Bioequivalence & Bioavailability

Yerasi and Vurimindi, J Bioequiv Availab 2015, 7:2
http://dx.doi.org/10.4172/jbb.1000217

Research Article Open Access

Evaluation of Frog as an Animal Model to Study the Fraction of Oral Dose Absorbed in Humans

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Abstract

To evaluate single pass intestinal perfusion method in frog for the prediction of absorption in man and also to evaluate the predictability of this model to classify drugs correctly under biopharmaceutical classification system (BCS). Single Pass Intestinal Perfusion (SPIP) studies were performed in Frogs of the species *Rana tigrina* using established method for rats with some modifications. Permeability was determined for each selected drug in 6 frogs and the results were presented as mean ± SD. Effective permeability coefficient (P_{eff}) of 12 drugs was calculated. Permeability assessment of some carrier transported drugs which are also substrates for CYP enzymes was also done. Correlation of frog P_{eff} with fraction of dose absorbed (FA) in man was done. Rank order comparison of permeabilities obtained in this study with two other absorption models (human jejunal perfusion, rat intestinal perfusion) was made. The calculated P_{eff} values correlated well with reported P_{eff} values of probe drugs. Good correlation was found between P_{eff} of humans and frogs (r^2=0.942). The permeability classification based on frog intestinal permeability of drugs is in high agreement with previously introduced classification, and all the compounds are placed in correct categories as they belong to. The results of this study provided a basis that, as a permeability model in the early drug discovery stage, the single pass intestinal perfusion frog model can be used for the biopharmaceutics classification system. This model may represent a valuable alternative to the low speed and high cost of conventional animal models (typically rodents) for the assessment of intestinal permeability.

Keywords: Effective permeability coefficient; Bioavailability; Single pass intestinal perfusion; Fraction absorbed; Biopharmaceutical classification system; Frog intestinal perfusion

Introduction

An estimated 40% of new molecular entities fail to be new drugs because of poor biopharmaceutical properties, namely solubility and permeability [1]. Solubility is easily quantifiable in vitro and can be manipulated by formulation strategies, while permeability is more complex to be altered for improved performance in human beings. Moreover Permeability is an important factor, which governs absorption of orally administered drugs. Hence, screening of drug candidates for permeability properties is imperative to select right candidate for development to prevent late surprises [2].

A rapid, time and resource sparing technology to predict human oral absorption has been a goal of biopharmaceutical scientists for generations. Both early discovery and early development teams would benefit from such models. The savings in time and resources clearly justify the continued effort to improve existing models and investigate / validate new models.

Different in vitro methods are available to assess the absorption potential of early-stage compounds such as adenocarcinoma cell line derived from human colonic epithelial cell monolayers (Caco-2), Madin-Darby Canine Kidney (MDCK) cells, parallel artificial membrane permeation assay (PAMPA), excised animal tissues in Using chambers. These techniques have been recently reviewed and critically examined in terms of reliability, throughput potential and related advantages and limits in their actual applicability [3-6]. Among these different approaches, the methods based on drug transport across intestinal epithelial cell monolayers, such as Caco-2 cells, are at present the most frequently and successfully exploited in drug discovery [7]. In fact, they show functional properties of the human intestine, giving good correlations with the fraction absorbed in humans for a variety of drug compounds [8-10]. However, some important drawbacks, such as long cell growth cycles, possibility of microbial contamination, high costs, and relatively wide inter-experiment and inter-laboratory variations, limit their use as high-throughput screening systems [10,11].

Animal models come into picture as an alternative for prediction of human drug absorption. The rat *in-situ* intestinal perfusion is a commonly used technique for the assessment of permeability of drugs and new chemical entities. Effective permeability coefficients (P_{eff}) were determined in rats, *in-situ*, for 14 compounds using a single pass intestinal perfusion (SPIP) model. The *in-situ* technique provided a greater correlation with intestinal absorption in man than did Caco-2 and MDCK cell lines [12]. In contrast, in another study, No correlation (R^2 = 0.29) was found in the bioavailability between rat and human, while a correlation was observed with R^2 = 0.8 between human and rat intestinal permeability of drugs with both carrier-mediated absorption and passive diffusion mechanisms [13]. Although dog has been commonly employed as an animal model for studying oral absorption in drug discovery and development, a comparison of bioavailability of 43 drugs in dogs and humans, showed a poor correlation (R^2 = 0.512) between the two species [14]. Monkey may be a good model for predicting oral absorption in humans, but is a very expensive model.

Hence there is a clear need for the development of a new simple model for the study of intestinal absorption of drugs. Hence in this study we have developed SPIP using frog as the animal model. The

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Received December 09, 2014; **Accepted** January 02, 2014; **Published** January 29, 2015

Citation: Yerasi N, Vurimindi H and Devarakonda K (2015) Evaluation of Frog as an Animal Model to Study the Fraction of Oral Dose Absorbed in Humans. J Bioequiv Availab 7: 068-073. doi:10.4172/jbb.1000217

purpose of the present study was to examine the P_{eff} predictability of the frog in-situ single pass intestinal perfusion model and to enable the prediction of human P_{eff} directly using this model and also to classify the drugs according to BCS.

Materials and Methods

Chemicals

The test drugs used in this study were of the highest grade. Metaprolol, ranitidine, cimetidine, ketoprofen, naproxen, atenolol, fluvastatin, ciprofloxacin, propranolol were provided by Dr.Reddy's laboratories as gift samples. Hydrochlorthiazide, verapamil, furosemide were provided as gift samples by alkem labs,India. Antipyrine was purchased from Himedia chemicals, India. All other chemicals used in this study were purchased from Sigma. The HPLC solvents methanol, acetonitrile, triethylamine, orthophosphoric acid, were purchased from Fisher Chemicals and were all HPLC grade.

Composition of perfusion solutions

The perfusion buffer composition was as follows: CaCl2 × 2H2O, 0.98 mM, KCl 2.58 mM, Na_2HPO_4 0.66 mM, NaH_2PO_4 5.1 mM, NaCl 84 mM, d-glucose 3.0mM with pH 6.8 (with NaOH) phenol red (50 mg L^{-1}) was added to the solution as a non-absorbable marker. The pH was adjusted to 7.4 and the osmolality, measured by the freezing point depression method, was 230 ± 10 mOsm kg^{-1} (Osmette A, Precision Systems Inc., Natick, MA) isotonic for amphibian [15] Preliminary experiments showed that there was no adsorption of the compounds to the catheters and the tubing. Test drug concentrations used in the perfusion studies were determined by dividing the highest prescribed dose by 250 ml, the accepted gastric volume, in order to represent the maximal drug concentration present in the intestinal segment. Solutions of test drugs were prepared with blank perfusion buffer. Drugs which were insoluble in perfusion buffer were solublised using less than 1% methanol.

Frog *in-situ* single pass intestinal perfusion technique

Frog *in situ* perfusion studies were performed using established SPIP method for rats [16] with few modifications. Animal care and handling throughout the experimental procedure were performed in accordance with the "Principles of Laboratory Animal Care" (NIH publication # 85-23, revised in 1985). Frogs of the species *Rana tigrina*, an Indian frog were used for the experiments.

Frogs were fasted for 24 hours prior to the start of the experiment. Each frog was anaesthetized and maintained with a combination of intraperitoneal injection of 230 mg/kg b.wt. of phenobarbital sodium and 25 mg/kg b.wt. of thiopentone sodium. After the onset of deep anesthesia, abdomen was opened by a midline longitudinal incision and approximately 15 to 20 cm length of intestine immediately after stomach was selected, rinsed with frog's ringer and cannulated at both sides. Care was taken in handling the small intestine to minimize the surgery in order to maintain an intact blood supply. Initially the contents of the intestine were flushed out with blank perfusion solution, then with the test solution and then perfused with test solutions at a flow rate of 0.2 ml/min using syringe pump for 90 min after 30 min of equilibration. The perfusate samples were collected at every 10 min. Water flux was quantified with the help of concentration change of phenol red (non-absorbable inert marker). The length and radius of the perfused segment was measured at the end of the experiment and the animal was euthanized by the removal of the heart. Permeability for each drug was determined in 6 frogs and the results were presented as mean ± SD. Samples were stored at -20°C until analysis.

Calculation of Effective permeability coefficient (P_{eff}) and absorption rate constant (K_a)

Effective permeability coefficient (P_{eff}) was calculated from the steady-state concentration of compounds in the collected perfusate (17). Steady state, which was assessed by a constant concentration of phenol red, was reached 30-40 min after the beginning of the experiment. P_{eff} value was calculated using equation (1), according to the parallel tube model [18].

$$P_{eff} = -Q\, ln[C_{out\ corr} / C_{in}] / 2\pi rl \quad (1)$$

Where Q is perfusion flow rate (ml/min); C_{in} is inlet concentration (µg/ml); $C_{out\ (corr)}$ is outlet concentration of compound which is corrected for water flux using phenol red concentration (µg/ml) [C_{out}

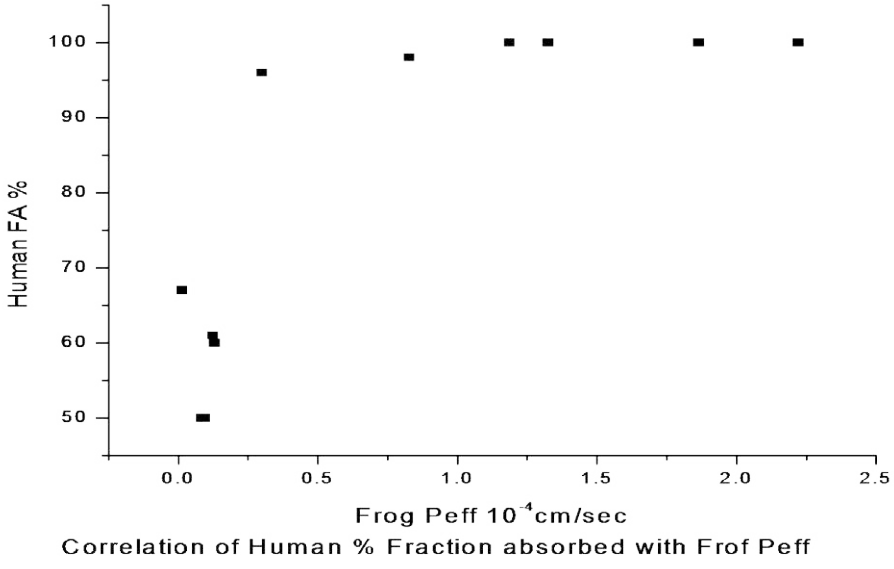

Figure 1: Correlation of Human % Fraction absorbed with Frog P_{eff}.

$_{(corr)} = C_{outmeasured} \times [\text{phenol red}]_{in}/[\text{phenol red}]_{out}]$, r is the radius of the frog intestine (cm). l is the length of the intestinal segment (cm). The concentrations obtained from the perfusate were corrected for changes in the water flux at each time interval using the above equation.

Intestinal absorption rate constant, k_a, was calculated for each 10 min interval, utilizing following relationship:

$$k_a = Q\left[C_{out\ corr} / C_{in}\right] / V$$

where V is the volume of perfused intestinal segment ($=r^2\pi l$) Initial 30 min duration was allowed for attainment of steady state absorption in intestine and k_a was determined for all subsequent 10 min intervals. An average k_a was then calculated for each perfusion experiment.

HPLC analysis

All compounds were assayed following standard HPLC methodology given in literature [19-31]. Optimized HPLC Conditions used for the determination of tested compounds is depicted in Table 1 and mobile phase composition used for the analysis is given in Tables 1 and 2.

Results and Discussion

The permeabilities of twelve model drugs were determined using the single pass intestinal perfusion technique in frogs as described. These compounds were stable in perfusion buffer, were soluble at the experimental conditions used. A wide variety of compounds belonging to all four classes of biopharmaceutical classification system are included in the study, since BCS guidance recommends the development of a permeability model based on method suitability to classify drugs with the use of reference standards. Physicochemical properties of the twelve model drugs and their respective concentration used in the perfusion study are given in Table 3. All the compounds except cimetidine and ciprofloxacin are among the model drugs suggested for use in establishing suitability of a permeability method by FDA. HPLC methods adopted from literature were optimized for the estimation of chosen model drugs and calibration curves were constructed. Perfusion studies were carried out for each drug following same perfusion protocol. Outlet perfusate samples collected were analysed for each drug. P_{eff} and K_a were calculated after analysis by the method described. The steady state values of the effective permeability coefficients of both phenol red and antipyrine throughout the perfusion experiment were stable indicating that the intestinal epithelial cells in the frog model possess normal mucosal transport properties and metabolic functions. Furthermore the stable transmucosal transport of antipyrine indicates that no changes in membrane integrity occurred during the entire length of the experiment. The mean P_{eff} values of the drugs, the mean apparent absorption rate constant (K_a) calculated in this study and the corresponding percentage of drug absorbed in humans (FA) are summarized in Table 4. Also the P_{eff} values determined by rat model, caco-2, and parallel artificial membrane model (PAMPA) collected from literature are also tabulated in Table 4 for comparison. Figure 1 shows the correlation of human % fraction absorbed with frog P_{eff}. P_{eff} values of the drugs obtained in this study were plotted against their % fraction absorbed in humans obtained from literature. Frog P_{eff} values of compounds determined by this technique on extrapolation using this plot (Figure 1) give % fraction absorbed (FA) in humans. Rank order comparison of permeabilities obtained in this study with two other absorption models (human jejunal perfusion, rat intestinal perfusion) were made (Figures 2 and 3). Plot of P_{eff} of test compounds in humans and frogs showed good correlation (R^2=0.942) which is depicted in Figure2. Comparison of P_{eff} of model drugs in humans & frogs were made in Figure 5. Compounds having high permeability showed P_{eff} greater than 0.3×10^{-4}cm/min. Compounds having low permeability showed P_{eff} less than 0.3×10^{-4}cm/min. Comparision of permeabilities of test durgs with internal standard metaprolol was done in Figure 4. Metoprolol was chosen as the internal permeability standard because its FA is well documented [22] and is 96%, which is close to the 90% FA specified in the BCS guidance as the border for high permeability drugs. All the drugs having permeability greater than or equal to metaprolol are classified as high permeability compounds and those having permeability less than metaprolol are classified as low permeability compounds.

Drug	Mobile phase[a]	Flow rate mL/min	λ (nm)
Metaprolol	A	0.7	230
Naproxen	B	0.8	235
Ranitidine	C	0.8	270
Cimetidine	D	1.2	254
Ketoprofen	E	0.8	257
Hctz	F	0.8	270
Verapamil	G	1.3	230
Atenolol	H	0.8	220
Antipyrine	I	0.8	244
Fluvastatin	J	0.9	220
Furosemide	K	0.7	275
Ciprofloxacin	L	1.0	254

Table 1: HPLC Conditions Used for the Analysis of Tested Compounds.

Mobile phase	Composition
A	50% methanol, 50% phosphate buffer pH 7.4;
B	50% acetonitrile, 50% Milli-Q water
C	20% acetonitrile, 80%,20 mM phosphate buffer pH 7.4
D	20%methanol,80% 1% acetic acid bufferpH3.0;
E	65% methanol,35% 0.7% phosphate buffer pH 3.5
F	20% acetonitrile, 80% Milli-Q water
G	3% phosphate buffer pH 7.4 20 mM, 24% Milli-Q water, 40% acetonitrile, 33% methanol
H	15% methanol in Milli-Q watercontaining 0.005MHCland 0.5Msodium chloridepH3.0
I	55% methanol, 45% phosphate buffer pH 5.2
J	75% methanol, 25% Milli-Q water;
K	55% methanol,1% acetic acid buffer pH3.0
L	55% methanol,45% phosphate buffer pH 5.2;

Table 2: [a] Mobile phase Composition.

S. No.	Drugs	Mol Wt.	Log P	Conc. Used (µg/mL)
1	Metaprolol	267.3	1.6	50
2	Naproxen	230.2	2.8	100
3	Ranitidine	314.4	1.3	100
4	Cimetidine	252.3	-0.5	40
5	Ketoprofen	254.2	3.2	60
6	Hctz	297.7	-0.5	20
7	Verapamil	454.6	4.7	100
8	Atenolol	266.3	0.5	40
9	Antipyrine	188.0	0.3	50
10	Fluvastatin	411.4	4.5	30
11	Furosemide	330.0	1.4	40
12	Ciprofloxacin	331.3	2.3	30

Table 3: Physicochemical properties of drugs used in the perfusion study.

	Effective	Permeability	Coefficient	X 10^{-4}	cm/min				
Compound	Frog[d]	human[a]	Rat[b]	CACO - 2[c]	PAMPA[c]	BCS[a]	Frog[d]	Human[a] FA %	K_ax10^{-4}/min
Metaprolol	0.3 ± 0.052	1.3 ± 10-4	0.20 ± 0.04	0.23	0.035	H	H	96	1.2
Naproxen	1.865 ± 0.17	8.3 ± 4.8	1.19 ± 0.12	0.39	0.106	H	H	100	7.2
Ranitidine	0.094 ± 0.07	0.27 ± 0.06	0.073 ± 0.06	0.004	0.005	L	L	50	0.37
Cimetidine	0.129 ± 0.06	0.3 ± 0.05	0.105 ± 0.06	0.007	0.0	L	L	60	0.516
Ketoprofen	2.22 ± 0.23	8.4 ± 3.3	1.55 ± 0.34	-	0.167	H	H	100	8.88
Hydrochlorthiazide	0.013 ± 0.002	0.04 ± 0.05	0.001 ± 0.001	0.005	0.0	L	L	67	0.052
Verapamil	1.186 ± 0.08	6.7 ± 2.9	0.65 ± 0.05	0.117	0.074	H	H	100	4.74
Atenolol	0.083 ± 0.05	0.2 ± 0.2	0.060 ± 0.06	0.002	0.0	L	L	50	0.332
Antipyrine	1.325 ± 0.12	4.5 ± 2.5	0.96 ± 0.13	0.28	0.132	H	H	100	5.3
Fluvastatin	0.827 ± 0.07	2.4 ± 1.8	0.50.04	--	-	H	H	98	3.3
Furosemide	0.0124 ± 0.03	0.04 ± 0.04	0.117 ± 0.08	0.001	0.006	L	L	61	0.05
Ciprofloxacin	0.2 ± 0.85	-	0.155 ± 1.98	0.028	0.0017	L	L	-	0.8

a. Winiwarter et al., 1998; Takamatsu et al.,1997; Takamatsu et al.,2001; Lennernas et al 2002; Lennernas et al,1995;
b. Fagerholm et al.,1996;Kim et al., 2006.
c. Zhu et al.,2002; Bermajo et al.,2003.
Determined in this study

Table 4: The mean P_{eff} values of the drugs, the mean apparent absorption rate constant (K_a) calculated in this study and the corresponding percentage of drug absorbed in humans (FA) are summarized.

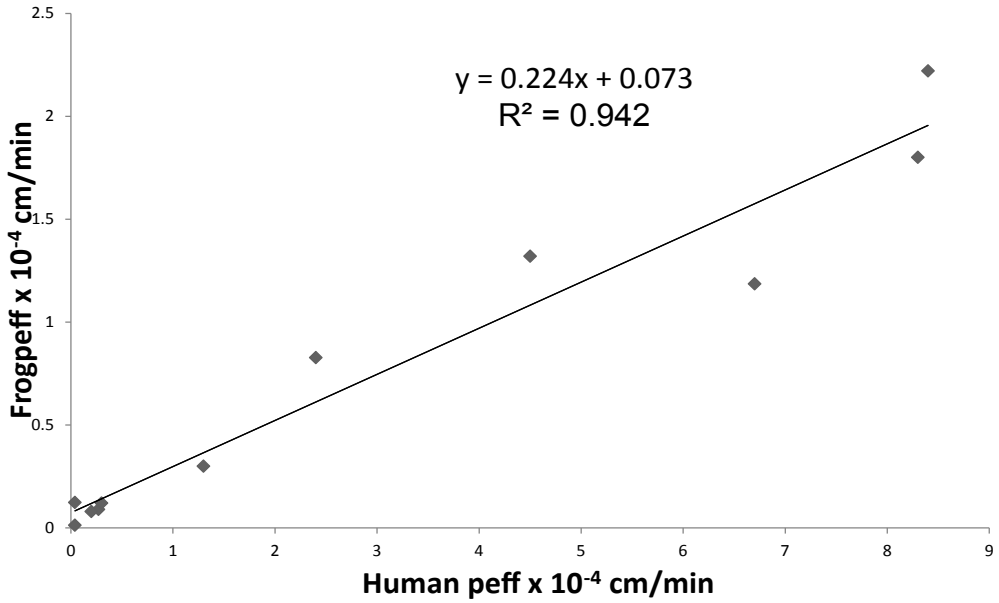

Figure 2: Differential effects of efflux or absorptive mechanisms between human and frog may also account for the variability.

A direct comparison of human and frog P_{eff} data shows that the two methods correctly assign a given drug's BCS permeability classification (Figure 5). The relatively large amount of scattering in the permeability correlation between humans and frogs, particularly with the high permeability drugs, may be attributed to the different models, macroscopic versus microscopic and experimental setup, Loc-I-Gut versus single pass perfusion, used when measuring human or frog permeability, respectively. Differential effects of efflux or absorptive mechanisms between human and frog may also account for the variability seen in Figure 2. The permeability determinations for each test drug and the internal reference are plotted in Figure 4. From the obtained results, it is provided that the presented classification based on frog intestinal permeability of drugs is in high agreement with previously introduced classification, and all the compounds are placed in correct categories as they belong to. The perfusion method allows for the control of drug concentration, pH, osmolarity, intestinal region, and flow rate. The model integrates aspects of drug transport and metabolism in that all the physiological factors influencing drug passage are present. Frog intestinal perfusion data can be utilized for the prediction of % FA in humans for passively and actively transported drugs. It is a useful technique to classify compounds according to BCS with appropriate passively and actively absorbed reference compounds, demonstrating a relationship between frog intestinal P_{eff} and % FA in humans.

Conclusion

In conclusion, the single pass intestinal perfusion in frog model predicted the P_{eff} adequately. With the predicted P_{eff} value, it may be possible to simulate the *in vivo* plasma concentration-time profile.

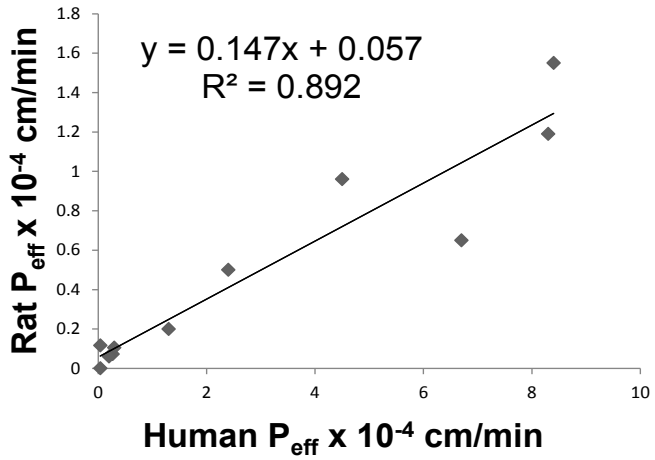

Figure 3: Rank order comparison of permeabilities obtained in this study with two other absorption models.

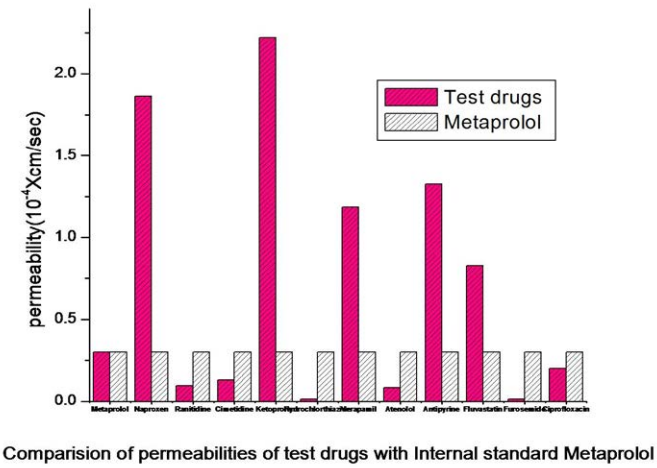

Figure 4: Comparision of permeabilities of test durgs with internal standard metaprolol.

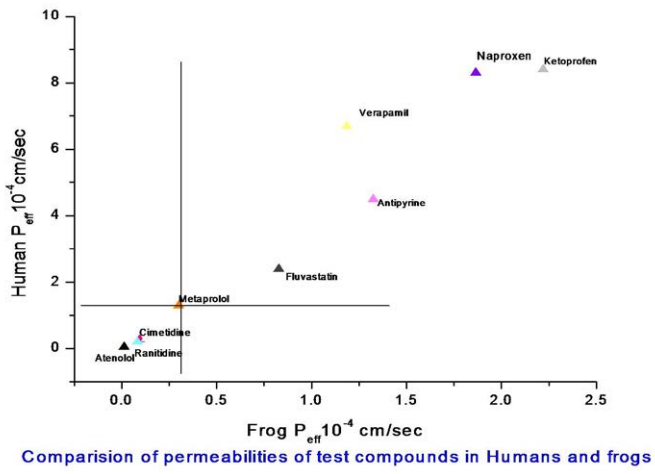

Figure 5: Comparision of permeabilities of test compounds in Humans and Frogs.

In addition, the results of this study provided a basis that, as a permeability model in the early drug discovery stage, the single pass intestinal perfusion frog model can be used for the biopharmaceutics classification system. This may result in the discovery of promising clinical candidates.

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