Prediction of Human Pharmacokinetics Utilizing In Vitro Chewing Method and Physiologically Based Pharmacokinetic (PBPK) Analyses for Abuse-Deterrent Hydrocodone Bitartrate Extended Release Tablets

Workshop: Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls

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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

1. Background

   A. Opioid Crisis

   B. Abuse Deterrent Formulation (ADF)

2. Case Study: Hydrocodone Extended Release Tablets

   A. In Vivo Chewing and Dissolution method

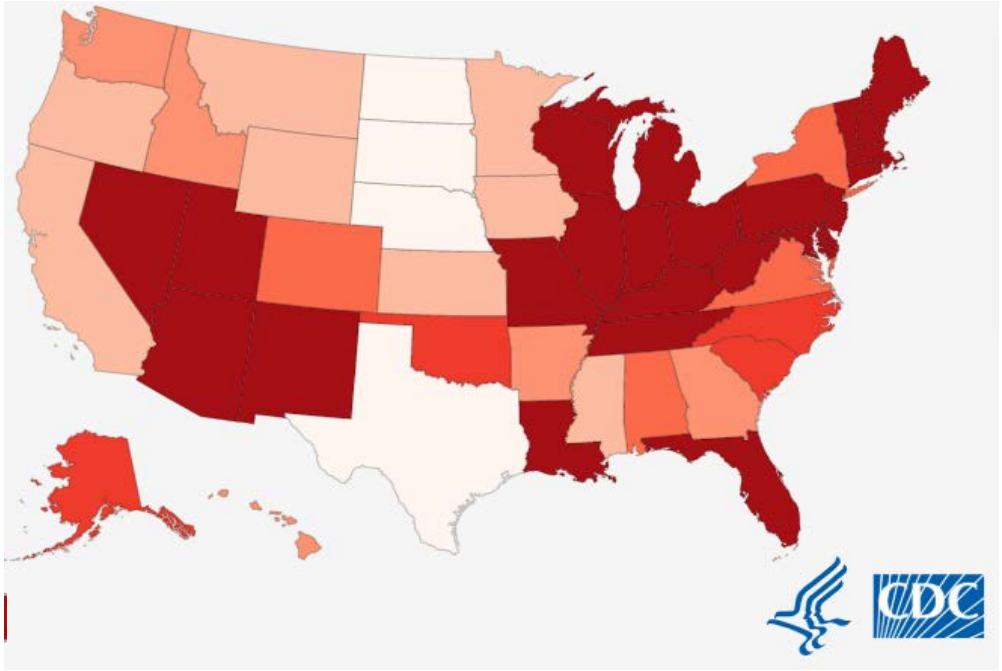
   B. Application of PBPK model to predict in vivo behavior of impact of different types of physical manipulation e.g., crushing, chewing or administered as intact tablet

   C. Product-Specific Guidance

   D. Potential Application

PBPK: Physiologically Based Pharmacokinetic

Drug Overdose Deaths by State, US 2017



- Drug overdose deaths continue to increase in the United States.
- From 1999 to 2017, more than 702,000 people have died from a drug overdose.
- Serious public health issue.

CDC: https://www.cdc.gov/drugoverdose/data/statedeaths/drug-overdose-death-2017.html

Abuse Deterrent Formulation

- Deterrence to abuse potential achieved via several mechanisms e.g., physical/chemical barrier, agonist/antagonist, prodrug etc.
- Development of abuse deterrent formulation is one of several steps to fight this epidemic.
- FDA approved several abuse deterrent opioid formulations.

Opioid ADF Approvals

NDA #	API	Trade Name	Approval date	Dosage Form	Labeling for Abuse Deterrence
022272	Oxycodone	**OxyContin**	04/05/10	ER Tablet	IV, IN
022321	Morphine/Naltrexone	**Embeda**	10/17/14	ER Capsule	IN, Oral (crushed)
206627	Hydrocodone	**Hysingla ER**	11/20/14	ER Tablet	IV, IN, Oral (chewed)
206544	Morphine	**MorphaBond ER**	10/02/15	ER Tablet	IV, IN
208090	Oxycodone	**Xtampza ER**	04/26/16	ER Capsule	IV, IN
208603	Morphine	**Arymo ER**	01/9/2017	ER Tablet	IV, IN
209777	Oxycodone	**RoxyBond**	04/20/2017	Tablet	IV, IN

IV: intravenous; IN: intranasal

https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/abuse-deterrent-opioid-analgesics

Abuse Deterrence via Chewing Route

- Chewing extended-release opioid tablets prior to ingestion is one of several methods used by drug abusers to disable the extended release mechanism of the tablet with the goal to achieve high opioid plasma concentrations (Cmax) within a short period of time (Tmax).

- Research project aimed at developing an *in-vitro* chewing method which can predict *in-vivo* opioid availability following chewing of opioid ER tablets.

Development of an In Vivo Predictive Method for Determining Opioid Availability Following Chewing of Solid Oral Opioid Drug Products

- **Objective:** To develop an in vitro chewing method which can predict in vivo opioid availability following chewing of opioid drug products.

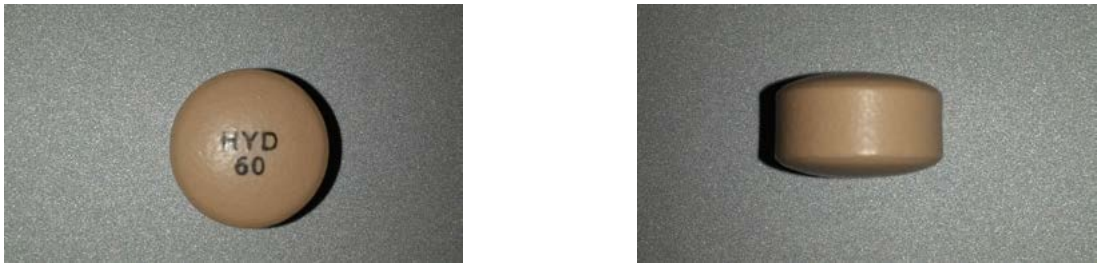
- **Impact:**

  – Can be a useful tool for generic/new ADF product development

  – Can be recommended in product-specific guidance as an in vitro option in lieu of currently recommended in vivo chewing studies if the in vitro method can be sufficiently validated.

Case study: Hydrocodone Bitartrate Extended Release Tablet

- Hydrocodone bitartrate ER tablet was recognized by FDA as having abuse-deterrent properties that are expected to deter misuse and abuse via chewing.

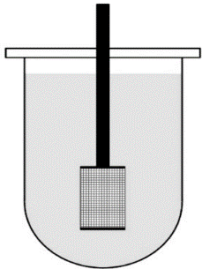


Hydrocodone bitartrate 60 mg ER Tablets

In Vitro Chewing Method for Determining Opioid Availability Following Chewing

Hydrocodone bitartrate ER tablets at 60 mg

Erweka DRT 3 chewing apparatus



FDA-recommended dissolution method (USP I, 100 rpm, 900 mL SGF pH 1.2)

- Tablets are placed between two chewing jaws
- Chewing process consists of up and down strokes of the lower jaw and a shearing (twisting) movement of the upper jaw

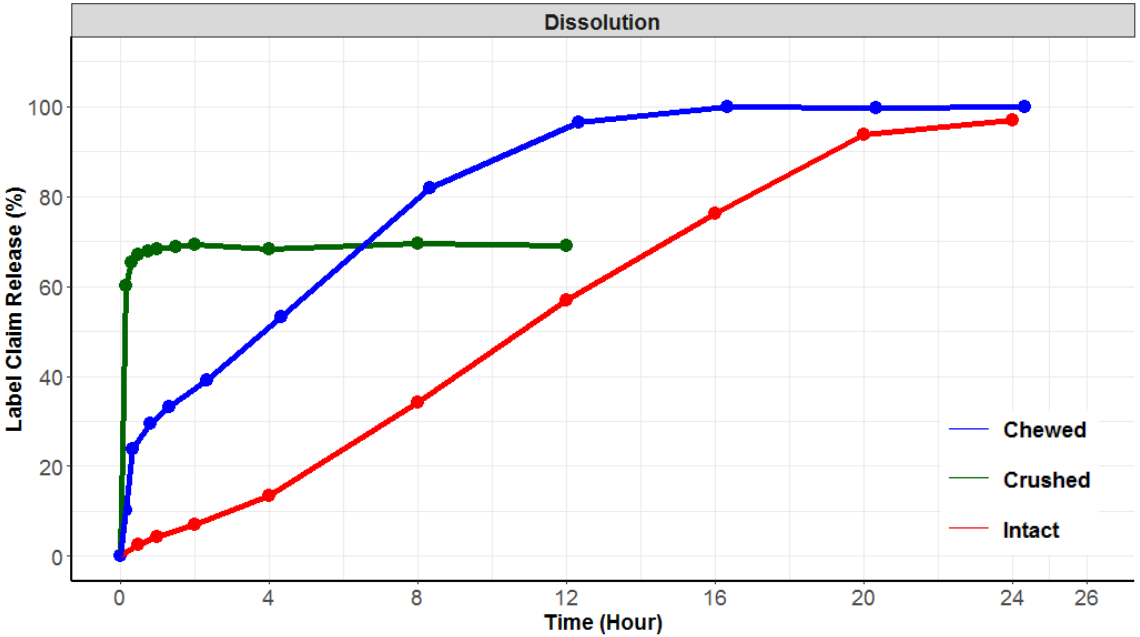
Test conditions	
Temperature	37±0.5°C
Chewing frequency (cycles/min)	40
Twisting angle (degree)	20º
Gap between the jaws (mm)	4.3 mm
Media type	Artificial saliva at pH 6.8
Media volume	40 mL
Pre-warming time	10 min
Chewing force	≈ 400 N

Externbrink, Sharan et al. 2019, International Journal of Pharmaceutics

FDA Dissolution Methods: https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm

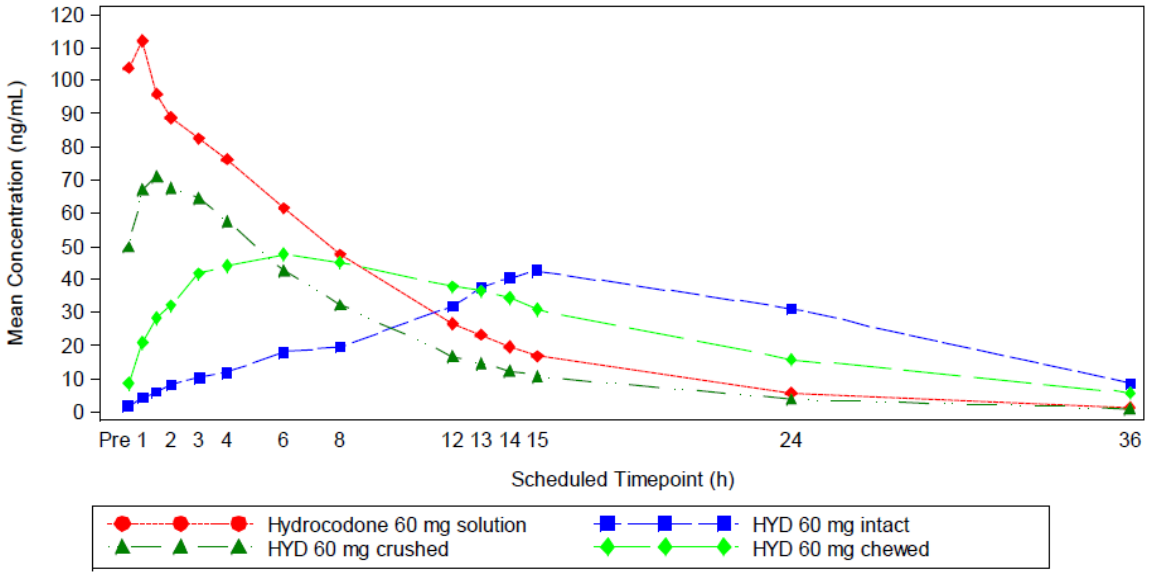
PSG: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Hydrocodone%20bitartrate_oral%20ER%20tablet_NDA%20206627_RV07-18.pdf

In Vitro Release Results



Externbrink, Sharan et al. 2019, International Journal of Pharmaceutics

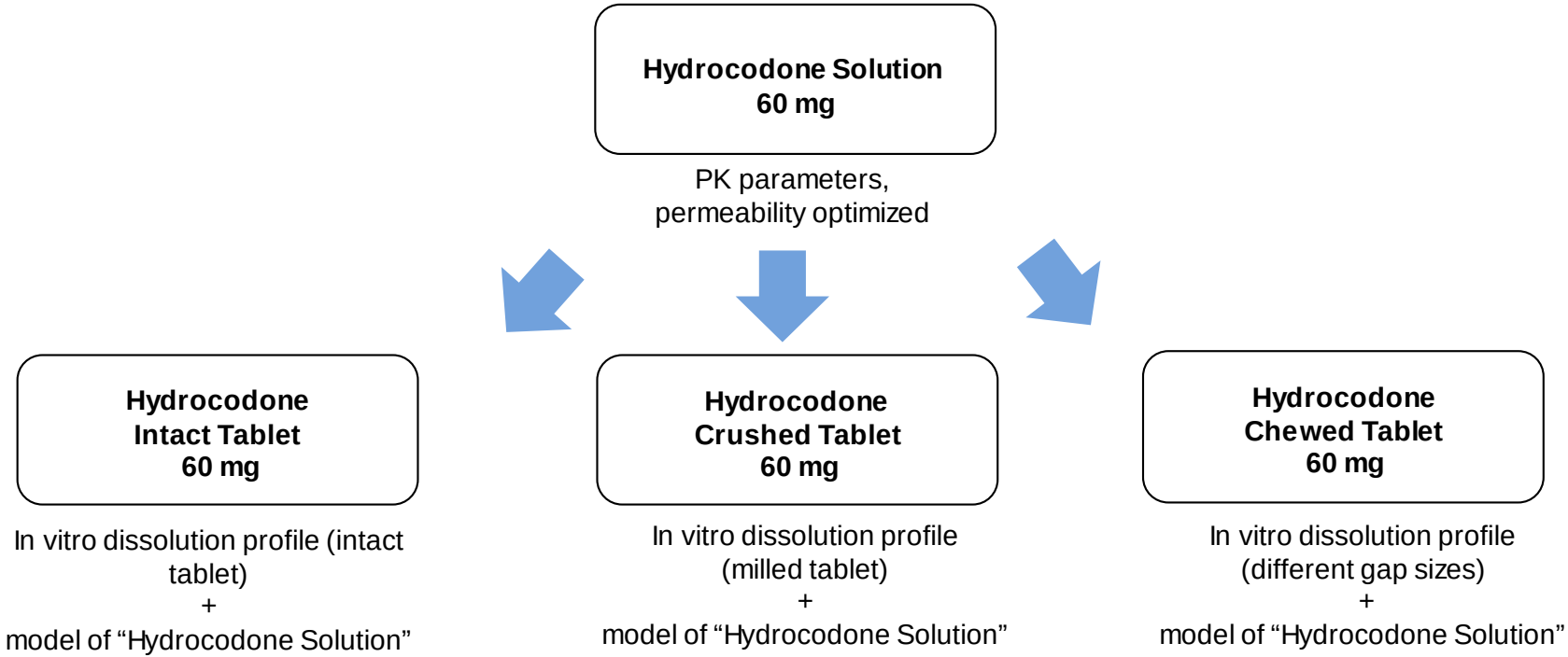
Mean Plasma Hydrocodone Concentration After Administration of Hydrocodone Solution and Intact, Crushed, Chewed and Intact form of Hydrocodone Bitartrate ER Tablet



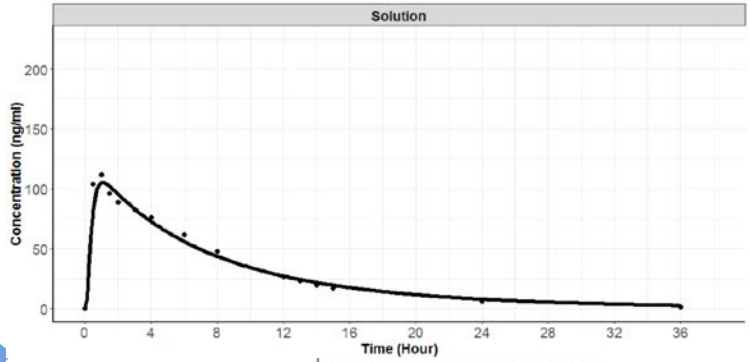
- Single-center, double-blind, randomized, crossover study
- Non-dependent recreational drug users with moderate experience with opioids

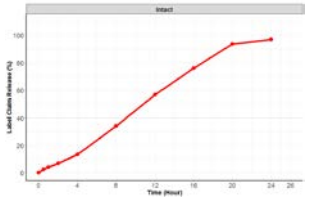
Clinical Pharmacology Review; NDA-206627 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206627Orig1s000ClinPharmR.pdf

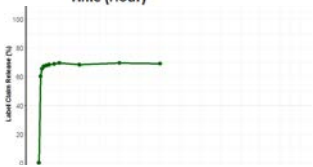
Model Development and Validation

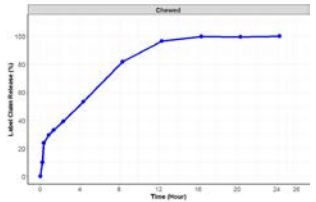


Model Development and Validation



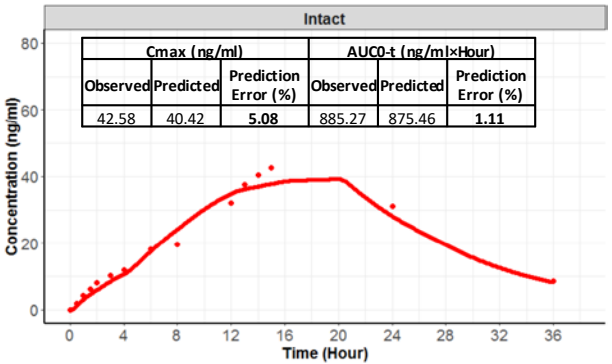






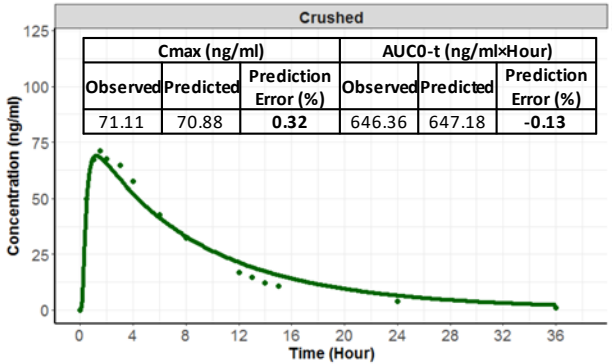
Intact

Cmax (ng/ml)			AUC0-t (ng/ml×Hour)		
Observed	Predicted	Prediction Error (%)	Observed	Predicted	Prediction Error (%)
42.58	40.42	**5.08**	885.27	875.46	**1.11**



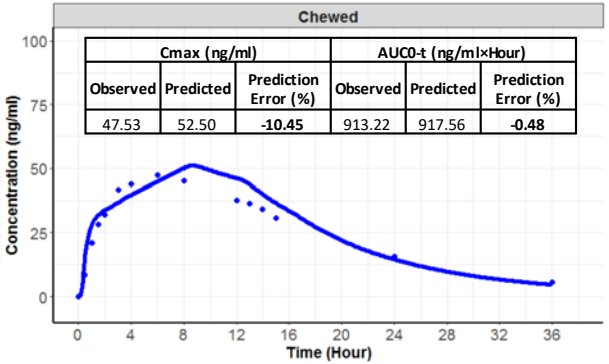
Crushed

Cmax (ng/ml)			AUC0-t (ng/ml×Hour)		
Observed	Predicted	Prediction Error (%)	Observed	Predicted	Prediction Error (%)
71.11	70.88	**0.32**	646.36	647.18	**-0.13**



Chewed

Cmax (ng/ml)			AUC0-t (ng/ml×Hour)		
Observed	Predicted	Prediction Error (%)	Observed	Predicted	Prediction Error (%)
47.53	52.50	**-10.45**	913.22	917.56	**-0.48**



Product-Specific Guidance (PSG)

- FDA publishes PSGs to facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval.

- PSGs describing the Agency's current thinking and expectations on how to develop generic drug products therapeutically equivalent (TE = PE + BE) to specific reference listed drugs.

- For two products to be considered bioequivalent, there should be no significant difference in the rate and extent of absorption of the active moiety, which are usually measured by Cmax (the maximum drug concentration) and AUC (the area under the concentration-time curve), respectively.

PE = Pharmaceutically Equivalent
FDA Product Specific Guidance Webpage: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

Draft Guidance on Hydrocodone Bitartrate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Hydrocodone bitartrate

Dosage Form; Route: Tablet; extended release; oral

Recommended Studies: Two bioequivalence studies (1–2) and two in vivo comparative pharmacokinetic (PK) studies for abuse deterrence assessment (3–4)

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 20 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional Comments: Naltrexone or other opioid antagonist should be incorporated to block the pharmacodynamic (PD) effects of the opioid. The opioid antagonist should be administered well in advance of opioid dosing to achieve adequate blockade of opioid receptors. The most common approach is to administer 50 mg of naltrexone at the following times: (1) 12 hours prior to dosing; (2) at the time of study drug dosing; and (3) 12 hours after the last dose of study drug. Consult with a physician who is an expert in the administration of opioids for an appropriate dose of narcotic antagonist.

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 20 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional Comments: See comments in Study 1.

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3. Type of study: Fasting, comparative oral PK study of chewed drug products
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 60 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional Comments: See comments in Study 1. Patient-relevant chewing conditions that can discriminate between test and reference products' ability of deterring chewing should be identified. Determine relevant PK parameters including maximum concentration (C_{max}), [illegible] under-the-curve (AUC_{0-t} and $AUC_{0-\infty}$), and time to maximum concentration (T_{max}). Applicants should submit partial AUCs (e.g., $AUC_{0\text{-}3\ hours}$ and $AUC_{0\text{-}4\ hours}$) as supportive data.

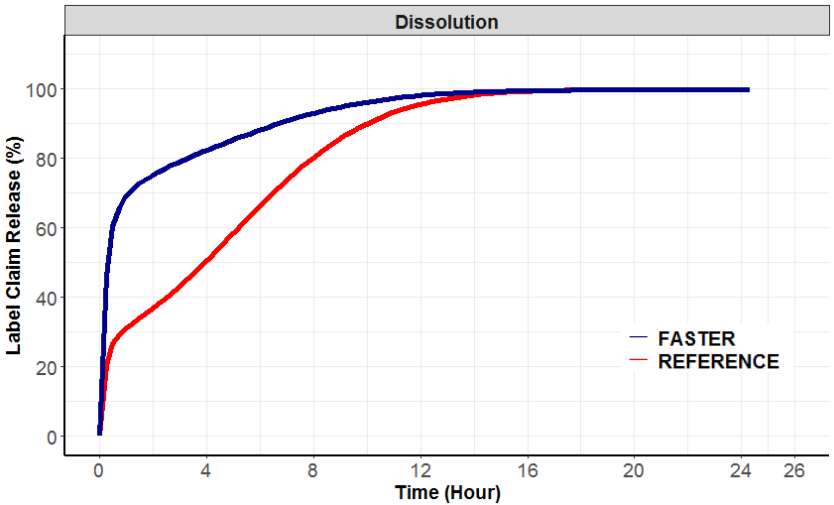
Analytes to measure (in appropriate biological fluid): Hydrocodone in plasma

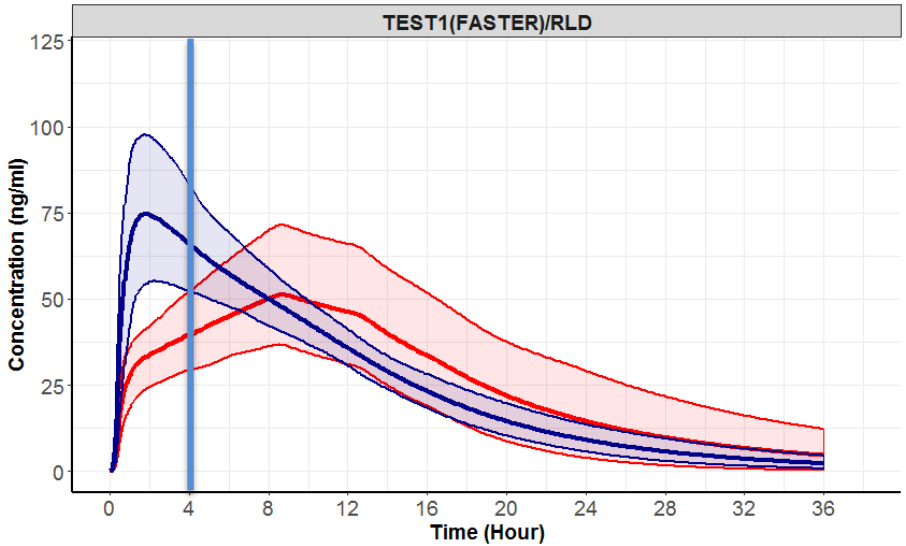
Bioequivalence based on (90% CI): Hydrocodone
Abuse deterrence based on (upper 95% confidence bound): Hydrocodone

Fasting comparative oral PK study of chewed drug products.

In addition to Cmax, AUC, partial AUCs e.g., AUC0-3hours and AUC0-4 hours as supportive data.

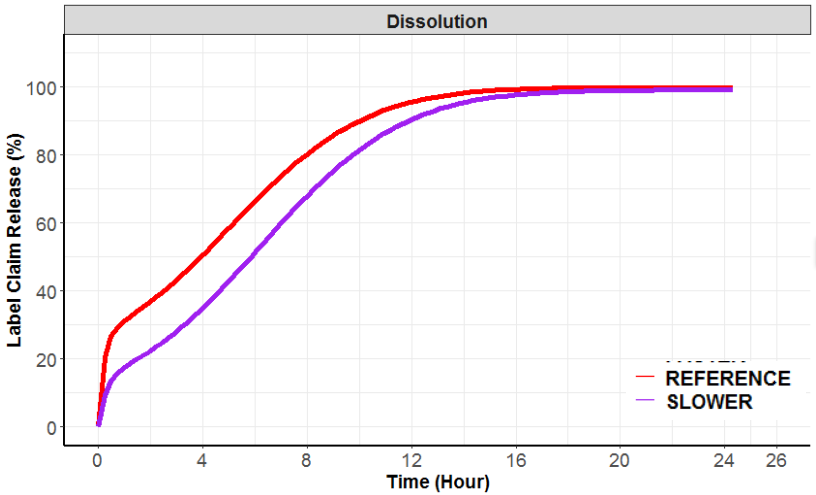
Virtual Comparative Oral Pharmacokinetic Study of Chewed Drug Products (TEST1/RLD)

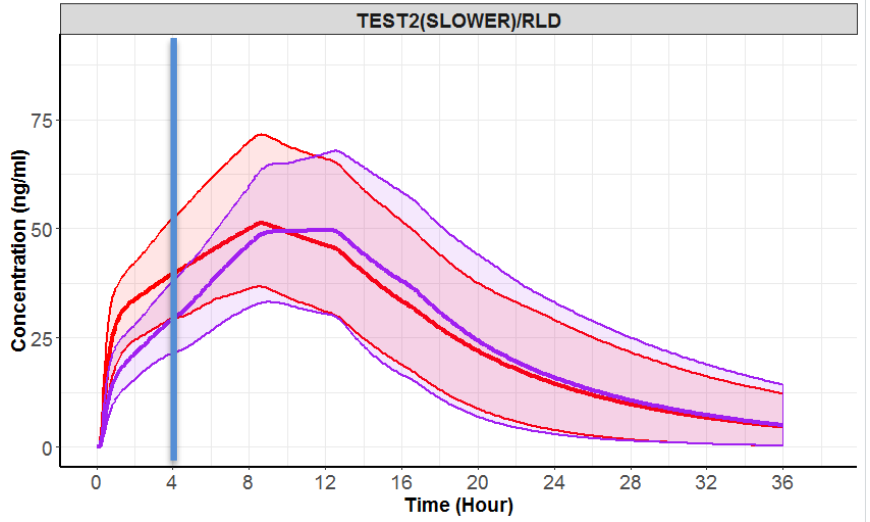




Cmax		AUC		pAUC 0-3 hour		pAUC 0-4 hour	
GMR	Upper 95% Confidence Bound	GMR	Upper 95% Confidence Bound	GMR	Upper 95% Confidence Bound	GMR	Upper 95% Confidence Bound
146.27	155.78	104.22	112.25	221.84	235.67	208.24	220.52

Virtual Comparative Oral Pharmacokinetic Study of Chewed Drug Products (TEST2/RLD)





Cmax		AUC		pAUC 0-3 hour		pAUC 0-4 hour	
GMR	Upper 95% Confidence Bound	GMR	Upper 95% Confidence Bound	GMR	Upper 95% Confidence Bound	GMR	Upper 95% Confidence Bound
98.69	105.75	96.20	106.48	62.42	66.76	65.45	69.78

Potential Challenges/Future Direction

- Validation of in vitro chewing method in combination with PBPK model to discriminate comparative oral chewing PK study
- Formulation development/Clinical study: NIPTE/Biopharma

Summary

- PBPK model for hydrocodone bitartrate ER tablet developed
- In vitro method of artificial chewing in combination with PBPK Modeling and Simulation can be helpful in predicting the in vivo behavior of hydrocodone bitartrate ER tablet after chewing followed by oral ingestion.
- Modeling & Simulation provides an important tool to support new and generic drug development:
  - Efficiency of clinical studies, test alternative scenarios

Thank You!

- Model-Informed Drug Development Pilot Program (New Drug Development) https://www.fda.gov/drugs/development-resources/model-informed-drug-development-pilot-program
- For information about Model-Informed Drug Development Pilot Program (New Drug Development) please contact MIDD@fda.hhs.gov
- Alternative approaches to demonstrate bioequivalence: Applicants can submit their proposal through FDA's Pre-ANDA program.
- Pre-ANDA Program Information: https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm578012.htm
- For questions about submitting Pre-ANDA meeting requests for complex generic drug products online please contact PreANDAHelp@fda.hhs.gov

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