Poster Number

W1021

μFlux in Vitro-in Vivo Correlation (IVIVC) Testing Trans-Membrane Permeation and BSC Class II Formulation Challenges

T.Webb[1], J. Maxwell[1], B. Hilker[1], and J. Cacace[1]

[1]CoreRx, Clearwater, Florida, 33710, United States of America

CONTACT INFORMATION: Travis.Webb@corerxpharma.com; Jejuan.Maxwell@corerxpharma.com; Brent.Hilker@corerxpharma.com; Janice.Cacace@corerxpharma.com

2017 AAPS ANNUAL MEETING & EXPOSITION

PURPOSE

A previous design of experiments (DoE) was used to developed a generic BSC Class II suspension utilizing a fiber optic probe (FO) monitoring system via regression analysis. DoE and regression analysis provided a generic formulation which matched dissolution profile, USP Assay, and physical characteristics (XRPD, Particle Size, and Rheology) of the reference listed drug (RLD).

However, when the bioequivalence (BE) study was conducted the generic outperformed the RLD having increased bioavailability (BA) by ~1.5 times greater. The difference in BE may have occurred due to changes in the concentration of excipients that are difficult or cannot be quantified with consistency, accuracy, or relevance.

Our focus turned to methods that could discriminate against formulation differences which may not present using traditional in-vitro dissolution techniques. The μFlux side by side cell monitors *in-vitro* transport across a membrane that is a model for gastrointestinal *in-vivo* absorption (GIT-0), Figure 1. The μFlux provides real time monitoring of dissolution and equilibrium Flux (∂c/∂t) to provide IVIVC testing. Herein we demonstrate the challenges to develop an equivalent BCS class II suspension.

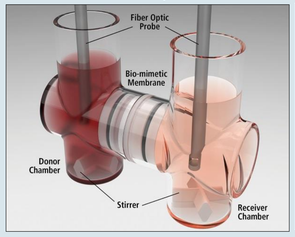

Figure 1. Pion® μFlux apparatus

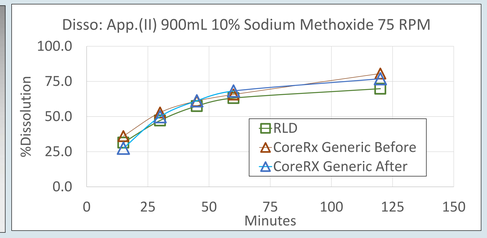

Figure 2. Dissolution profiles RLD and CoreRx formulations (n=6).

METHOD(S)

Disso Media: 10% sodium methoxide. μFlux Media: 20 mL 0.2M PBS pH 7, 20 mL 0.2M PBS pH 12. PION μFlux apparatus. PVDF membrane, GIT-0 Lipid solution, PION Rainbow® in situ fiber optic probes with PDA (200-720 nm) with 2 mm stainless steel probes (Pion, Billerica MA). Minitab® statistical processing software. CoreRx Generic Formulations were prepared by microfluidizing a stock suspension and aliquoted to individually prepared vehicles. Reagents: **Excipient A** BASF (Greenville OH), **Excipient B** (Dow Corning Midland MI), **Excipient C** (Vanderbilt Minerals Norwalk CT).

IVIVC tests were randomized including both the RLD and generic formulations. Sample preparation: 5 mL of suspension was pre-dispersed in 20 mL of 0.1N HCL. 8.3 mL was transferred to the donor cell containing 11.7 mL of 0.05 M potassium phosphate buffer, final pH 6.8. Acceptor cell: 20 mL 0.05 M potassium phosphate buffer at pH 12. This increased the solubility of the drug in the aqueous acceptor media and protonated the solution. Run conditions: stirring 300 RPM, cross stir bar, temperature 37°C, sampling interval 1 minute, wavelength 276nm.

RESULT(S)

Dissolution results for the (RLD □) compared to the CoreRx formulation that was super bioavailable (CoreRx Generic Before △) showed a similar profile, Figure 2, with ~75% released in 120 minutes. .

IVRT studies (side by side membrane permeability) showed consistently higher equilibrium flux for the (RLD □) versus (CoreRx Generic Before △) with good repeatability, Figure 3. Although the trend was inverse to the BE data; these results indicated that there was an inherent difference between the two formulations.

The RLD suspension formulation contains several excipients. IVRT testing revealed **excipient A** as the component which effects membrane transport. The effect of **excipient A** was evaluated at 0.5%, 0.75%, 1.0% and 1.5% w/v from a stock microfluidized suspension. All other formulation variables were confirmed to be matching to the RLD. The results of the study, Figure 4, showed that **excipient A** is inversely proportional to equilibrium flux rate.

A new formulation was prepared; (CoreRx Generic After △) with 0.5% **excipient A** which also showed disso comparable to (RLD □), Figure 2. However, the new (CoreRx Generic After △) is clearly a better match to the (RLD □) equilibrium flux (∂c/∂t) Figure 3.

Statistical Mann-Whitney Analysis *(1)* was performed to confirm equilibrium flux match: The slope (∂c/∂t) for each of the six test lot runs (T) is compared to each of the RLD runs (R) as a %ratio (T/R), Table 1. The ratios are ranked from smallest to largest. The 8th and 29th ordered individual ratios are the lower and upper limits, respectively, of the 90% confidence interval. Because the 90% confidence interval falls between 75% and 133.3% the products are considered a match for IVRT.

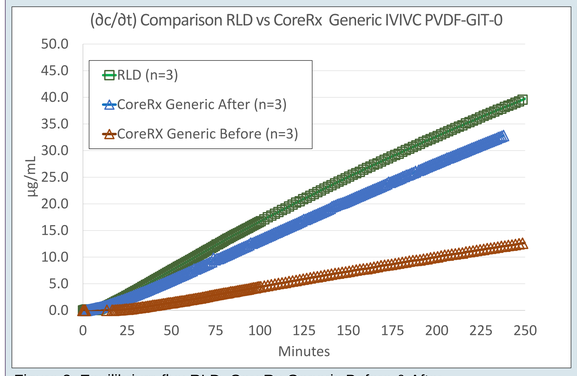

Figure 3. Equilibrium flux RLD, CoreRx Generic Before & After.

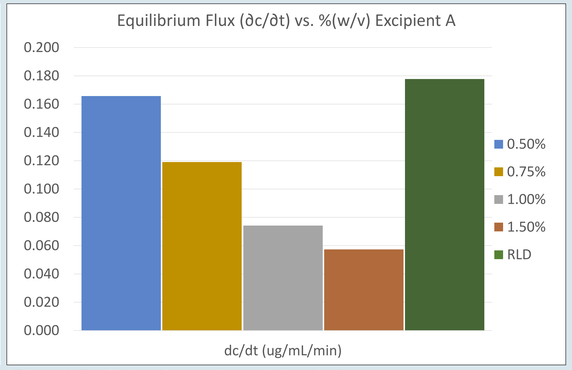

Figure 4. Equilibrium flux varying excipient A wt%. .

Order	Ratio	
1	102.31%	
2	103.06%	
3	105.43%	
4	106.19%	
5	109.28%	
6	110.53%	
7	110.72%	
8	**111.53%**	**Pass Criteria: Ratio @8 > 75%**
9	112.61%	**Meets Pass Criteria**
10	113.89%	
11	114.38%	
12	114.92%	
13	115.21%	
14	115.76%	
15	118.26%	
16	119.61%	
17	120.23%	
18	120.23%	
19	122.17%	
20	122.75%	
21	123.56%	
22	123.71%	
23	123.89%	
24	123.89%	
25	124.15%	
26	124.62%	
27	130.12%	
28	130.12%	
29	**132.14%**	**Pass Criteria: Ratio @29 < 133.3%**
30	133.65%	**Meets Pass Criteria**
31	134.41%	
32	134.41%	
33	135.05%	
34	135.05%	
35	145.39%	
36	145.39%	

Table 2. Mann-Whitney (T/R) (dc/dt) ranking order.

(T) CoreRx Generic After	(R) RLD					
	2.11	2.19	1.96	2.12	2.37	2.3
2.42	114.9%	110.7%	123.7%	114.4%	102.3%	105.4%
2.62	124.1%	119.6%	133.6%	123.6%	110.5%	113.9%
2.85	135.1%	130.1%	145.4%	134.4%	120.2%	123.9%
2.44	115.8%	111.5%	124.6%	115.2%	103.1%	106.2%
2.85	135.1%	130.1%	145.4%	134.4%	120.2%	123.9%
2.59	122.7%	118.3%	132.1%	122.2%	109.3%	112.6%

Table 1. Mann-Whitney (T/R) (dc/dt) ratios.

CONCLUSION

The root cause for the difference in equilibrium flux was correlated to the %w/v of **excipient A**. Based on the IVRT and Mann-Whitney analysis the new formulation is equivalent to the RLD. BE testing is required to confirm. IVIVC μFlux testing was able to discriminate against formulation differences that traditional methods cannot, and is recommended to evaluate BSC class II drug product performance. Because the formulation composition had changed an excipient which is proven to affect the CQAs of the drug product some additional studies are required: D.O.E. (PSD, viscosity, excipient A), stability, dissolution method development, flocculation, and API dispersion.

REFERENCE

1. "GUIDANCE FOR INDUSTRY Nonsterile Semisolid Dosage Forms Scale-Up and Post approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation SUPAC-SS https://www.fda.gov/downloads/Drugs/Guidances/UCM070930.pdf

core RX DEVELOPMENT AT OUR CORE®

Pion