The development of *in vivo* predictive dissolution (IPD) system, mini-gastrointestinal simulator (mGIS), for BCS class IIb drug. The case study of anticancer drug; Dasatinib.

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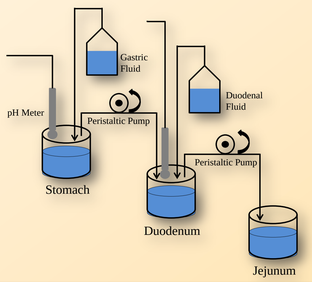
Objective

Approved oral anti-cancer drugs are often weak base drugs, which have unique physicochemical characteristics and well dissolve in an acidic environment. Those medications dissolved in the gastric pH will potentially supersaturate/precipitate in vivo, as the dissolved drug enters from acidic environment in the stomach to the higher pHs in the small intestine. Currently, the USP apparatus, golden standards, have been used to determine the dissolution profile of pharmaceutical candidates/products. Unfortunately, those systems cannot predict in vivo dissolution for weak base drugs, because it does not simulate the physiological pH changes seen in the human body. 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 clinically, moreover, cancer patients often take anti-acid reducing agents to relieve acid reflex, which elevates the gastric pH to reduce drug solubility and, hence, potentially reduce oral bioavailability of oral cancer drugs (Drug-Drug Interaction: DDI). 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 new biopredictive dissolution system with small scale, mini-gastrointestinal simulator (mGIS), which takes into account the various pH changes seen throughout the gastrointestinal (GI) tract. Oral anti-cancer drug, dasatinib, is used as a model drug to develop mini-GIS to predict better oral bioavailability and clinical implication.

The Condition of USP Dissolution and Diagram of mGIS

pH	Volume	Paddle Speed	Buffer
1.2	50 mL	50 rpm	0.01 N HCl
6.5	50 mL	50 rpm	50 mM Phosphate Buffer



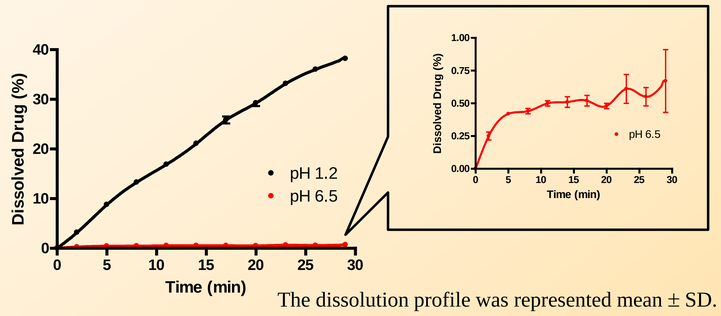
Dissolution of dasatinib (20 mg tablet) was performed in 50 mL buffer (pH 1.2 or 6.0 HCl and pH 6.5 Phosphate buffer) with mini-USP and mGIS for 30 min

Table 1. Physicochemical Characteristics of Dasatinib and Other Anti-Cancer drugs

Name	MW	pKa	LogP	Solubility (acid)	Solubility ~pH6.5	Dose
Dasatinib	488.0	3.1, 6.8, 10.8	1.8	18 mg/mL at pH 2.6	insoluble > pH 7	20, 50, 70, 80, 100, 140 mg
Gefitinib	446.9	5.4, 7.2	4.02	21 mg/mL at pH 1	< 1 µg/mL at pH 7	250 mg
Erlotinib	393.4	5.4	2.7	~ 0.4 mg/mL at pH 2	~ 8 µg/mL at pH 7	25, 100, 150 mg
Nilotinib	565.9	2.1, 5.4	4.51	~ 10 mg/mL at pH 1	< 0.1 mg/mL > pH 4.5	150, 200 mg
Axitinib	386.4	4.8		1.8 mg/mL at pH 1.1	0.2 µg/mL at pH 7.8	1, 5 mg
Ketoconazole	531.4	2.9, 6.5	4.35	9.36 mg/mL at pH 1.8	22.2 µg/mL	200 mg

Results

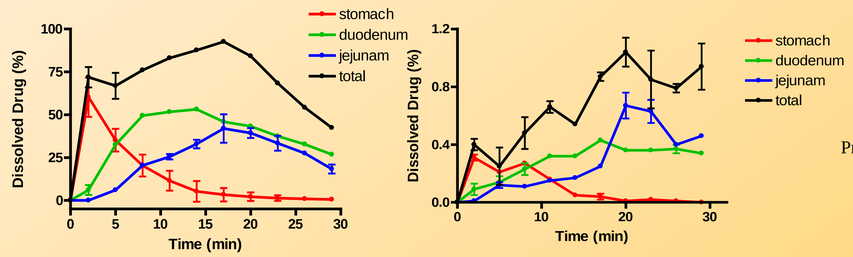
Figure 1. Dissolution Profiles of Dasatinib with USP



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

Dasatinib dissolved up to 40% (Conc: ~ 0.16 mg/mL) for 30 min, while one quickly reached plateau and dissolved around 0.7% (Conc: ~ 0.002 mg/mL) with 50 mM Potassium Phosphate butter, pH 6.5

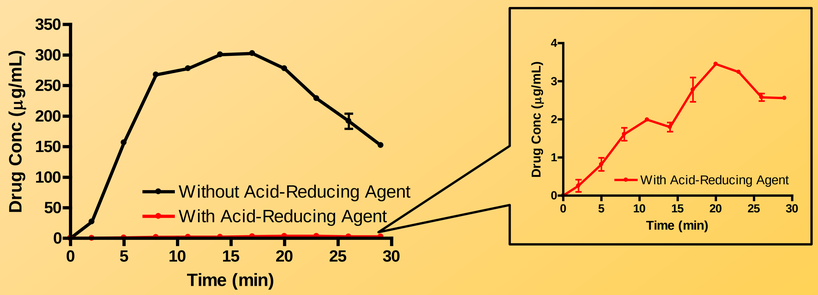
Figure 2. Dissolution Profiles of Dasatinib with Mini-GIS (Acid-Reducing Agent)



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

Dasatinib dissolution reached the peak at 17 min, which exhibited more than 90% of dose, during 30 min, while one with elevated gastric pH (average gastric pH ~6.0) exhibited only 1% of dissolution during 30 min, which indicates the reduction of dasatinib absorption and, hence, the risk of patients not to have therapeutic benefits from medications.

Figure 3. Available Dasatinib in the Small Intestine with or without Acid-Reducing Agent



The dissolution profile with mGIS was represented as the sum of drug concentration in duodenal and jejunal chambers. (mean ± SD. N=3)

Table2. Chemical/Physical/Pharmacological Parameters of Dasatinib

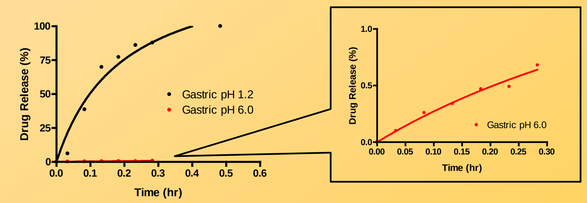
		Dasatinib
MW		488[a]
Dose	**mg**	100
Dose Volume	**mL**	250
Solubility	**mg/mL**	18 (at pH2.6)[a]
logP		1.8
pKa		3.1, 6.8, 10.8[a]
Human Peff	**x 10^{-4} cm^2/s**	1.5*
Body weight	**kg**	70
Vc/F	**L/kg**	17.7[b]
CL	**L/h**	404.8[c]

In situ perfusion study in Mice

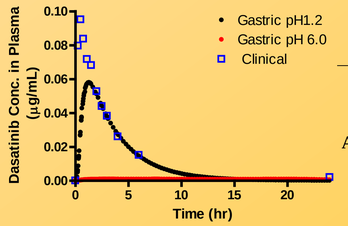
	P^{eff} (x 10^{-5} cm/s)
Metoprolol	1.3 ± 0.2
Dasatinib	2.7 ± 0.3

*Permeability number of metoprolol was used for Dasatinib (high permeability drug) in this *in vivo* prediction. a – Highlights of prescribing information:http://packageinserts.bms.com/pi/pi_sprycel.pdf b – Dai G. et al. J Clin Pharmaco 2008; 48(11) c – Christopher, LJ. et al. Drug Metabo Dispo 2008; 36

Figure 4. In vivo Prediction of Dasatinib with Co-Administration of Acid Reducing Agents by GastroPlus™



Predicted dissolution profiles of dasatinib were used for GastroPlus™ simulation based on mGIS dissolution results.



	Clinical Data[c]	pH 1.2 GIS	pH 6.0 GIS
C_{max} (ng/mL)	105 ± 29	61 ± 3	1 ± 0
T_{max} (h)	0.5	1.2 ± 0.1	8.8 ± 3.5
AUC_{∞} (ng/mL h)	314 ± 42	247 ± 5	27 ± 3

Population Simulator (n=100) was performed with the dissolution profiles of dasatinib from mGIS with gastric pH 1.2 and 6.0, which was simulation for co-administration of acid-reducing agents. With co-administration of antacids and proton pump inhibitors, a 40-60 % reduction in dasatinib AUC and Cmax was reported. GastroPlus with mGIS dissolution profiles suggested larger reduction than those reports.

Conclusion

USP dissolution apparatus do not provide any in vivo insight based on dissolution profiles for BCS class IIb drugs like dasatinib, which has pH-dependent solubility. On the other hand, mGIS displays supersaturation and precipitation and demonstrates the feasibility of predicting in vivo dissolution and, hence, absorption.

Acknowledgement

This work was supported by Grant# HHSF223201310144C