An Integration of Absorption Chamber with USP II Dissolution Apparatus

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INTRODUCTION

Traditional (USP) dissolution tests have been used in the pharmaceutical industry to perform quality control of manufacturing process for drug products, and also to compare performance of different drug product formulations during the late stage of the drug development process. It has been a subject of multiple debates if differences in the dissolution profile would be biorelevant, i.e. would lead to the significant changes in the *in vivo* absorption properties of active pharmaceutical ingredients (API). The goal of this study was to develop a method enabling simultaneous monitoring of dissolution of the drug product in the compendial apparatus at the same time providing the means to assess kinetic of API penetration into the absorption chamber separated from the dissolution vessel by a lipophilic membrane.

MATERIALS AND METHODS

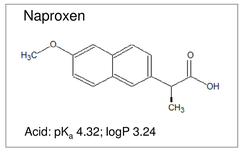

Figure 1. Chemical structure and phys.-chem. properties of NPX

Naproxen (NPX, Figure 1) was selected as a model compound for this "proof of concept" study. Over the counter Brand Name NPX sodium 220 mg dose liquid gel capsules (Alive® Liquid Gels, Bayer) and the Generic NPX sodium caplets (the same dose, generic supermarket brand) were used in the study as model drug products (Figure 2). Concentration monitoring in both dissolution and absorption chambers was enabled through fiber optic UV probes connected to the Rainbow Dynamic Dissolution Monitor instrument (Pion Inc).

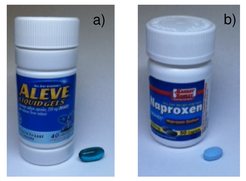

Figure 2. Naproxen drug products used in the study: Brand Name (a) and Generic (b).

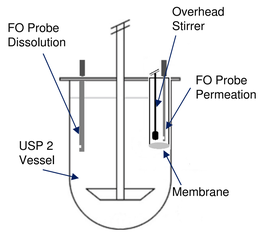

Figure 3. Schematic of Dissolution – Flux device used in this study.

Receiver chamber integrated with permeation membrane, overhead stirrer and fiber optic (FO) UV probe (Figure 3) was inserted in the standard 900 mL vessel of USP 2 apparatus. A filter-supported artificial membrane (Double-Sink™ PAMPA[1]) with 3.8 cm^2 area was separating the dissolution (donor) compartment from the receiver compartment contained 15 mL of Acceptor Sink Buffer at pH 7.4 (ASB, Pion Inc). The integrated fiber-optic UV probes were positioned in the donor and receiver compartments allowing real time concentration monitoring in both chambers (Figure 3).

Table 1. Parameters of the Dissolution-Flux Assay

Donor media, first 30 min	800 mL	SGF	pH 1.6
Donor media, after 30 min	1000 mL	FaSSIF	pH 6.5
Acceptor media	15 mL	ASB	pH=7.4
run time	16	hours	
DOSE	220	mg	
Path length for donor	5	mm	tip
Path length for acceptor	20	mm	tip
Temperature	37	C	
Stirring in donor	100	rpm	
Stirring in acceptor	undefined		
Membrane	GIT	Lot No.	520358

Flux Measurements

Flux (J) of a drug through a membrane is defined as the amount of drug crossing a unit area perpendicular to its flow per unit time. In the one-dimension steady-state approximation it may be expressed through the effective permeability coefficient P_e and concentration $c(t)$ in the donor compartment as follows

$$J(t) = \frac{dm}{A \cdot dt} = P_e \cdot c(t) \qquad (1)$$

RESULTS AND DISCUSSION

The experiment began in 800 mL at pH 1.6 simulating gastric conditions and then after 30 min media in the dissolution vessel was converted to FaSSIF by adding 200 mL of specially formulated concentrate. Figures 4 and 5 show dissolution and appearance profiles of NPX studied with Flux apparatus.

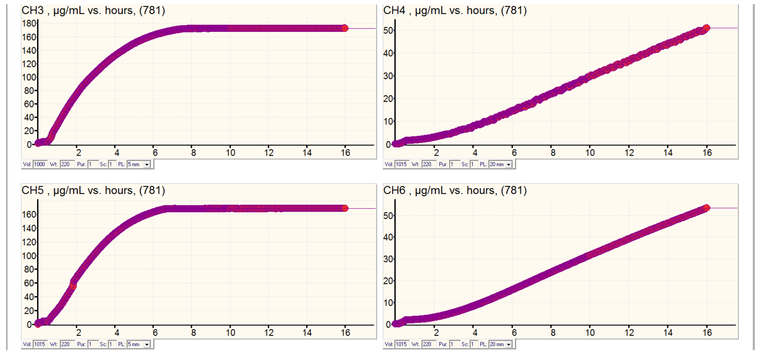

Figure 4. Dissolution profile (on the left) and appearance profile (on the right) for the Brand Name NPX product.

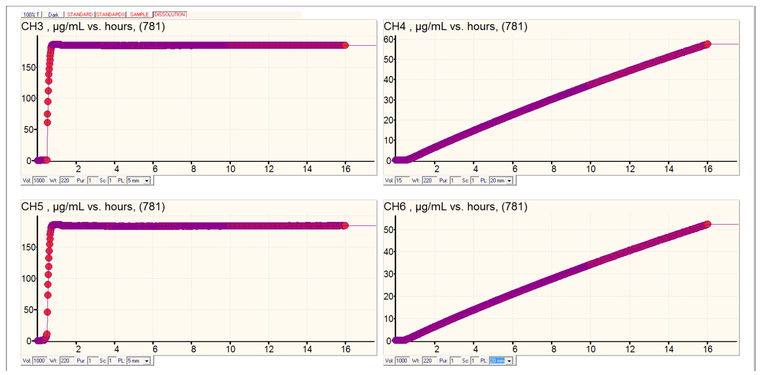

Figure 5. Dissolution profile (on the left) and appearance profile (on the right) for the Generic NPX product.

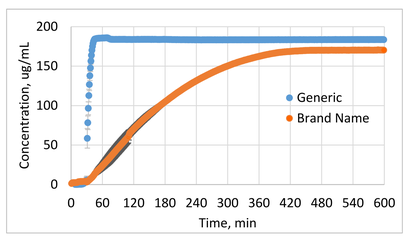

Figure 6. Averaged dissolution profile (n = 3) for the Generic (blue) and Brand Name (orange) NPX products.

Brand Name and Generic NPX products have very different release profiles (Figure 6) one being consistent with extended release (Brand Name) and the other with immediate release profiles.

RESULTS AND DISCUSSION

It is interesting to note that Generic Brand had no dissolution in SGF for the first 20 min that resulted in no flux generated during this period of time (figure 7, b). In contrary Brand Name product released some NPX in first 30 min. NPX as an acid had highest permeability at lowest pH value that explains quite substantial flux even when concentration of NPX was so low (Figure 7, a).

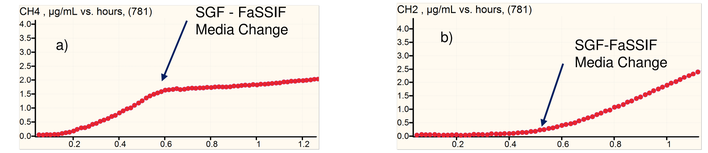

Figure 7. Initial concentration-time profile of the NPX in the receiver chambers for a) Brand Name product and b) Generic product.

Maximum flux for Generic product establishes immediately after the SGF-FaSSIF media change and then remains nearly constant for the duration of the experiment while for the Brand Name formulation flux reaches its maximum value after about 3.5 hours from the media change offset time (Figure 8).

Flux values reflecting different time slices of the experiment are presented in the Table 2.

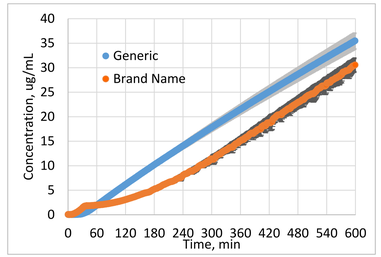

Figure 8. Concentration-time profile of NPX in receiver compartment for the first 10 hours of the experiment.

Table 2. Flux values for different time segments of the assay.

	Flux, µg/(cm^2·min)		
Product / Time Period, min	20 - 30	40 - 100	200 - 600
NPX- Brand Name	0.30 (0.04)	0.05 (0.01)	0.25 (0.01)
NPX-Generic	< 0.01	0.29 (0.02)	0.24 (0.02)

CONCLUSIONS

Developed setup allowed combining conventional dissolution studies with investigation of permeation of the released compound into absorption chamber.

Pilot experiments demonstrated good reproducibility of results for both dissolution (donor) and receiver chambers.

Acceptor Sink Buffer (ASB) in the receiver chamber allowed to maintain sink conditions for the studied API despite of limited volume (15 mL) of the compartment.

The device can become an alternative platform to the bi-phasic dissolution method (e.g. Ref. 2) for *In Vivo* Predictive Dissolution(IPD) studies.

Current study encourages further research that in particular can address proper scaling for better *in vitro – in vivo* correlations.

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1. A. Avdeef, O. Tsinman. PAMPA — A drug absorption in vitro model. 13. Chemical selectivity due to membrane hydrogen bonding: In combo comparisons of HDM-, DOPC-, and DS-PAMPA models. *Eur. J. Pharm Sci.* **2006**, *28* (1), 43-59.
2. D. M. Mudie, Y. Shi, H. Ping, P. Gao, G.L. Amidon, G.E. Amidon. Mechanistic analysis of solute transport in an in vitro physiological two-phase dissolution apparatus. *Biopharm. Drug Dispos.* **2012** 33, 378–402.