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In Vitro Modelling Of Propranolol Immediate Release And Extended Release Formulations Using A Three Chamber Dissolution Apparatus

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PURPOSE

Finding appropriate *in-vitro* models to predict *in-vivo* performance of oral dosage forms has always been challenging for the pharmaceutical industry. In recent years, there has been a push to improve the biorelevance of *in-vitro* testing in an attempt to model complex *in vivo* processes, such as supersaturation and precipitation.

In this study, a three chamber dissolution apparatus was used to analyse three formulations of Propranolol (BCS class I drug) and the results were compared to *in vivo* data.

METHOD(S)

Dissolution testing was performed using a three chamber dissolution apparatus (FloVitro™) with cells representing the stomach, intestine, and the systemic circulation (Figure 1). One immediate release (IR) formulation (80 mg) and two extended release (ER) formulations of propranolol (80 mg) were tested at 37°C for 24 hours.

Dilute HCl (pH 1.2) and phosphate buffer (pH 6.8) were used as dissolution media, and the flow rates were 2 mL/min and 4.1 mL/min respectively. The volumes in the gastric, intestinal and systemic cells were 40 mL, 200 mL & 1709 mL respectively. Stirring speeds in the cells were 300 rpm, and drug concentration was measured using inline spectrophotometry at 290 nm. The results were compared to those of a previous *in-vivo* study, with a scaling factor of 406.18.

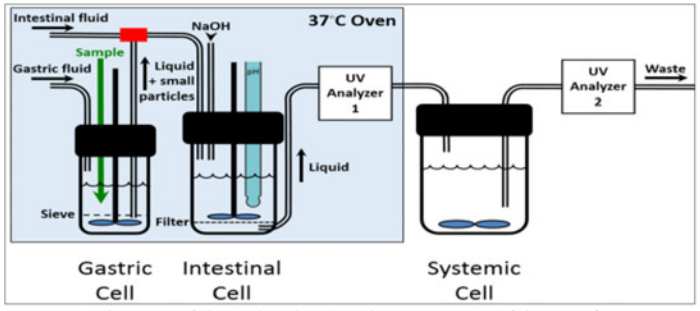

Figure 1. Schematic of three chamber dissolution apparatus (FloVitro™) .

RESULT(S)

No significant difference was observed between the curve obtained using the three chamber dissolution apparatus and the scaled *in-vivo* data for the IR formulation, as shown in Figure 2. Level A IVIVC was achieved with an R^2 value of 0.9588, as shown in Figure 3.

Using the same *in-vitro* method, both ER capsules had a later T_{max} and a lower C_{max} than the IR tablet. Statistically significant differences were found for the dissolution profiles for both ER products over the first 12 hours (two tailed t-test $P<0.05$); while both ER formulations had a similar T_{max}, they had a significantly different C_{max}.

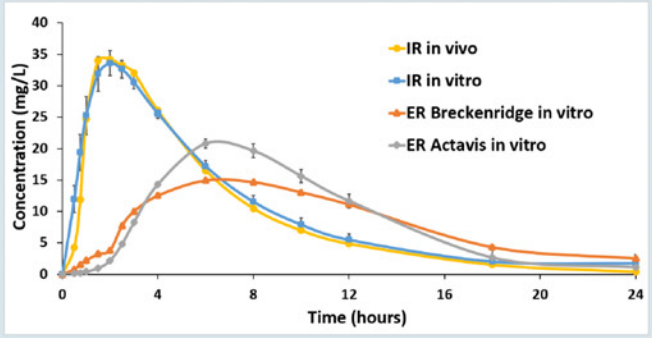

Figure 2 . Drug concentration time profiles of propranolol *in vivo*, IR and ER formulations. Yellow, blue, red, grey lines represent *in vivo,* Pliva IR, Breckenridge ER and Actavis ER respectively. Each data point represents mean ± SD (n=3).

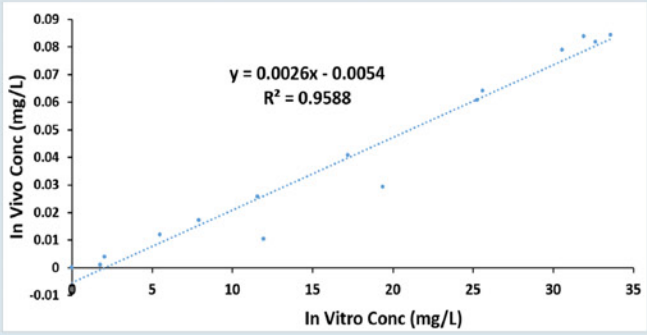

Figure 3 . Levy plot showing correlation between *in vivo* IR propranolol concentration and FloVitro™ IR propranolol concentration.

CONCLUSION(S)

The high R^2 value of 0.9588 indicates a strong correlation between the *in-vitro* and *in-vivo* data. This data could be applied to check performance of a generic product versus an innovator, predict the effect of a formulation change, or detect batch to batch variability.

As significantly different dissolution profiles were obtained for the different ER release formulations, it is possible to examine the potential differences in release characteristics of formulations using the three chamber dissolution apparatus. This could be useful during the formulation development phase, prior to clinical trials, to show a 'rank-order' of different prospective formulations.

Further research is ongoing to test the utility of the three chamber dissolution apparatus with BCS class II drugs and novel bio-enabling formulations, such as co-crystals, amorphous solid dispersions, and lipid-based formulations.

ACKNOWLEDGMENTS

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