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In vitro-in vivo relationship development for oxybutynin chloride extended-release tablets to assess bioequivalence

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PURPOSE

- Oxybutynin (DITROPAN XL®) has received approval by the United States Food and Drug Administration (US FDA) for the treatment of urge urinary incontinence/ urgency and frequency in unstable bladder conditions associated with detrusor instability or hyperreflexia (Reference Listed Drug, RLD)[1].
- Oxybutynin chloride extended release (ER) tablets available in the market today have been formulated as an osmotic-controlled release oral delivery system (OROS) or matrix-based formulation design.
- The objective was to develop physiologically based pharmacokinetic (PBPK) absorption models that would allow to simulate PK profiles for oxybutynin hydrochloride under fed and fasting conditions for the marketed OROS and the enteric-coated matrix formulations.
- We aimed at establishing in vitro-in vivo relationships (IVIVRs) for oxybutynin chloride ER tablets formulated either as OROS or enteric-coated matrix formulations currently available in the market to evaluate the relationship between in vitro dissolution and PK profiles.

METHODS

- Dissolution and plasma PK data were collected from Abbreviated New Drug Applications (ANDAs) submitted to the US FDA. In these ANDAs, the generic drug products were evaluated against the reference drug product (DITROPAN XL®) in randomized single dose, two-way crossover (consistent with the in vivo BE study design recommended in the current Product-specific Recommendation[2] for Oxybutynin chloride ER tablets) or two-treatment, four-period, two-sequence, single oral dose, crossover, fully replicated BE studies in healthy adult human subjects under fasting and fed conditions.
- GastroPlus™ was utilized for the present modeling task. PKPlus™ was employed for acquiring relevant PK parameters. Parameter fitting (Weibull function parameters) was performed utilizing the Optimization™ Module.
- Two separate exploratory IVIVRs were built, for the reference and the generic formulations due to their differing drug release mechanisms, leveraging the dissolution profiles and the in vivo plasma concentration profiles for the reference and the test drug products.
- The IVIVCPlus™ Module was utilized in the analysis. The traditional Wagner-Nelson (one-compartment) and the Mechanistic Absorption Model (MAM) methods were employed in the deconvolution step.

RESULTS

Parameter Sensitivity Analysis Leveraging the Developed Model for OROS Oxybutynin Revealed the Significant Impact of Weibull Function Parameters and Systemic Clearance on Exposure Metrics.

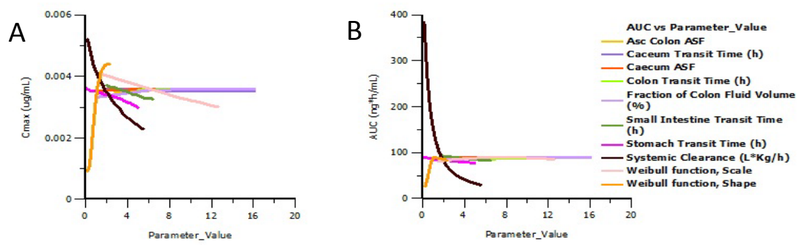

Fig 1. Parameter Sensitivity Analysis identifying model parameters that would impact exposure parameters (Cmax, AUC) following oxybutynin administration (RLD). Parameters (range) tested included fraction of colon fluid volume (1-100 %), stomach (0.083-5 h)/small intestine (2-6 h)/caecum (2-70 h)/colon (5-70 h) transit time, caecum/ascending colon ASF (20-300 % of baseline value), systemic clearance (20-300 % of baseline value), Weibull function scale and shape (25-200 % of baseline value). *The same parameters were identified as significant performing parameter sensitivity analysis for the generic drug product (not shown).

Developed Models Described Observed Data Reasonably Well.

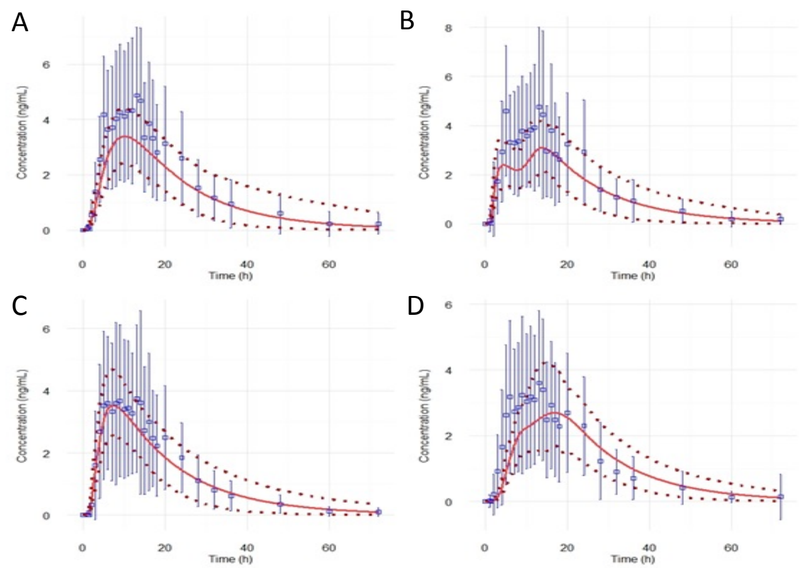

Fig 2. Simulated (mean, 5% and 95 % prediction intervals) versus observed PK profiles extracted from ANDAs submitted to the USFDA (Study 1-5) for the RLD (A and C) and the generic drug product (B and D) under fasting (A and B) or fed (C and D) conditions following administration of 15 mg oxybutynin hydrochloride extended release tablets. Simulated profiles were obtained leveraging the developed PBPK absorption models for the RLD and the generic products utilizing OROS and enteric-coated matrix delivery systems, respectively. Study design for Studies 1 to 5 can be either single dose, two-way crossover or two-treatment, four-period, two-sequence, single oral dose, crossover, fully replicated.

Predicted Multiple-peak Plasma PK Profiles Were Common with Matrix, and Not with OROS, Oxybutynin Formulations. Food Increased Tmax and Softened the Two-peak Phenomenon In Matrix Formulations. Food Had Minimal Impact On Cmax and AUC Following Administration of OROS Formulation.

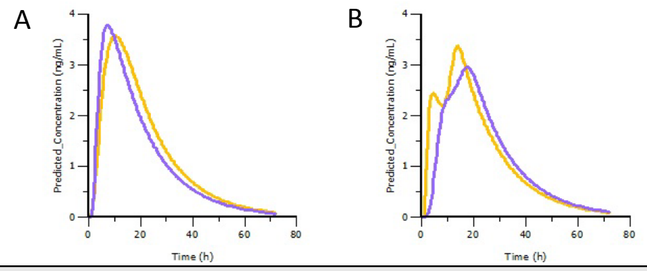

Fig 3. Simulated PK profiles following administration of 15 mg oxybutynin hydrochloride extended release tablets of the RLD (A) and generic (B) drug product under fasting (yellow) and fed (purple) conditions.

Developed IVIVRs Leveraging Dissolution and Pharmacokinetic Profiles for OROS and Enteric-coated Matrix delivery Systems Perform Well When the Wagner-Nelson Deconvolution Approach is Employed.

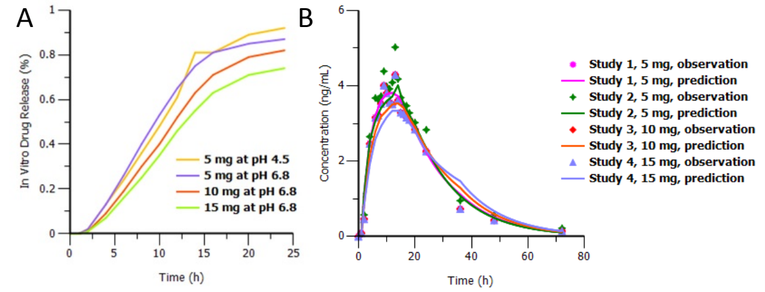

Fig 4. (A) Experimental dissolution drug profiles utilized for the developed of the IVIVR of the RLD product (5 mg) at pH conditions 4.5 and 6.8 and experimental dissolution drug profiles of the same RLD product at higher strengths (10 and 15 mg) obtained under the same experimental conditions as above. (B) Dose-normalized observed (symbols) and predicted (lines) oxybutynin plasma concentrations were either extracted from ANDAs submitted to the agency or generated leveraging the developed IVIVR, respectively. Studies 1 to 4 are PK profiles obtained following administration of the same RLD. The 5 mg strength at pH 4.5 and 6.8 coupled with PK data from Studies 1 and 2, respectively, were utilized for the development of the IVIVR with the Wagner-Nelson approach employed in the deconvolution step. Predictions corresponding to Studies 1 to 4 were generated utilizing the aforementioned IVIVR (the 5 mg at pH 4.5 and pH 6.8 dissolution profiles correspond to Study 1 and 2 predictions, respectively). Similar were the workflow and outcomes for the generic drug product (not shown).

Table 1. Prediction Errors (%) obtained following comparison between the observed and predicted PK profiles presented on Fig. 4B (Studies 1-4) for the exposure PK parameters Cmax and AUC. For comparison, the prediction errors generated from IVIVRs where the MAM deconvolution approach was employed are presented here. Cmax: maximum concentration, AUC: Area Under the Concentration versus time Curve

	Cmax (ng/mL)				AUC (ng/mL*h)			
Study	1	2	3	4	1	2	3	4
Deconvolution Approach								
MAM	20.9	33.6	26.0	28.5	9.2	23.9	9.8	12.7
Wagner-Nelson	11.2	20.1	17.5	22.1	-7.2	9.6	-7.2	-6.2

CONCLUSIONS

- PBPK absorption models for the OROS and the enteric-coated matrix formulations of oxybutynin hydrochloride ER tablets were developed and thoroughly validated against observed data under fasting and fed conditions.
- The aforementioned PBPK absorption models were leveraged and IVIVRs quantitatively describing the relationship between in vitro dissolution profiles for OROS or enteric-coated matrix formulations and their respective PK profiles were established.
- The developed IVIVRs are currently being evaluated on providing risk assessments for those oxybutynin hydrochloride strengths in vivo studies are not conducted.

REFERENCE, ACKNOWLEDGEMENT, AND DISCLAIMER

Reference:
1. FDA. *Ditropan Package Insert*, http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/017577s034,018211s017,020897s018lbl.pdf.
2. Oxybutynin hydrochloride ER tablet Product-specific recommendation, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm118381.pdf

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