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The Incorporation of Absorptive Phase into the *In Vivo* Predictive Dissolution (iPD) System to Predict Better *In Vivo* Dissolution for Ketoconazole and Raloxifene.

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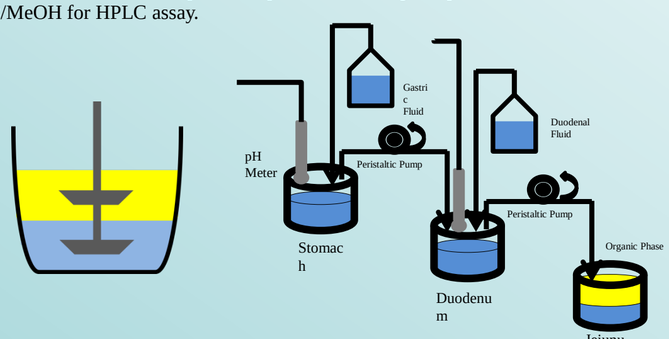
Objective

BCS class IIc and IVc drugs have unique physicochemical characteristics and dissolve with the constant dissolution rate regardless of physiological pH range. The USP apparatus, currently golden standards, have been used to determine the dissolution profile of pharmaceutical candidates/products of BCS class IIc and IVc, neutral drugs. Unfortunately, those systems cannot predict *in vivo* dissolution for neutral drugs because of high permeability and low solubility. Especially, the highly permeable BCS class IIc drugs like raloxifene would need the absorptive phase in the dissolution system to accurately predict *in vivo* dissolution. Therefore, there is a critical need to develop a biopredictive dissolution system, which will provide for better *in vivo* prediction to minimize the discrepancy between *in vivo* and *in vitro* dissolution profiles. In order to assure the therapeutic effects of drug products, better *in vivo* predictive dissolution methodology is required.

The goal for this presentation is to develop a newer biopredictive dissolution system for neutral drugs, BCS class IIc and IVc to predict *in vivo* dissolution. For those purposes, raloxifene, a BCS class IIc drug, and ketoconazole, a BCS class IIb drug, were adapted as model drugs to evaluate the impact of the presence of absorptive phase in the dissolution system.

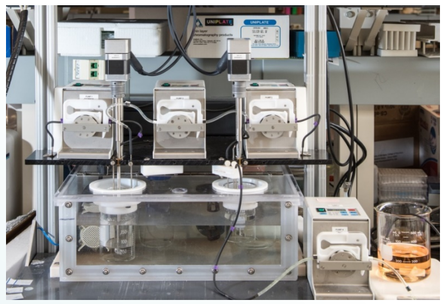
The Condition of USP Dissolution and Photo/Diagram of GIS

The impact of absorptive phase in the dissolution system for raloxifene and ketoconazole (highly permeable drugs, high log P) was investigated by gastrointestinal simulator (GIS) with the presence and absence of the organic phase (100 mL, 1-decanol) as an absorptive site and USP II (300 or 500 mL) with the presence and the absence of organic phase. The samples were taken at the specific time point. The supernatant was obtained by the centrifugation, 17,000 x g for 1 min at the room temp. The supernatant and organic phase was mixed with H_2O/MeOH for HPLC assay.



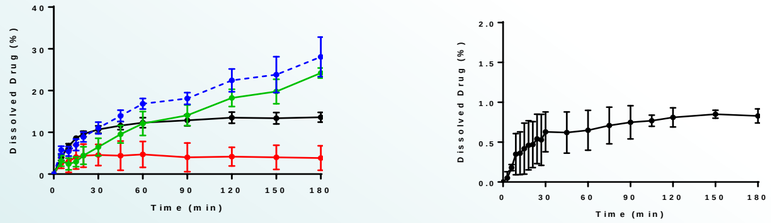
pH	Volume	Buffer
2.0	50 mL + 250 mL	0.01 N HCl
6.5	50 mL (GIS) 300/500 mL (USP II)	50 mM Phosphate Buffer
Two Phase	100 mL	1-Decano / Octanol

Table 1. Physicochemical Characteristics of Raloxifene and Ketoconazole



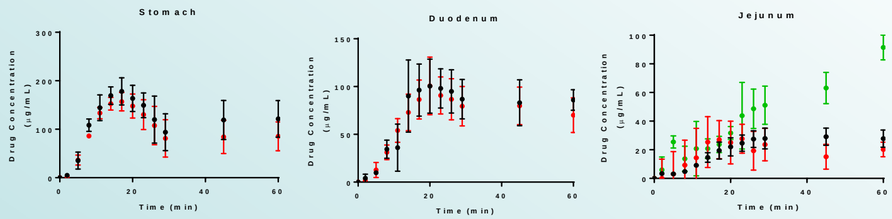
Name	Raloxifene	Ketoconazole
MW	504.6	531.4
pKa	7.95 (basic) 8.89 (acid)	6.5 (basic)
LogP	5.45	4.35
Solubility (water)	0.5 µg/mL	22.2 µg/mL
Dose	60 mg	200 mg
Absorption	~60% (BA ~2%)	~80%

Figure 1. The Dissolution Profiles of Raloxifene and Ketoconazole with USP II



Black, red, green and blue circles and lines represent observed dissolved drug amount (%) in the aqueous phase with the absence of absorptive phase, observed dissolved drug amount in the aqueous phase with the presence of absorptive phase, the observed dissolved drug amount in the absorptive phase, and the total of drug amount (aqueous and organic phases), respectively.

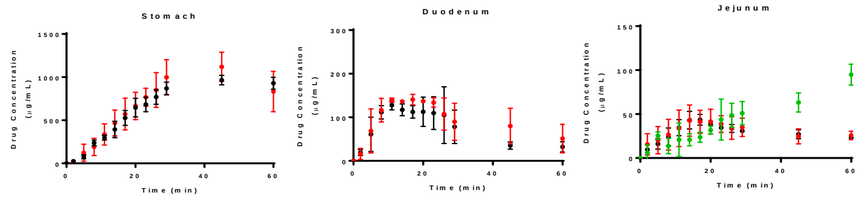
Figure 2. Dissolution Profiles of Raloxifene with GIS



The dissolution profile was represented mean ± SD. N=3-4

The concentration of raloxifene-time profiles in the gastric, the duodenal, and the jejunal chambers: Black, red, and green circles represent observed drug concentration with the absence of absorptive phase, observed drug concentration with the presence of absorptive phase, and the observed concentration in the absorptive phase, respectively. The range of concentration in the jejunal chamber was ~10- 30 µg/mL, which is still higher than its saturated concentration (~2 µg/mL) in 50 mM Potassium Phosphate butter, pH 6.5.

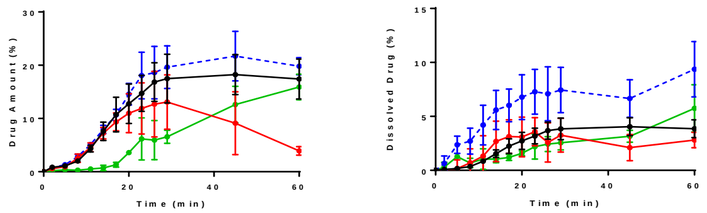
Figure 3. Dissolution Profiles of Ketoconazole with GIS



The dissolution profile was represented mean ± SD. N=3-4

The concentration of ketoconazole-time profiles in the gastric, the duodenal, and the jejunal chambers: Black, red, and green circles represent observed drug concentration with the absence of absorptive phase, observed drug concentration with the presence of absorptive phase, and the observed concentration in the absorptive phase, respectively. The range of concentration in the jejunal chamber was ~30- 100 µg/mL at 60 min, which is still higher than its saturated concentration (~10 µg/mL) in 50 mM Potassium Phosphate butter, pH 6.5.

Figure 4. The Dissolved Amount in Jejunal Chamber from GIS



The dissolution profile was represented mean ± SD. N=3-4

Black, red, green and blue circles and lines represent observed dissolved drug amount (%) in the aqueous phase with the absence of absorptive phase, observed dissolved drug amount in the aqueous phase with the presence of absorptive phase, the observed dissolved drug amount in the absorptive phase, and the total of drug amount (aqueous and organic phases), respectively.

Conclusion

Lowly soluble and highly permeable drugs (BCS class II drugs) would need the absorptive phase in order to better understand *in vivo* dissolution and to predict better oral absorption of test drugs. Especially, the presence of absorptive phase in the dissolution systems will have advantages to evaluate the dissolution and the oral absorption in the different oral formulations or the formulation changes, eq. bioequivalence and oral formulation development. GIS can displays supersaturation and precipitation and the incorporation of absorptive phase into the GIS will provide the advantage to evaluate the oral absorption.

Acknowledgement

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