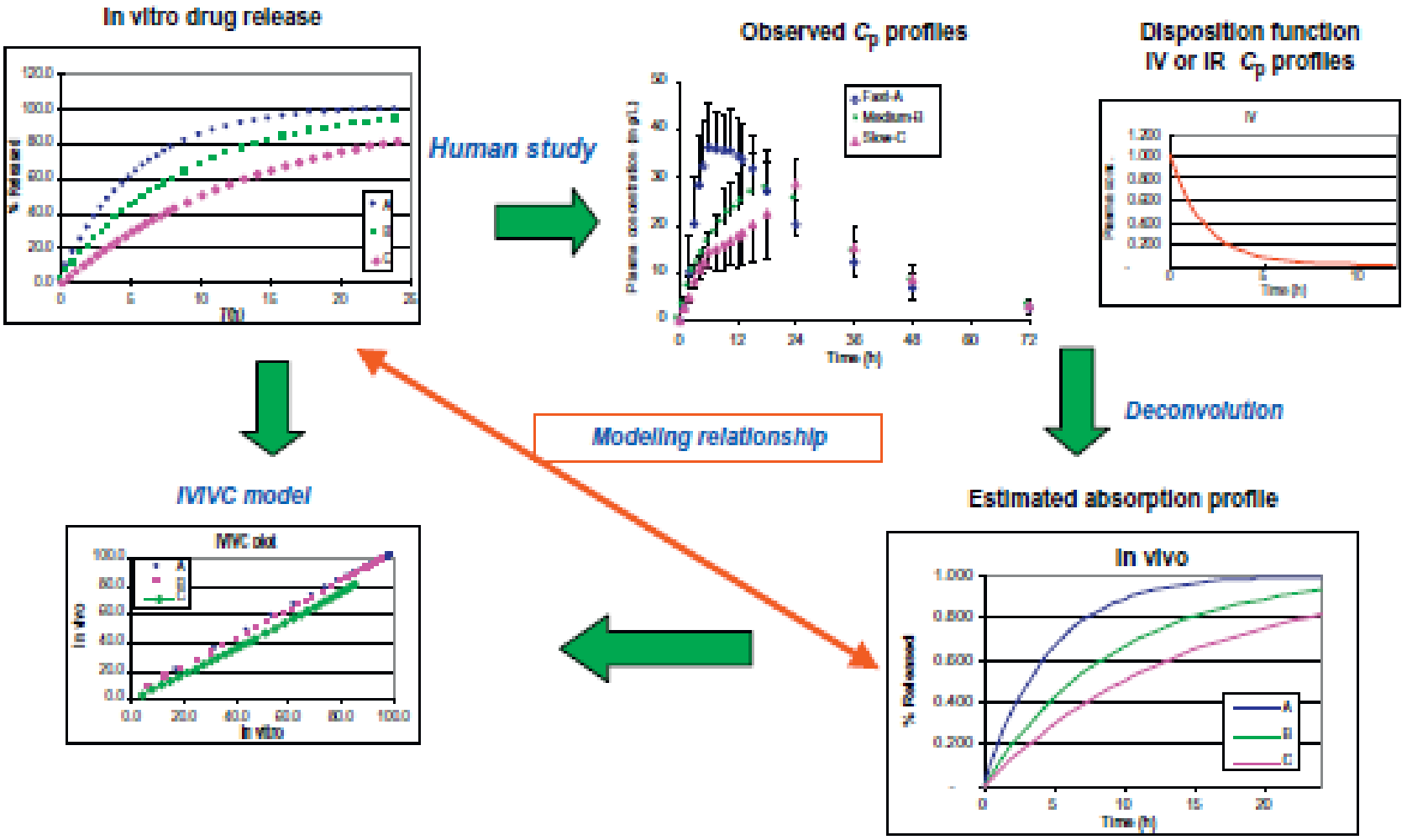
In Vitro/In Vivo Correlation (IVIVC)

- A predictive mathematical model describing the relationship between an in vitro property (usually the extent or rate of drug release) and a relevant in vivo response (e.g., plasma concentrations or amount of drug absorbed).

Level	In vitro	In vivo
A	Dissolution curve	Input (absorption) curves
B	Statistical moments: MDT	Statistical moments: MRT, MAT, etc
C	Disintegration time, Time to have 10, 50, 90% dissolved, Dissolution rate, Dissolution efficiency	C_{max}, T_{max}, K_a, Time to have 10, 50, 90% absorbed, AUC (total or cumulative),

Guidance for Industry. Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlation. 1997

Building a Level A IVIVC Model



Courtesy of Y. Qiu and J.Z. Duan. In Vitro/In Vivo Correlations: Fundamentals, Development Considerations, and Applications. Developing Solid Oral Dosage Forms. 2017

U.S. FOOD & DRUG ADMINISTRATION

Investigation of Drug Dissolution Failure and Its In Vivo Relevance

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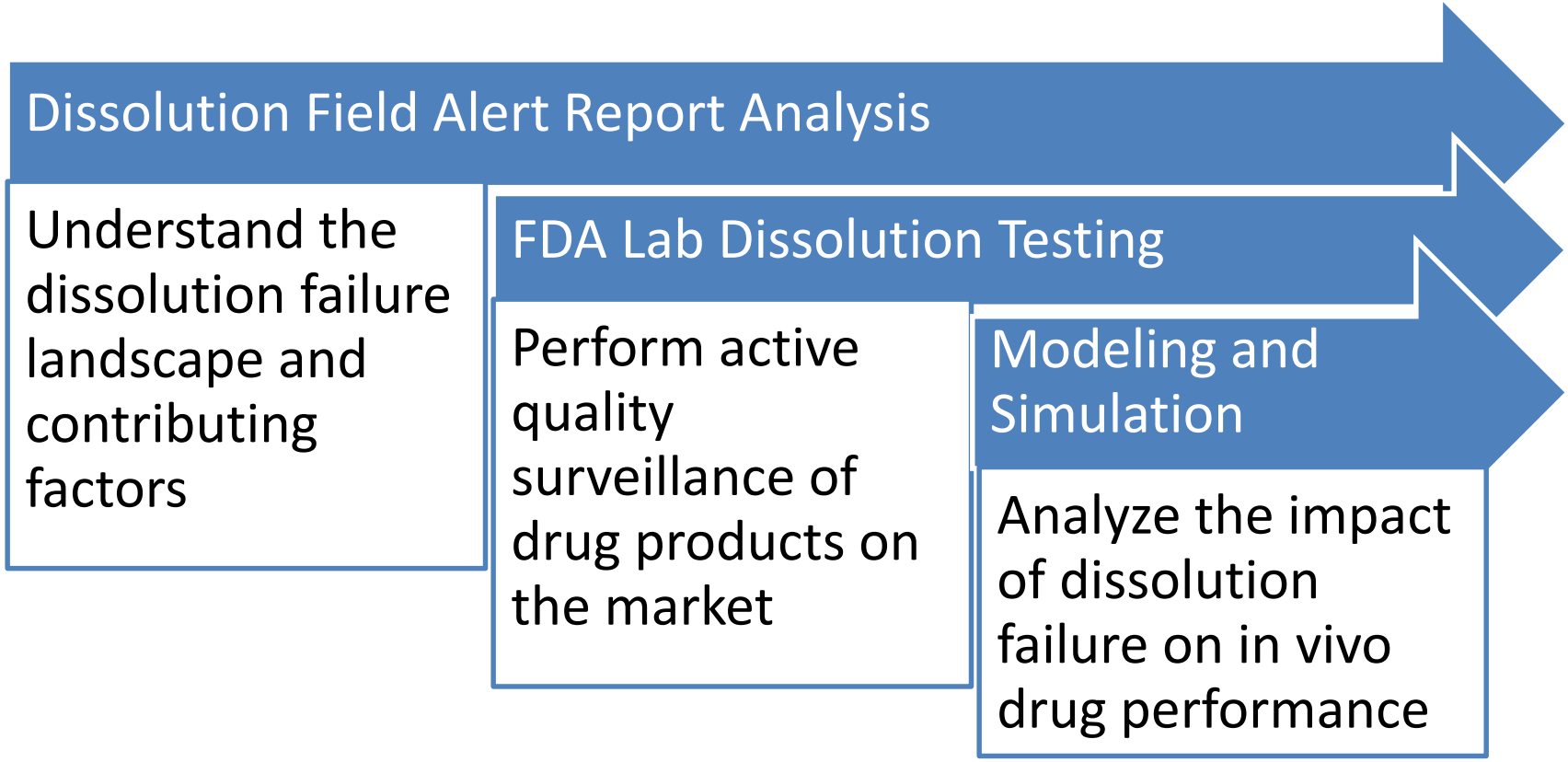
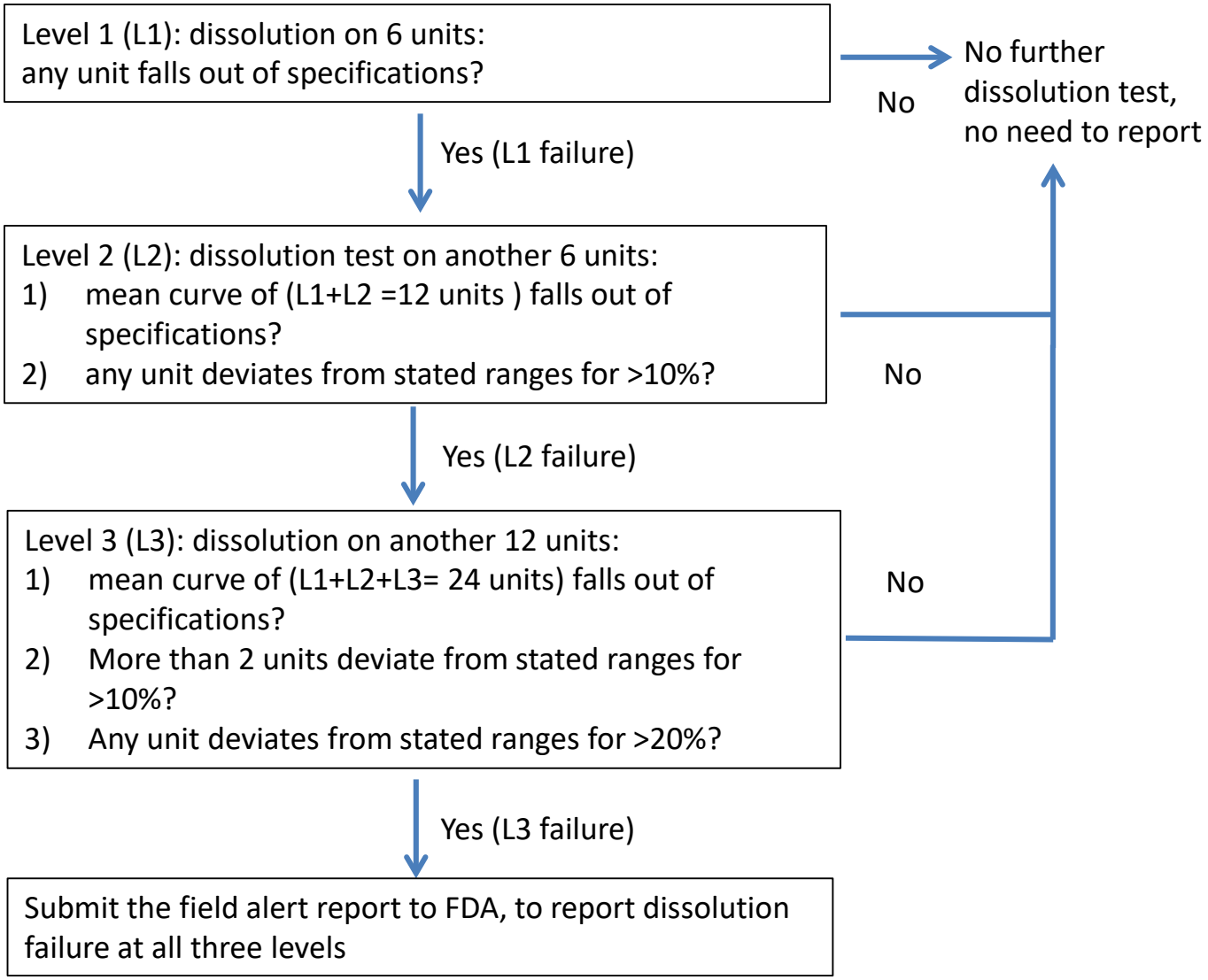


USP Dissolution Testing



http://www.pharmacopeia.cn/v29240/usp29nf24s0_c711.html

Dissolution Field Alert Reports Analysis

Data

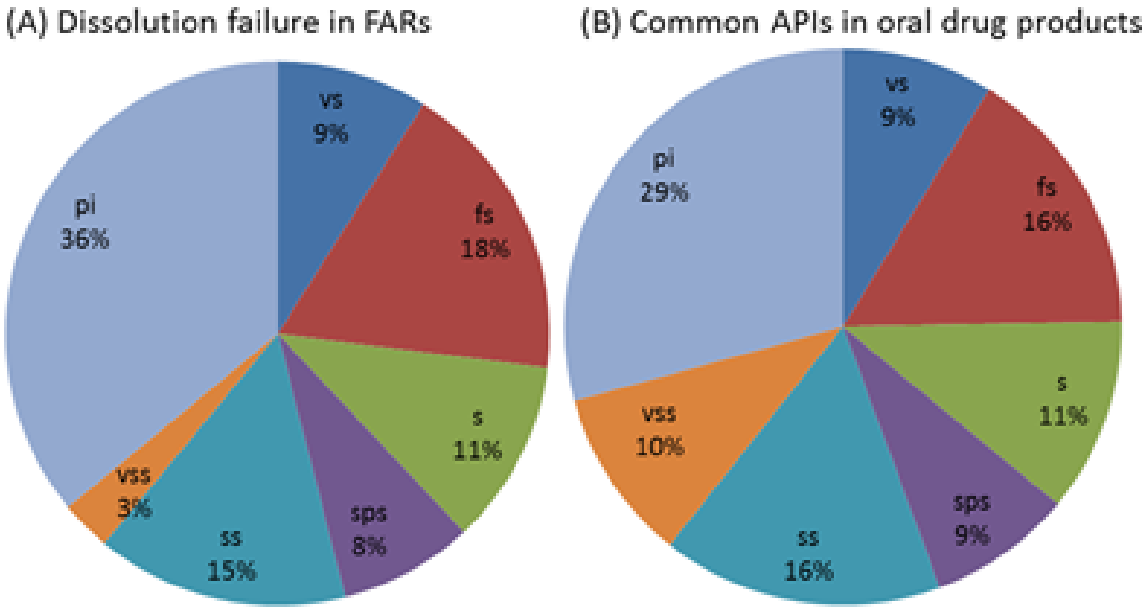
- 370 Entries of dissolution failure reports of solid oral dosage forms (Jan 2005 – Sep 2014)
- Drug name, solubility, new drug application (NDA) or abbreviated new drug application (ANDA), manufacturer, strengths, failure month, stability conditions, packaging, root cause determination, and proposed corrective actions

Analysis

- 7 solubility categories
- Immediate release (IR) vs Modified release (MR)
- ANDA vs. NDA

Sun et al. Dissolution failure of solid oral drug products in field alert reports. J Pharm Sci. 1302-1309. 2017

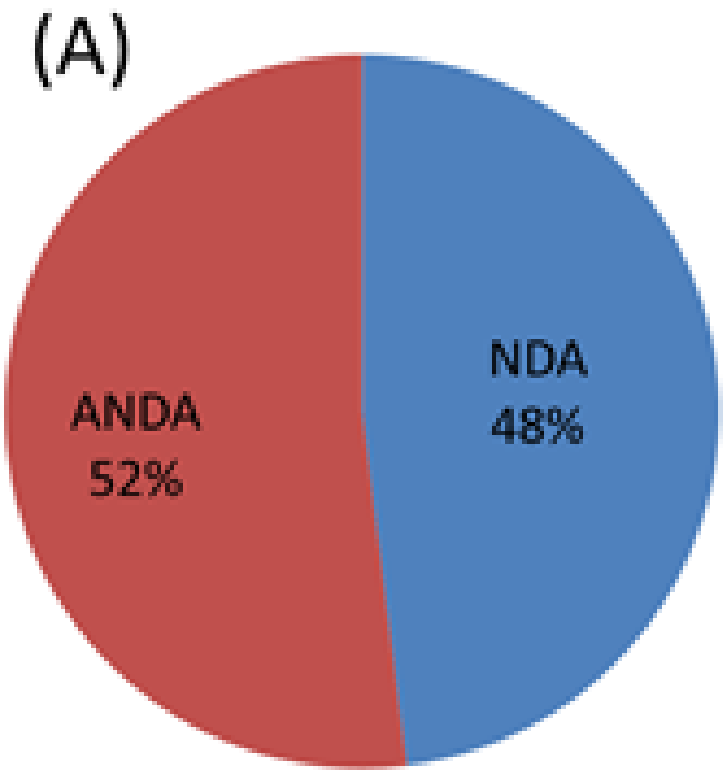
Distribution of Dissolution Failure in Different Solubility Categories

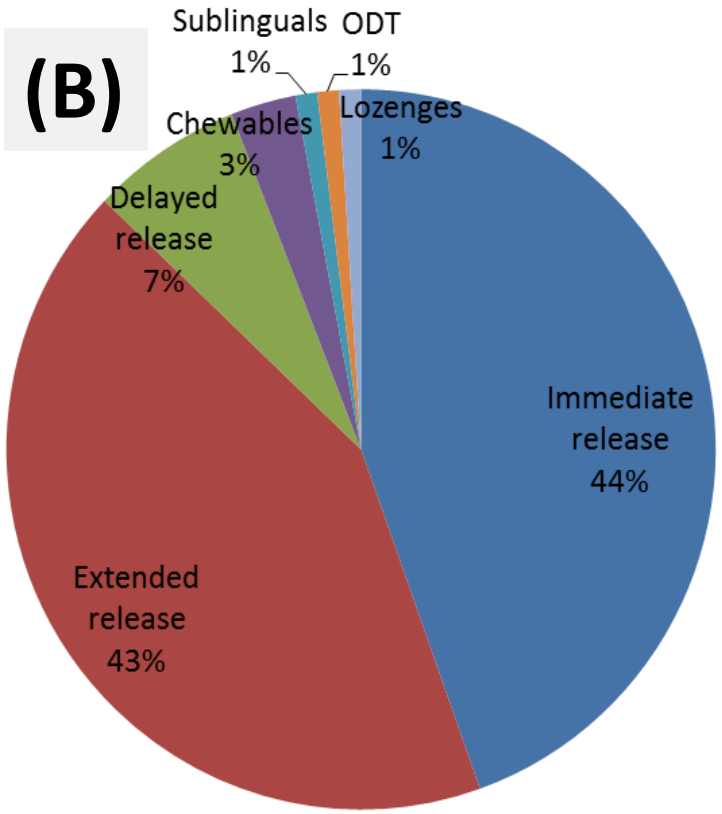


Solubility definition	Parts of solvent required for 1 part of solute	Solubility range (mg/mL)
Very soluble (vs)	< 1	> 1,000
Freely soluble (fs)	From 1 to 10	100 – 1,000
Soluble (s)	From 10 to 30	33 – 100
Sparingly soluble (sps)	From 30 to 100	10 – 33
Slightly soluble (ss)	From 100 to 1,000	1 – 10
Very slightly soluble (vss)	From 1,000 to 10,000	0.1 – 1
Practically insoluble (pi)	> 10,000	< 0.1

Sun et al. Dissolution failure of solid oral drug products in field alert reports. J Pharm Sci. 1302-1309. 2017

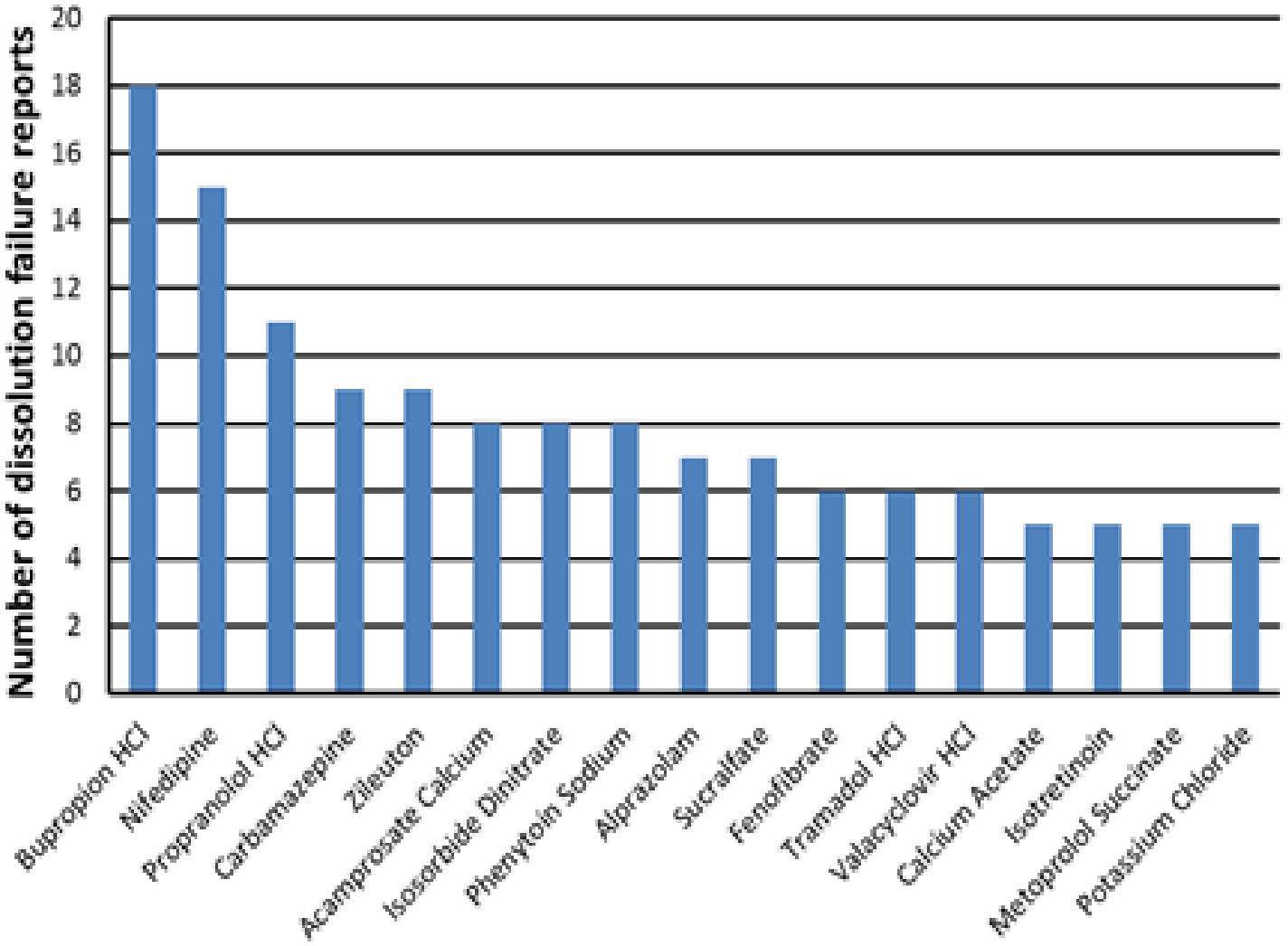
Distribution of Dissolution Failure in (A)NDAs and Different Solid Oral Dosage Forms





Sun et al. Dissolution failure of solid oral drug products in field alert reports. J Pharm Sci. 1302-1309. 2017

Drug Products with High Dissolution Failure

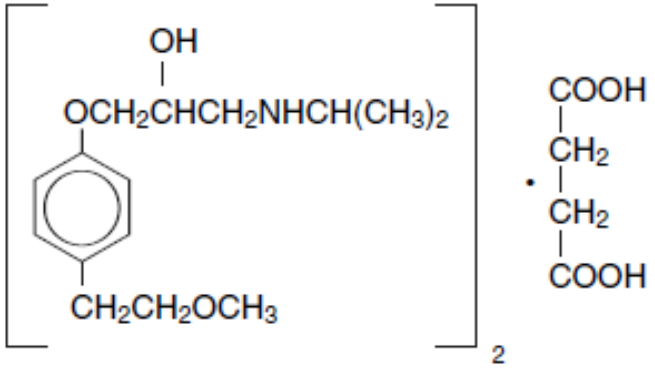


Model Drug Product Selection for Dissolution Testing

- Solubility category
- Release profile
- Number of NDA/ANDA (≥2)
- Current marketing status
- Field alert information

Dissolution test conducted in Office of Regulatory Affairs (ORA) and CDER Office of Pharmaceutical Quality/Office of Testing and Research Labs

Investigation of Metoprolol ER Tablet Dissolution Failure



Drug substance: Metoprolol succinate

Molecular weight: 652.8

Biopharmaceutical classification (BCS) 1 compound

TOPROL-XL® : 25, 50, 100, 200 mg
Once daily administration

Indications: Hypertension, Heart failure, Angina pectoris

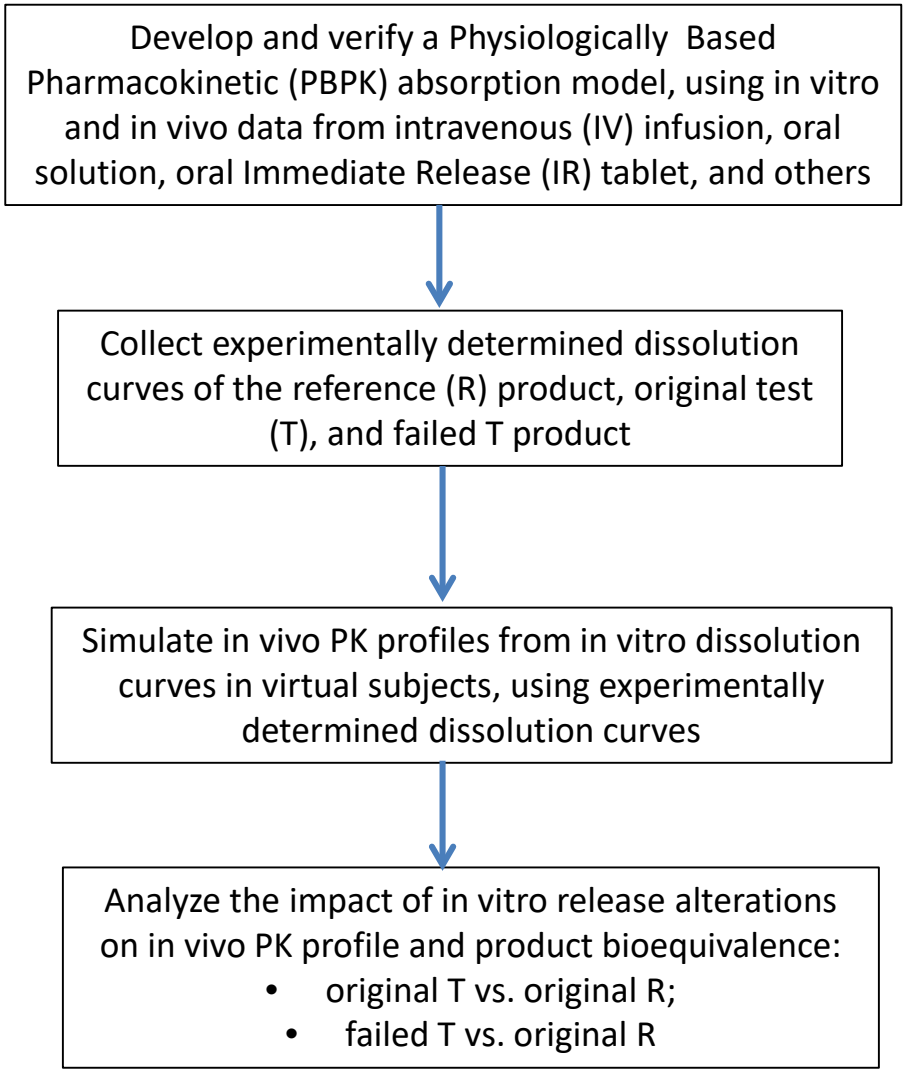
Mechanism of action: β_1-selective (cardioselective) adrenoceptor blocking agent

Absorption
Rapid and complete absorption

50% bioavailability after first pass, 65-70% relative bioavailability compared to IR tablets

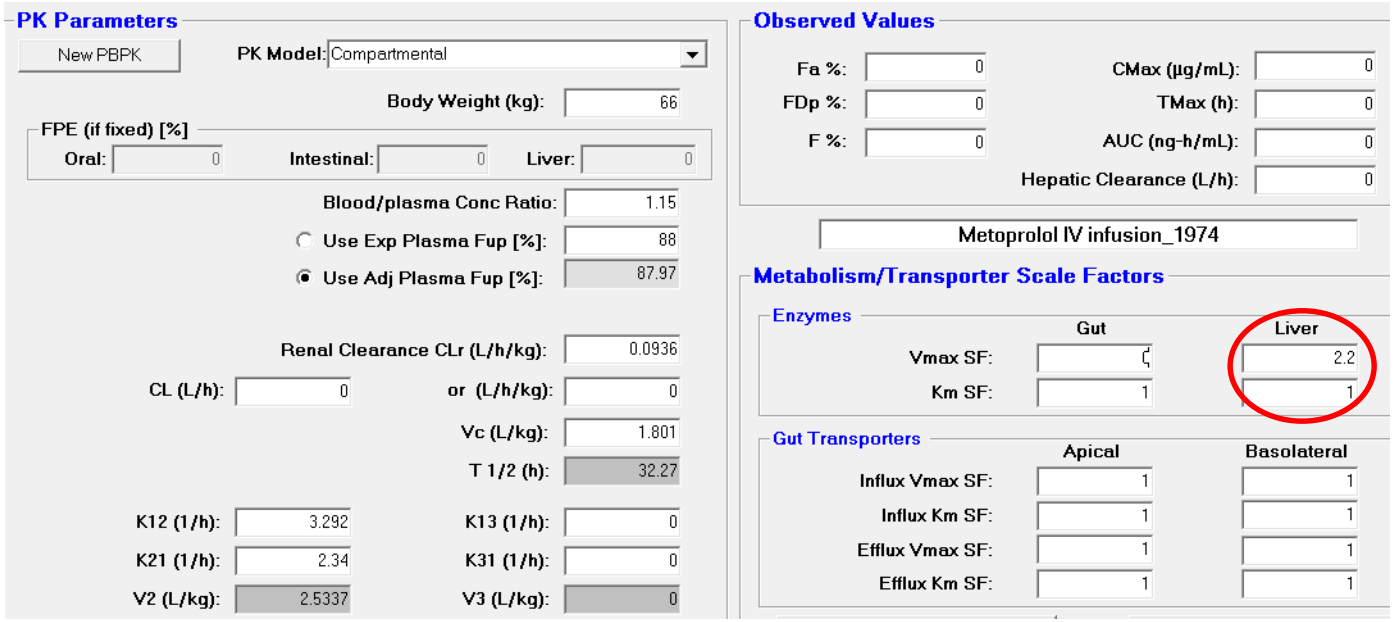
Food does not significantly affect bioavailability

Overall Strategy of Modeling and Simulation to Investigate the Impact of Dissolution Difference



Zhou T, Chow E, Wen H, Zhang X, Jiang W, Zhao L. Evaluation of the impact of in vitro release alterations on pharmacokinetics of metoprolol succinate extended-release (ER) tablets using the physiologically based pharmacokinetic (PBPK) absorption model. AAPS Annual Meeting, Denver CO (2016)

Metoprolol

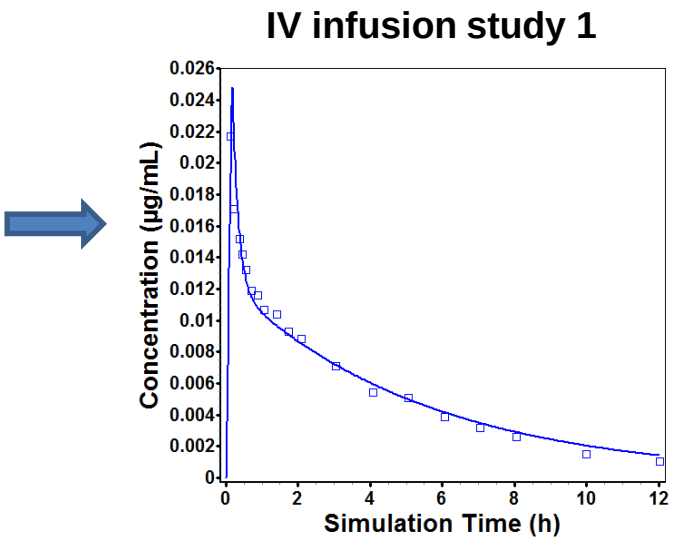


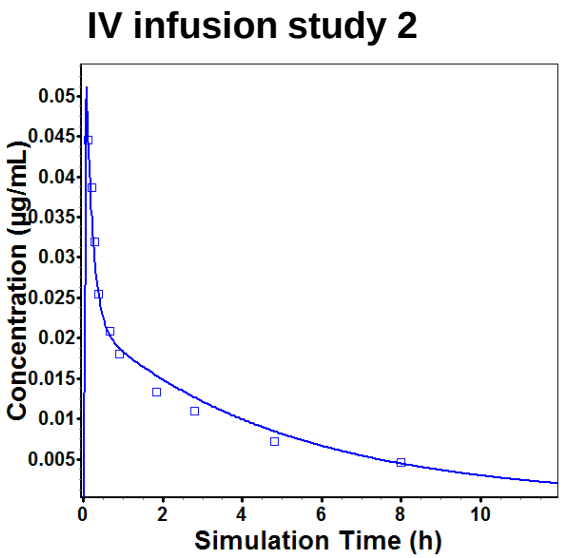
Input the collected and calculated parameters in the software

Total CL = $CL_h + CL_r$

Optimize the liver Vmax scaling factor

Liver Vmax
SF =2.2





Metoprolol Immediate Release (IR)

Optimization of the gut enzyme Vmax SF and ASFs of the small intestinal segments, using oral solution and IR tablet data.

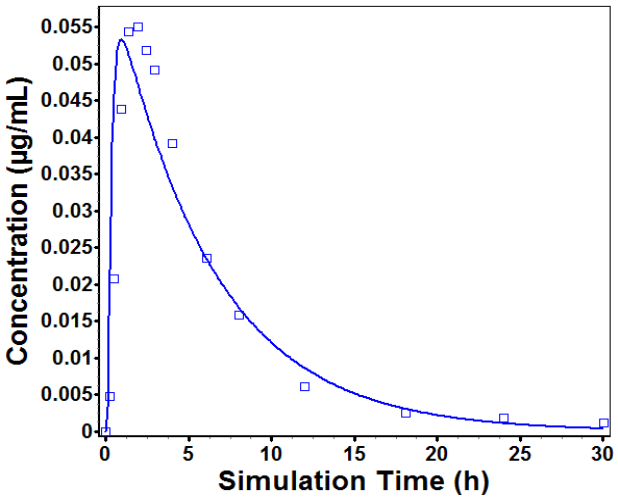
Compartment Data					
Compartment	Peff	ASF	pH	Transit Time (h)	Volume (mL)
Stomach	0	0.0	1.30	0.25	47.80
Duodenum	1.34	8.000	6.00	0.26	43.01
Jejunum 1	1.34	8.000	6.20	0.93	160.2
Jejunum 2	1.34	8.000	6.40	0.74	[illegible]
Ileum 1	1.34	8.000	6.60	0.58	97.98
Ileum 2	1.34	8.000	6.90	0.42	72.85
Ileum 3	1.34	8.000	7.40	0.29	51.63
Caecum	1.34	0.022	6.40	4.27	48.96
Asc Colon	1.34	0.049	6.80	12.82	51.90

In the "Gut Physiology" module, optimize ASFs of small intestinal segments

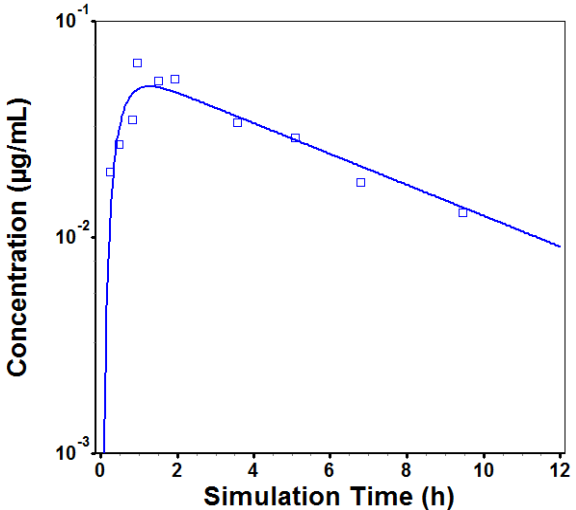
SF: Scaling factor
ASF: Absorption scaling factor

After optimization

Oral solution study



Oral IR tablet study



Metoprolol Extended Release (ER)

Compartment	Peff	ASF	pH	Transit Time (h)
Stomach	0	0.0	1.30	0.25
Duodenum	1.34	8.000	6.00	0.26
Jejunum 1	1.34	8.000	6.20	0.95
Jejunum 2	1.34	8.000	6.40	0.76
Ileum 1	1.34	8.000	6.60	0.59
Ileum 2	1.34	8.000	6.90	0.43
Ileum 3	1.34	8.000	7.40	0.31
Caecum	1.34	5.000	6.40	45.00
Asc Colon	1.34	5.000	6.80	45.00

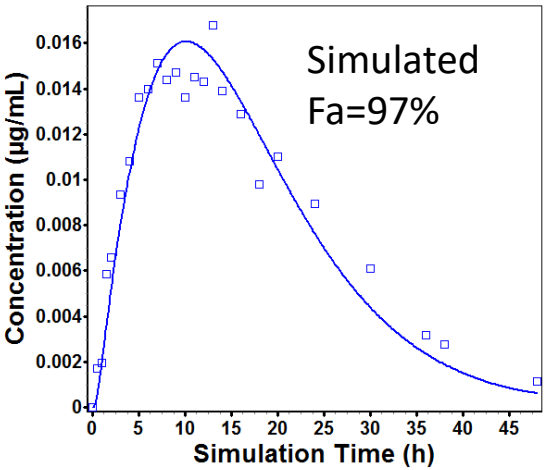
Optimize ASFs and transit times of large intestinal segments

Gamma scintigraphic image showing the GI position of ^{51}Cr labeled metoprolol ER tablet pellets 28 hours after administration

Sandberg A et al. *J Clin Pharmacol* 1990; 30(2): S2-S16.

Mayo Clinic researchers found in 27 healthy people:
"The average transit time through just the large intestine (colon) was 40 hours."
(http://www.mayoclinic.org/digestive-system/expert-answers/faq-20058340)

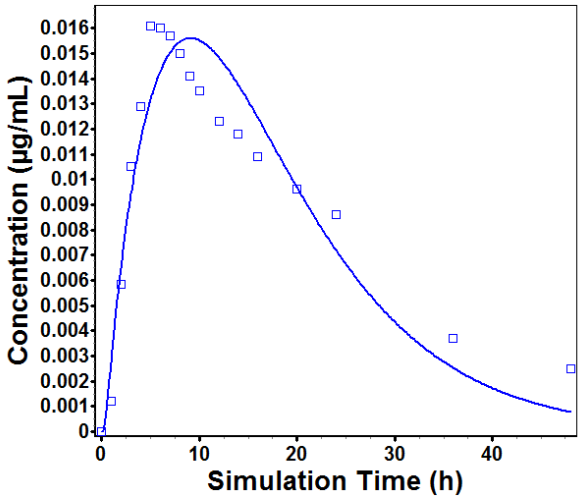
50 mg ER tablet RLD, fasting



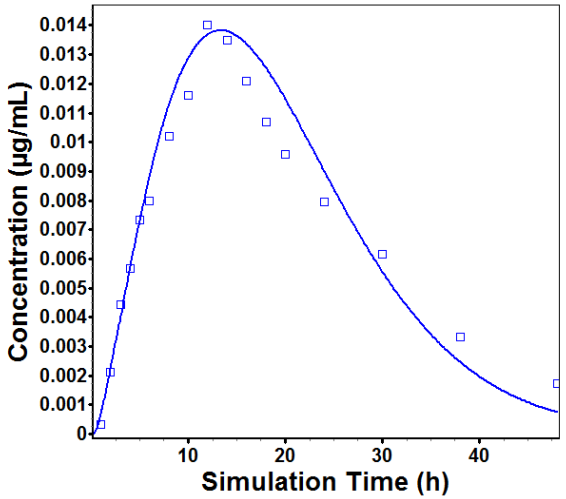
Metoprolol ER Tablet

Simulated vs. observed for ER tablets 50 mg RLD and Test products, fasting

ER tablet (Test)_50 mg fasting (example from 1 ANDA)

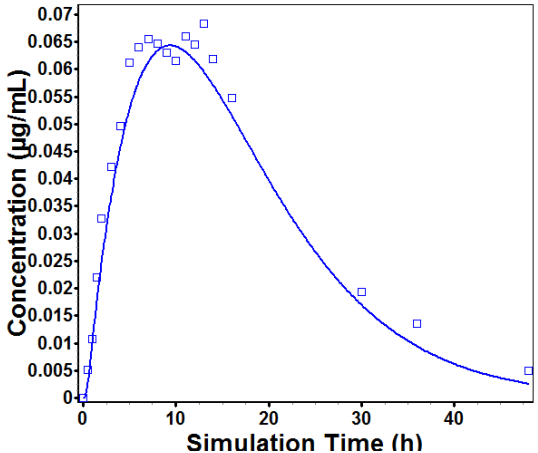


ER tablet (Test)_50 mg fasting (example from another ANDA)

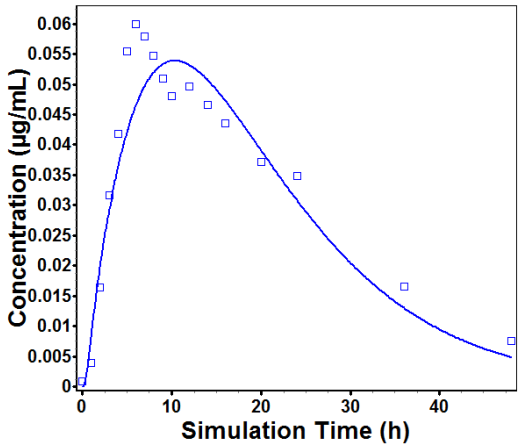


Verification of the model using 200 mg fasting data

ER tablet (RLD)_200 mg fasting (mean from 3 ANDAs)



ER tablet (Test)_200 mg fasting (example from 1 ANDA)

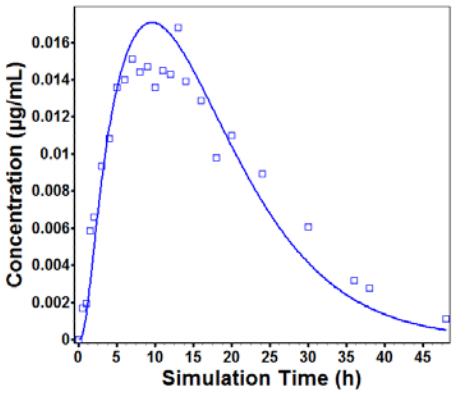


Verification of the Model

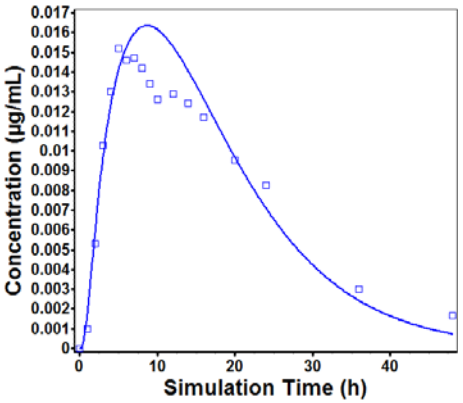
Verification of the model using fed data, 50 mg and 200 mg

50 mg fed

ER tablet (RLD)_(mean from 6 ANDAs)

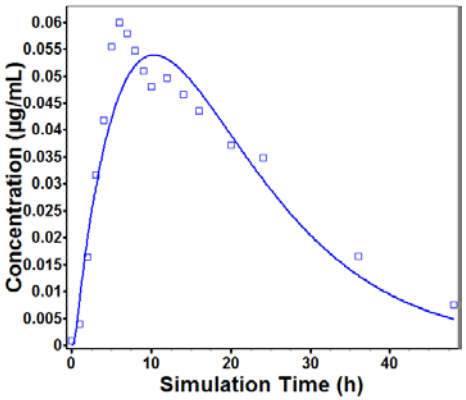


ER tablet (Test)_ (example from 1 ANDA)

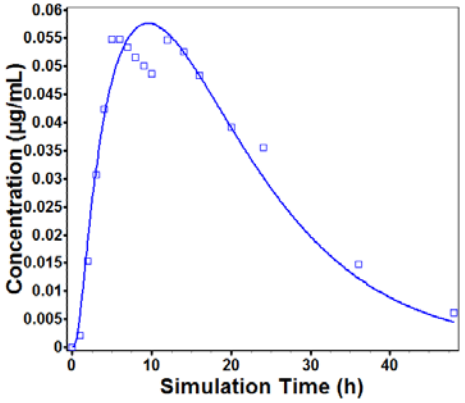


200 mg fed

ER tablet (RLD)_ (mean from 3 ANDAs)



ER tablet (Test)_ (example from 1 ANDA)

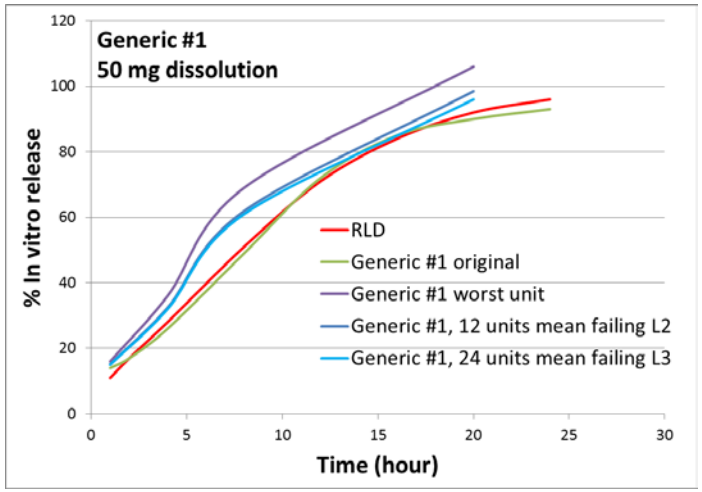


A mechanistic PBPK absorption model has been successfully developed and verified.

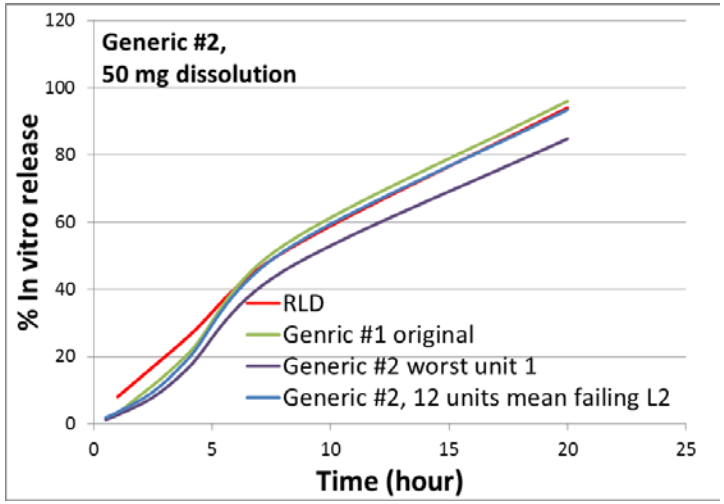
Metoprolol Dissolution

Dissolution failure data, experimentally determined

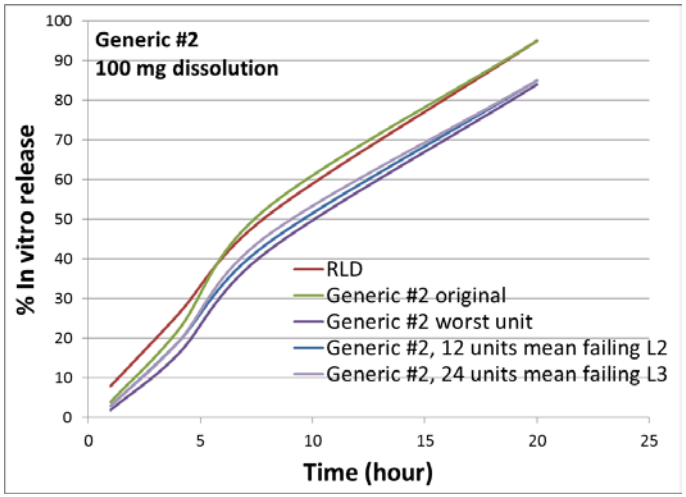
Generic #1 (50 mg)



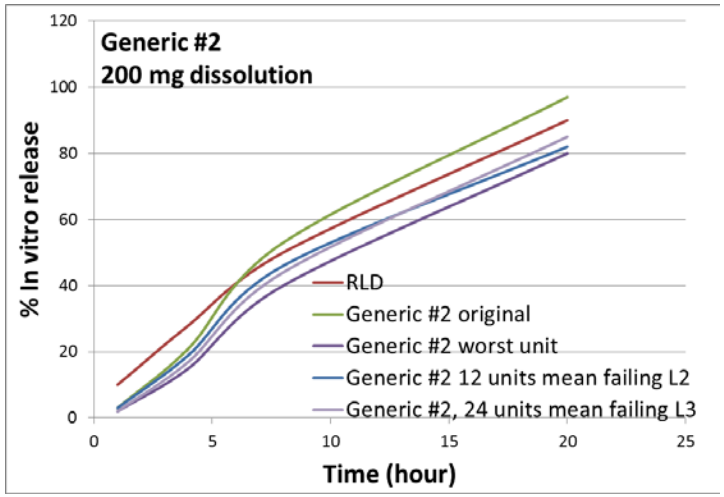
Generic #2 (50 mg)



Generic #2 (100 mg)



Generic #2 (200 mg)

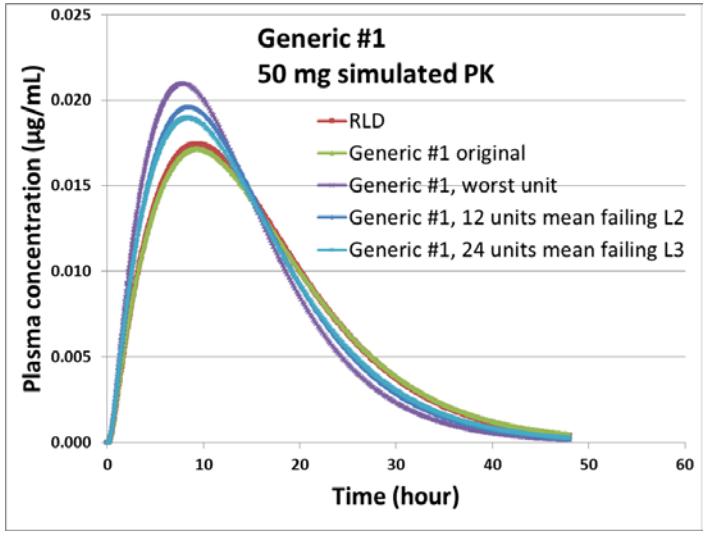


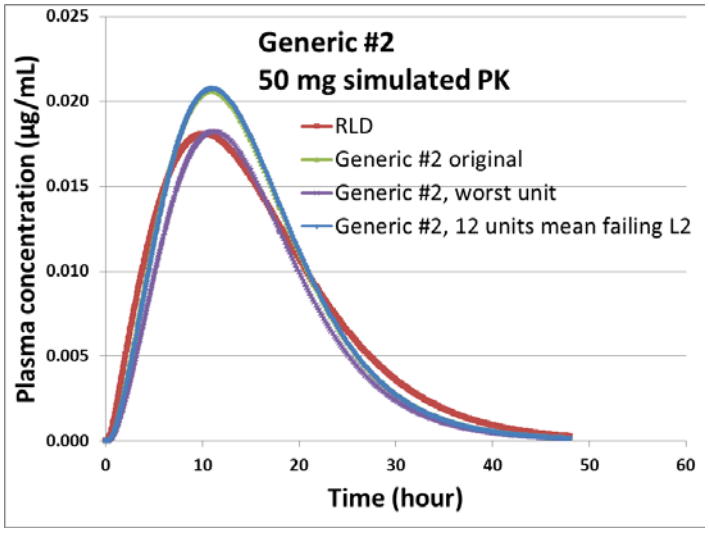
F2 Comparison of Dissolution Profiles

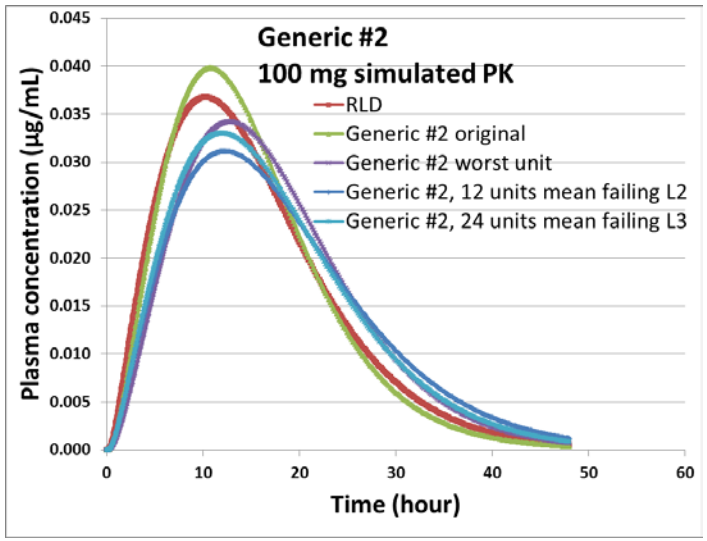
F2 values for the failed dissolution curves

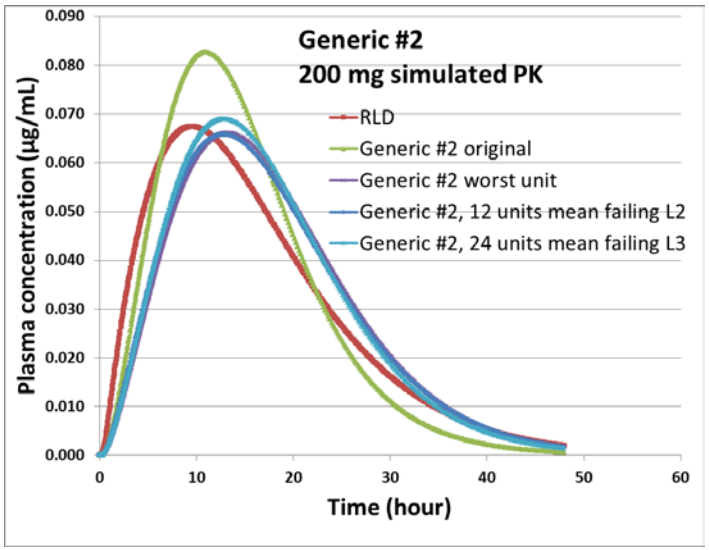
Drug product	Strength (mg)	Normal dissolution profile	Single unit out of stated range (Worst unit among 24 tested units)		12 units mean failing L2 (mean)		24 units mean failing L3 (mean)	
		Original T vs. Original R	Failed T vs. Original T	Failed T vs. Original R	Failed T vs. Original T	Failed T vs. Original R	Failed T vs. Original T	Failed T vs. Original R
Generic #1	50	80	43	45	54	57	56	61
Generic #2	50	70	57	56	85	69	L3 dissolution experiments not conducted for 50	
	100	75	54	52	58	56	60	57
	200	60	48	49	54	57	55	55

Simulation of the PK Profiles from Experimentally Determined Dissolution









Virtual Bioequivalence Study Simulation

			Original dissolution profile	Worst unit among 24 tested units	12 units mean failing L2	24 units mean failing L3
Drug product	Strength	PK metrics	Original T vs. Original R	Failed T vs. Original R	Failed T vs. Original R	Failed T vs. Original R
Generic #1	50 mg	C_{max}	1.05	1.27	1.14	1.12
		$AUC_{0\text{-}inf}$	1.00	1.00	1.00	1.00
		$AUC_{0\text{-}t}$	0.99	1.00	1.00	1.00
Generic #2	50 mg	C_{max}	1.12	0.98	1.10	L3 dissolution experiments not conducted for 50 mg
		$AUC_{0\text{-}inf}$	1.00	1.00	1.01	
		$AUC_{0\text{-}t}$	1.00	1.00	1.01	
	100 mg	C_{max}	1.11	0.91	0.92	0.96
		$AUC_{0\text{-}inf}$	1.00	1.00	0.99	0.99
		$AUC_{0\text{-}t}$	1.00	1.00	0.99	0.99
	200 mg	C_{max}	1.20	0.92	1.02	1.00
		$AUC_{0\text{-}inf}$	1.20	0.99	0.99	0.99
		$AUC_{0\text{-}t}$	1.20	0.99	0.99	0.99

T: test, R: RLD

Red highlighted numbers: 90% CI fall out of 80-125% BE range

U.S. FOOD & DRUG ADMINISTRATION

Development of an Innovative Chewing Method With In Vivo Relevance for Abuse Deterrent Opioid Products

Abuse Deterrent Opioid Product HYSINGLA

- Abuse deterrent opioid product development is one approach to fight the opioid epidemic

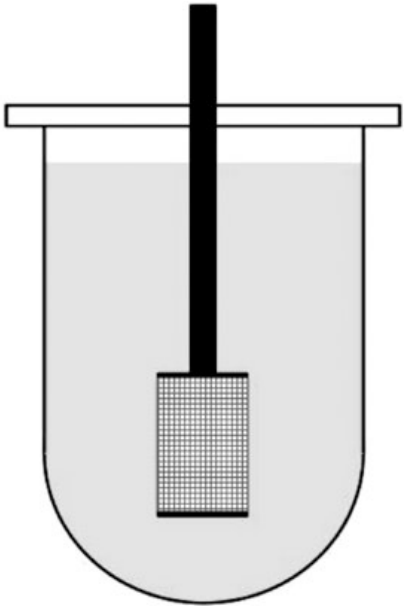
- HYSINGLA® (hydrocodone bitartrate ER tablet) was recognized by FDA as having abuse-deterrent properties that are expected to deter misuse and abuse via **chewing** in addition to intranasal/intravenous claims.

- HYSINGLA® Propriety technology

  - Combine increased tablet hardness with the formation of a viscous gel layer through the excipient polyethylene oxide, once the tablet comes into contact with water.

Dissolution Testing after Simulated Chewing

Investigate the effect of chewing time and gap size on drug release during simulated chewing experiments followed by dissolution testing



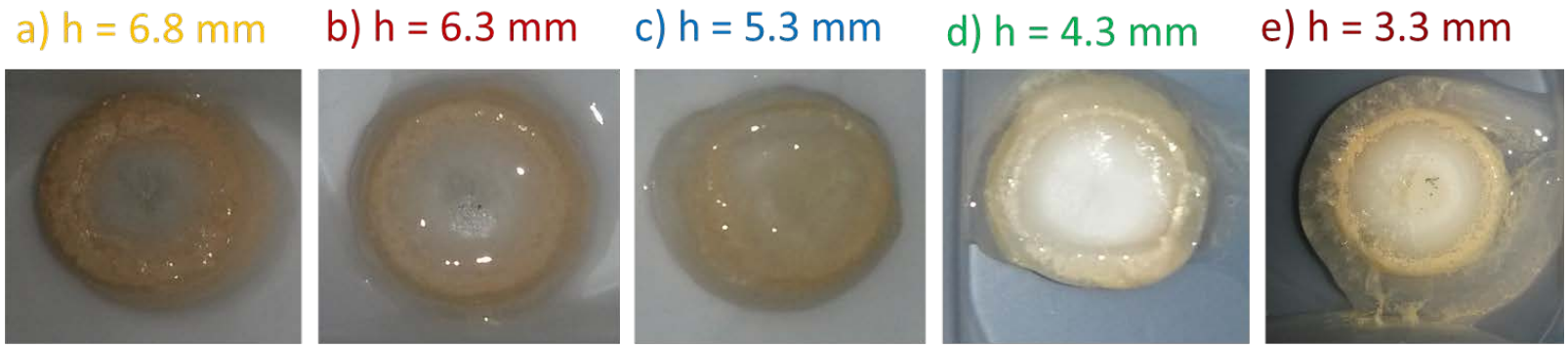
Chewing method
(Erweka DRT 3 chewing apparatus, Image courtesy of Erweka)

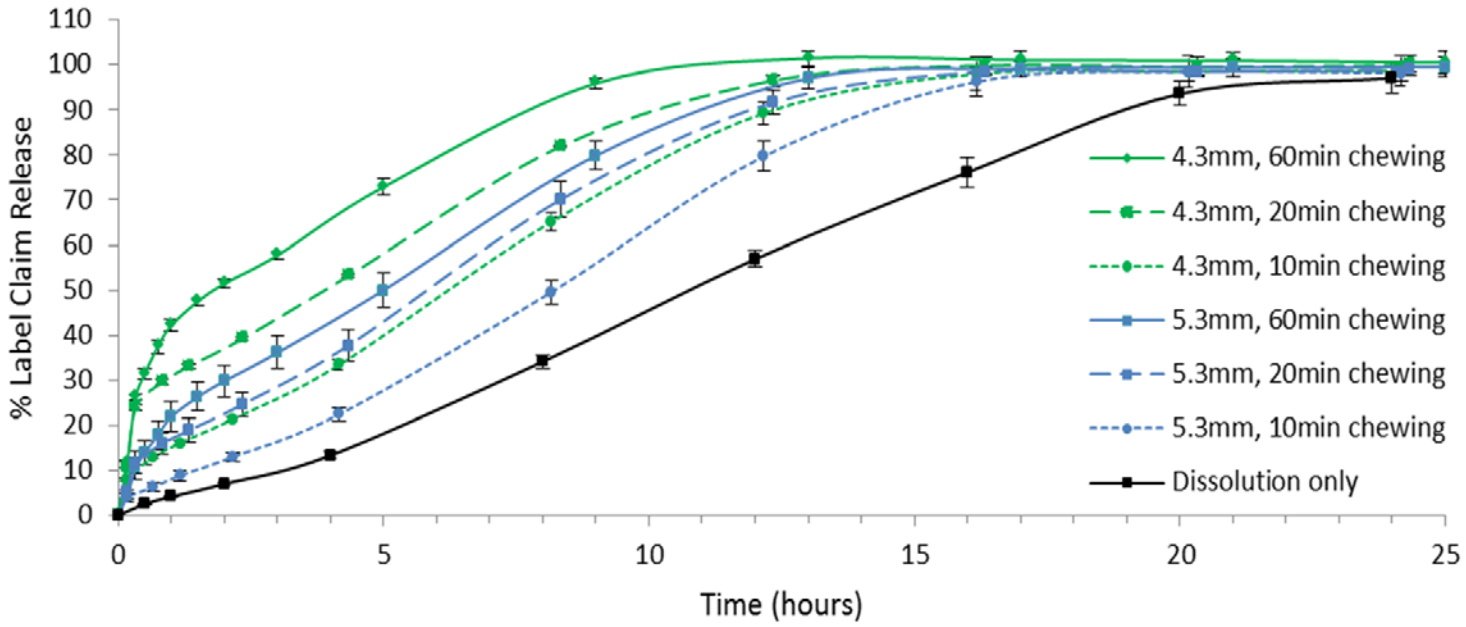
FDA recommended dissolution method

Basket, 100 rpm, 900 mL Simulated Gastric Fluid (SGF) pH 1.2

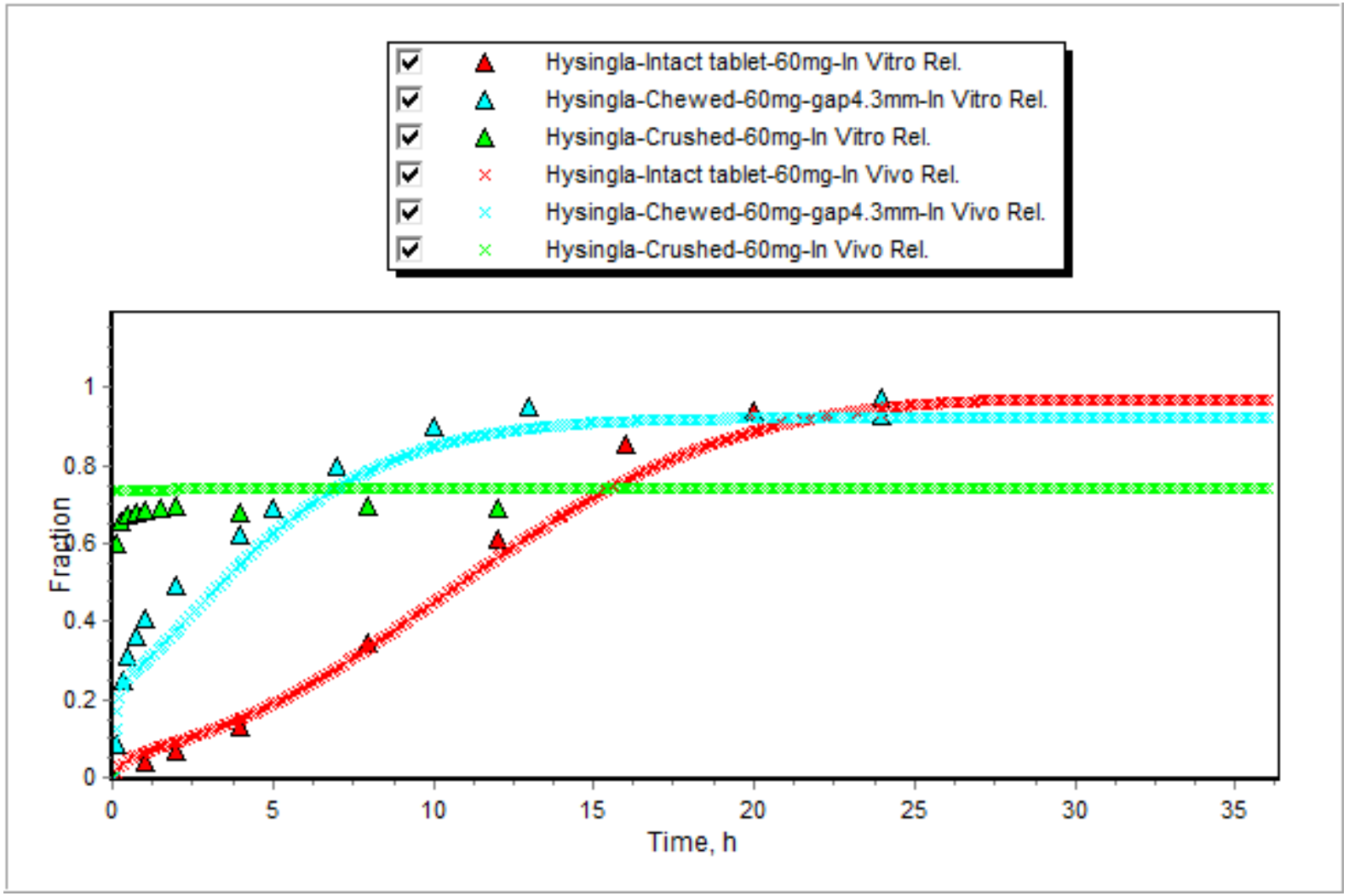
Externbrink A. et al. Development of in vitro chewing method for determining opioid availability following chewing of abuse-deterrant hydrocodone bitartrate ER tablet. Poster presentation at AAPS Annual Meeting and Exposition 2017, San Diego, CA, US

Drug Release After Simulated Chewing



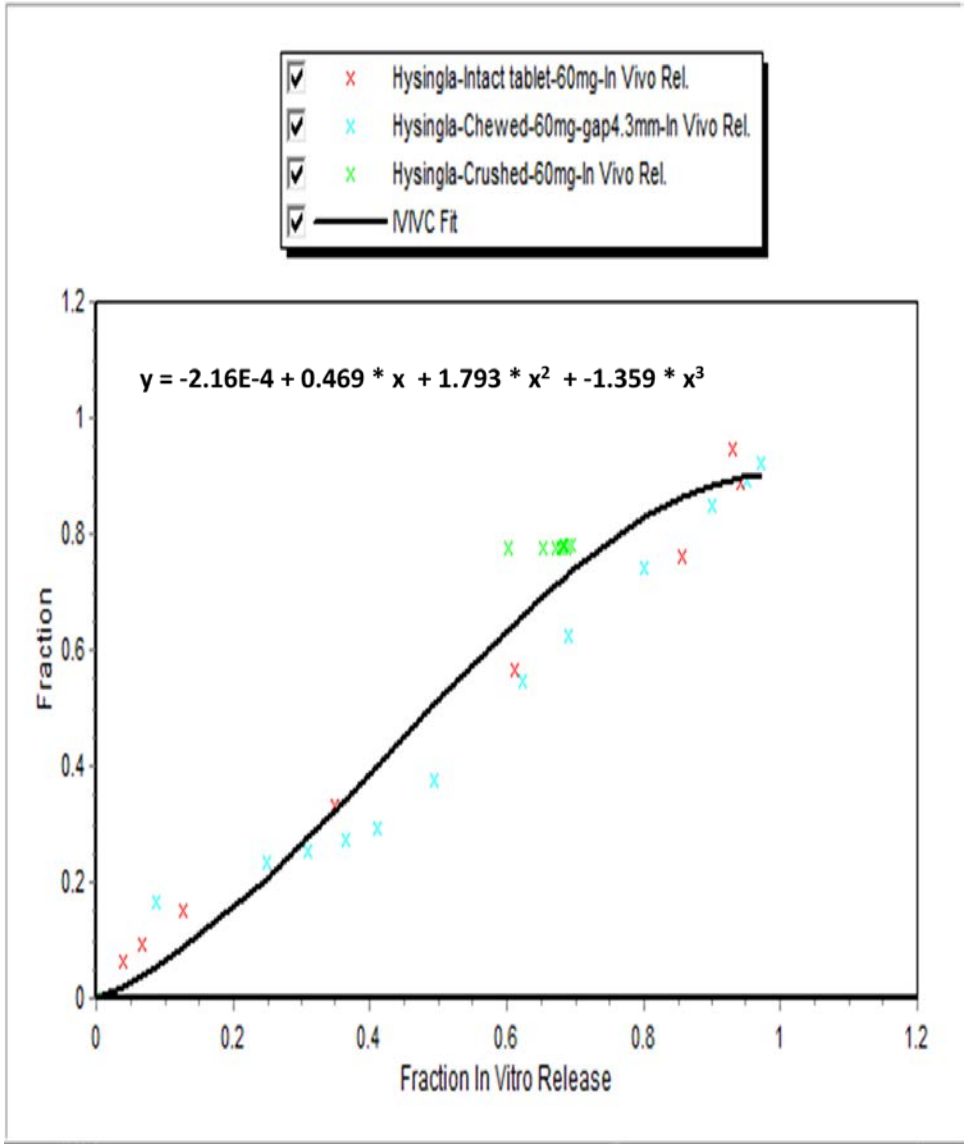


Observed In Vitro and PBPK Model Deconvoluted In Vivo Dissolution Profile Comparison



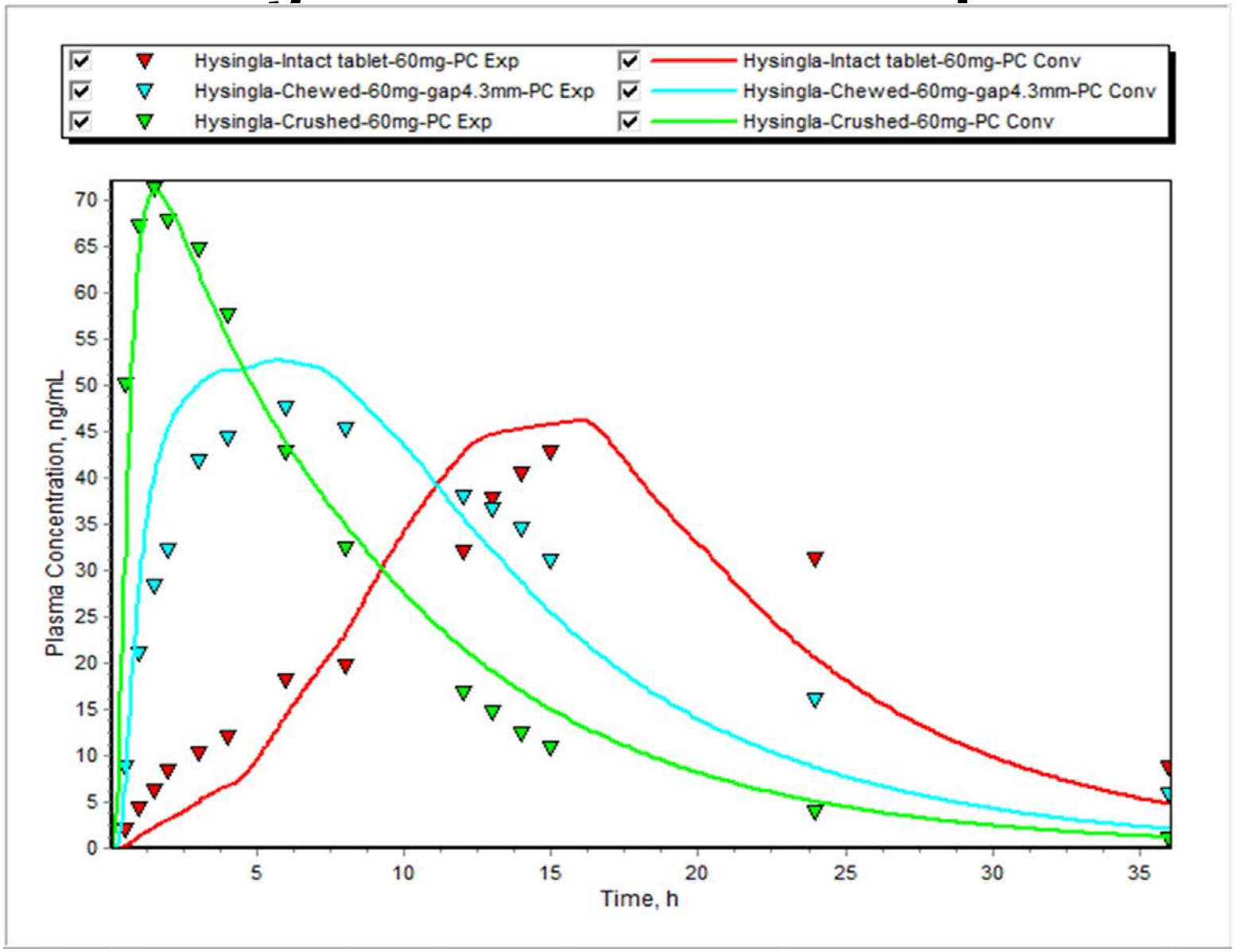
Sharan S. et al. Development of mechanistic in vitro in vivo correlation (IVIVC) of abuse-deterrent hydrocodone bitartrate ER tablet. Poster presentation at AAPS Annual Meeting and Exposition 2017, San Diego, CA, US

In Vitro In Vivo Correlation



Correlation Coefficient: 0.95

Observed and IVIVC Model Convoluted Plasma Drug Concentration Comparison



Prediction Error

	Cmax (ng/mL)			AUC (ng/mL*h)		
Drug Record	Obs.	Pred.	% Pred. Error	Obs.	Pred.	% Pred. Error
Hysingla-Intact tablet	42.58	46.18	-8.44	854.90	779.90	8.78
Hysingla-Chewed	47.53	52.62	-10.72	895.80	815.30	8.99
Hysingla-Crushed	71.11	70.88	0.32	633.00	680.20	-7.46
Mean Prediction Error			**6.48**			**8.42**

The percentage prediction error (% PE) for Cmax and AUC for intact, chewed and crushed forms of hydrocodone bitartrate ER tablet ranged between 0.3 to 10.7 % and 7.5 to 9 % respectively.

Development of an IVIVC model for hydrocodone bitartrate ER tablet is feasible

The newly developed in vitro method of artificial chewing can be helpful in predicting the in vivo behavior of hydrocodone bitartrate ER tablet after chewing followed by oral ingestion

Conclusions

- Dissolution testing is a useful surrogate for product quality and in vivo performance

- PBPK modeling can help quantify the in vivo risk of in vitro dissolution failure and potentially guide targeted surveillance activities

- An in vitro artificial chewing method was developed to predict the in vivo behavior of hydrocodone bitartrate ER tablet after chewing followed by oral ingestion

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U.S. FOOD & DRUG ADMINISTRATION

Thank you for your attention

Question?

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