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Research paper

Biopharmaceutical classification of drugs using intrinsic dissolution rate (IDR) and rat intestinal permeability

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ABSTRACT

The solubility and dissolution rate of active ingredients are of major importance in preformulation studies of pharmaceutical dosage forms. In the present study, passively absorbed drugs are classified based on their intrinsic dissolution rate (IDR) and their intestinal permeabilities. IDR was determined by measuring the dissolution of a non-disintegrating disk of drug, and effective intestinal permeability of tested drugs in rat jejunum was determined using single perfusion technique. The obtained intrinsic dissolution rate values were in the range of 0.035–56.8 mg/min/cm^2 for tested drugs. The minimum and maximum intestinal permeabilities in rat intestine were determined to be 1.6×10^{-5} and 2×10^{-4} cm/s, respectively. Four classes of drugs were defined: Category I: $P_{eff,rat} > 5 \times 10^{-5}$ (cm/s) or $P_{eff,human} > 4.7 \times 10^{-5}$ (cm/s), IDR > 1(mg/min/cm^2), Category II: $P_{eff,rat} > 5 \times 10^{-5}$ (cm/s) or $P_{eff,human} > 4.7 \times 10^{-5}$ (cm/s), IDR < 1(mg/min/cm^2), Category III: $P_{eff,rat} < 5 \times 10^{-5}$ (cm/s) or $P_{eff,human} < 4.7 \times 10^{-5}$ (cm/s), IDR > 1 (mg/min/cm^2) and Category IV: $P_{eff,rat} < 5 \times 10^{-5}$ (cm/s) or $P_{eff,human} < 4.7 \times 10^{-5}$ (cm/s), IDR < 1(mg/min/cm^2). According to the results obtained and proposed classification of drugs, it is concluded that drugs could be categorized correctly based on their IDR and intestinal permeability values.

1. Introduction

The solubility and dissolution rate of active ingredients are of major importance in preformulation studies of pharmaceutical dosage forms [1–6]. The formulation characteristics including shelf life, process behavior and even the bioavailability are affected by physicochemical properties of drug molecules [7]. The intrinsic dissolution rate (IDR) has been used to characterize solid drugs for many years [8,9]. For example, it could be used to understand the relationship between the dissolution rate and the crystalline form and also to study the effects of surfactants and pH on the solubilization of poorly soluble drugs [10,11]. IDR is generally defined as the dissolution rate of a pure drug substance under the condition of constant surface area, agitation or stirring speed, pH and ionic strength of the dissolution medium. The true intrinsic dissolution rate may be better described as the rate of mass transfer from the solid surface to the liquid phase. The apparatus for intrinsic dissolution testing was originally developed by John Wood which enables the calculation of the dissolution rate per square centimeter of the intrinsic ingredients of pharmaceutical products [12–14]. It has been suggested that it might be feasible to use IDR to classify drugs instead of using solubility [9]. The reason is that, just like permeability, IDR is a rate phenomenon instead of an equilibrium phenomenon. Therefore, it might correlate better with in vivo drug dissolution rate than solubility, although for drugs having either extremely high or low dose, discrepancies may exist between the solubility and the IDR methods [9] since dose is considered in the classification of solubility while intrinsic dissolution does not consider the effect of dose. On the other hand there are a number of in vitro and in situ experimental models have been developed that determine the intestinal absorptive potential of a drug and the mechanism of absorption [15,16]. Among these methods single-pass intestinal perfusion (SPIP) approach is the most frequently used technique that provides conditions closer to what is faced following oral administration. SPIP technique possesses a preserved microclimate above the intestinal membrane which makes it less sensitive to pH variations. This technique provides the unique advantages of experimental control (compound concentration and intestinal perfusion rate) and the ability to study regional differences; factors that may influence the intestinal absorption of a compound. In the present study, the intrinsic disso-

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lution rate and rat intestinal permeability (using SPIP technique) were measured for drugs with different physicochemical properties. The suitability of using IDR and permeability for biopharmaceutical classification of drugs was evaluated.

2. Materials and methods

2.1. Materials

Naproxen, atenolol, metoprolol, propranolol, verapamil hydrochloride and ibuprofen were provided from Shasun (Shasun Chemical & Drugs LTD., India). Ketoprofen and antipyrine were from Sigma (Sigma, Canada) and Hoechst (Hoechst, Germany), respectively. Furosemide and hydrochlorothiazide were provided from Fls (Fls, Italy). Ranitidine and cimetidine were obtained from Uquifa (Uquifa, Spain), and piroxicam was from Ciba-Geigy (Barcelona, Spain). Monobasic potassium phosphate (KH_2PO_4) and sodium hydroxide (NaOH) were purchased from Merck (Darmstadt, Germany).

2.2. Methods

2.2.1. Procedure of IDR measurement

A quantity of 100 mg of each drug was compressed at an average compression force of 7.84 MPa for 1 min to make non-disintegrating compacts using die and punch with a diameter of 6 mm. In order to prevent capping, in the case of piroxicam and carbamazepine the compression forces were 1.96 and 19.6 MPa, respectively. The surface area of the compacts was 0.2826 cm^2. The improved method of Wood et al. was used for disk dissolution studies [14]. Compacts were placed in a molten beeswax-mold in such a way that only one face could be in contact with dissolution medium. Dissolution study was conducted using USP II dissolution apparatus using 900 mL of phosphate buffer (pH = 6.8) at a temperature of 37 °C ± 1 °C as the dissolution media with paddle rotate at 100 rpm. Samples were collected through 0.45-μm syringe filters over a period of 8 h for low-soluble drugs and 20 min for highly soluble drugs. Sampling time intervals were 30 min and 2 min, respectively. All studies were carried out in triplicate. Absorbances were determined in triplicate using a UV–Vis spectrophotometer (UV160, Shimadzu, Kyoto, Japan) at the maximum absorbance wavelength for each active tested sample (Table 1). The cumulative amount dissolved per surface unit of the compact was plotted against time for each vessel. The slope of the linear region ($R^2 \geqslant 0.95$) was taken as intrinsic dissolution rate. IDR is easily calculated by

$$G = (dw/dt)(1/S) = DC_s/h \quad (1)$$

where G is the intrinsic dissolution rate (mg/min/cm^2); dw is the change in drug dissolved (mg); dt is the change in time (min); S is the surface area of the compact (cm^2); D is diffusion coefficient (cm^2/s); C_s is the solubility (mg/cm^3) and h is the stagnant layer thickness (cm).

2.2.2. Solubility studies

Solubilities were determined in at least triplicates by equilibrating excess amount of drugs in phosphate buffer solutions (pH = 6.8). The samples were kept in thermostated water bath at 37 °C and shaken at a rate of 150 rpm for 24 h. The absorbances of filtered and suitably diluted samples were measured with a UV–Vis spectrophotometer (UV160, Shimadzu, Kyoto, Japan) at the maximum absorbance wavelength for each active tested sample. The solubilities were calculated using calibration curves determined for each drug.

2.2.3. Measurement of rat intestinal permeability coefficients

The anesthesia and surgery were performed in accordance with a previously validated in situ intestinal perfusion method in rats [17]. Details of the procedure, analytical methods and also permeability coefficient calculation were explained in authors' published works [16,18,19]. Briefly, male Wistar rats (weight, 250–300 g; age, 7–9 weeks) were maintained on 12 h light-dark cycle and fasted 12–18 h before the experiment. On the day of experiment a single pass constant flow (2 ml/min) of drug containing perfusate (PBS pH = 7.2, 37 °C) was established through the ligated rat jejunal

Table 1
Experimental wavelength, Solubility, intrinsic dissolution rate (IDR), rat intestinal permeability ($P_{eff,rat}$), Human intestinal permeability ($P_{eff,human}$), Fraction dose absorbed in human (F_a) and respective class of tested compounds using different approaches.

Compound	Wavelength (nm)	Solubility (mg/l)	IDR (mg cm^{-2} min^{-1})	$P_{eff,rat}$ ($\times 10^5$ cm/s)	$P_{eff,human}$ ($\times 10^4$ cm/s)	Human F_a	Drug class				
							This work[a]	This work[b]	BCS	BDDCS	Dissolution based
Antipyrin	243	683271.6	56.79	5.9	5.60[f]	1.00[f]	I	I	I	I	I
Metoprolol	274	779580.8	34.64	3.3	1.20[c]	0.95[f]	I	III	I	I	I
Propranolol	288	71797.17	16.596	5.6	2.90[d]	0.90[f]	I	I	I	I	II
Verapamil	274	71602.64	16.192	7	5.00[j]	0.90[j]	I	I	I	I	I
Ketoprofen	261	2121.80	0.6348	9.6	8.70[d]	1.00[e]	II	II	I	I	II
Naproxen	262	1604.45	0.388	11	10.0[c]	1.00[h]	II	II	II	II	II
Carbamazepine	285	164.59	0.0355	6.2	4.30[d]	0.97[i]	II	II	II	II	IV
Ibuprofen	222	1315.41	0.2844	20	13.90[d]	0.99	II	II	II	II	–
Piroxicam	353	157.64	0.0739	7.9	6.65[d]	0.99[h]	II	II	II	II	–
Atenolol	224	16868.14	3.449	1.6	0.12[c]	0.50[f]	III	III	III	III	III
Cimetidine	219	46276.68	7.2	4.8	0.60[d]	0.79[g]	III	III	III	III	–
Ranitidine	228	>1000000	42.18	2.2	0.27[d]	0.50[f]	III	III	III	III	III
Furosemide	277	1464.42	0.58	3.3	0.30[e]	0.61[f]	IV	IV	IV	IV	IV

[a] Proposed class based on IDR and human intestinal permeability.
[b] Proposed class based on IDR and rat intestinal permeability rat intestinal permeabilities were taken from Ref. [16].
[c] Taken from Ref. [37].
[d] Taken from Ref.[28].
[e] Taken from Ref.[38].
[f] Taken from Ref.[39].
[g] Taken from Ref.[40].
[h] Taken from Ref.[41].
[i] Taken from Ref.[42].
[j] Taken from Ref.[43].

segment and the outlet samples were collected every 10 min in microtubes up to 90 min and stored at −20 °C until analysis. Finally the animal was euthanized with a cardiac injection of saturated solution of KCl. In all animal studies "Guide to the care and use of experimental animals" by Canadian Council on Animal Care was followed [20]. Permeability values were calculated using the following equation according to the parallel tube model:

$$P_{\text{eff}} = -Q \ln(C_{\text{out(corrected)}}/C_{\text{in}})/2\pi rl \quad (2)$$

where C_{in} and C_{out} are the inlet and outlet concentrations of the compound, respectively. C_{out} is corrected for volume change in segment using phenol red concentration in inlet and outlet tubing. Q is the flow rate (0.2 ml/min), r is the rat intestinal radius (0.18 cm) and l is the length of the intestinal segment [16,21].

3. Results

Current BCS (Biopharmaceutics Classification System) guidance defines an API as "highly soluble" when the highest dose recommended is soluble in 250 mL or less of aqueous media over the pH range of 1.2–7.5 [22]. However, the pH 6.8 is scientifically justified over pH 7.4 [22,23]. In order to set a condition for BCS classification of compounds and since small intestine is the major site for drug absorption, where the pH is about 6.8, IDR measurements were taken at pH 6.8. Table 1 shows the solubility of model drugs at 37 °C in pH 6.8. The high solubility of ranitidine in experimental condition and reaching viscous solution in high concentrations made it difficult to assay its exact solubility [24]. The determined intrinsic rates of dissolution are also given in Table 1. The presence of sink condition in dissolution medium during the experiment is upheld by comparison of the final concentration of drugs and their solubility in dissolution medium. As seen in the Table 1, the ranking order of aqueous solubility and IDR is almost but not exactly the same. In general, compounds with high solubility exhibited IDR of greater than 3 mg/cm^2/min but compounds with low solubility had IDR of less than 1 mg/cm^2/min. However, antipyrin, which showed greatest IDR amongst the tested compounds, was determined to be less soluble than ranitidine and metoprolol. Furosemide exhibited higher IDR but slightly lower solubility in comparison with naproxen. In the same way piroxicam exhibited higher IDR but slightly lower solubility in comparison to carbamazepine. This could be explained by the fact that unlike solubility, IDR is a rate phenomenon and, besides solubility is dependent on wettability and diffusivity of the compound [25].

The observed intestinal permeability values in rats for tested drugs [16] are also presented in Table 1. For comparison the respective intestinal permeability and fraction of dose absorbed in human are also cited. Classification of tested drugs based on their intestinal permeability and IDR for human and rat is shown in Figs. 1 and 2, respectively.

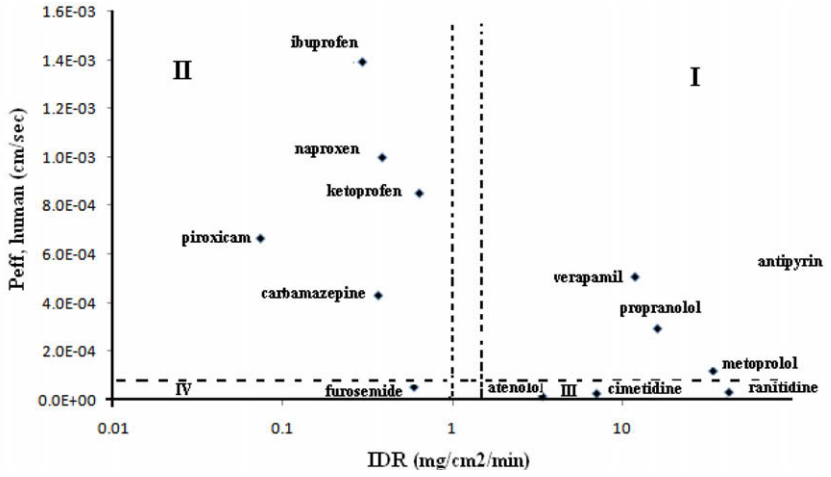

Fig. 1. Classification of tested drugs based on their human intestinal permeability and IDR.

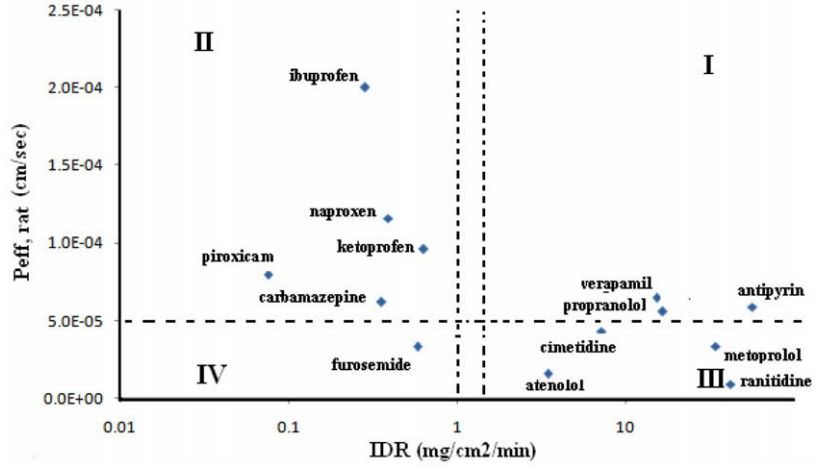

Fig. 2. Classification of tested drugs based on their rat intestinal permeability and IDR.

4. Discussion

Drugs are scientifically identified based on their solubility and human intestinal permeability [26]. The BCS consists of four drug categories: class I (highly soluble and highly permeable), class II (low soluble and highly permeable), class III (highly soluble and low permeable) and class IV (low soluble and low permeable). Since human intestinal permeability could be predicted with precision using the rat effective permeability values [16], the same classification can be constructed utilizing the solubility and rat intestinal permeability values [27]. IDR is a parameter which could be easily used to characterize the pure drug substance. The determination of this parameter allows laboratories to screen experimental drug formulations and to understand their behavior under different biophysical conditions. Table 1 shows the obtained solubility and IDR values in the present work for tested drugs. The obtained IDR values on the tested drugs in the present work are slightly greater than those reported by Yu et al. [9]. The difference might be ascribed to different methods of IDR measurement used in the two investigations. However, the ranking order of the obtained IDR values is the same. The obtained solubility data were in agreement with those in literature as well [28].

Comparing rat P_{eff} values with those of human showed a high regression correlation ($R^2 = 0.93$, $P < 0.0001$) for passively absorbed compounds confirming a close relationship between rat and human permeabilities [16]. The fraction of dose absorbed (F_a) in humans is the basis of the permeability classification. According to the FDA Guidance, an active pharmaceutical ingredient is highly permeable when the fraction of dose absorbed is 90% or more. The recently revised WHO Guidelines set a lower limit of 85% [29–31]. Yu et al. proposed to reduce the high permeability requirement for biowaiver from 90% to 85% [22,32]. On the basis of the relationship between permeability and fraction of dose absorbed [16], P_{eff} values greater than 5.09×10^{-5} and 4.7×10^{-5} cm/s in rat and human, respectively, correspond to $F_a > 85$, which were set as cut-off points for highly permeable drugs.

On the other hand, IDR correlates with the BCS solubility classification with 1–2 mg/min/cm^2 as a class boundary. It is seen that antipyrin, ranitidine and metoprolol with IDRs of 56.79, 42.18 and 34.64 mg/cm^2/min, respectively, have the higher values in comparison with others whereas carbamazepine and piroxicam have the lowest IDR in the series (IDR = 0.035 and 0.07 mg/cm^2/min, respectively). As was mentioned earlier, this order is almost the same for the solubility of mentioned drugs. However in the case of permeability this arrangement is not expected. The reason is that the investigated drugs belong to all four biopharmaceutical classes which means a drug with high IDR value may belong to high or low permeability classes.

In the present study, passively absorbed drugs are classified based on their intrinsic dissolution rates and human intestinal permeability values. IDR was expected to correlate more closely with in vivo dissolution dynamics of drug than solubility [9]. Therefore, it might be used to correct the assignment of a drug to a specific BCS class. The proposed classification is presented in Figs. 1 and 2 using human and rat jejunal permeability, respectively. Based on this classification, drugs are placed in four explicitly defined categories (I–IV) which are made by intersections of dashed lines drawn at the cut-off points for permeability and IDR. These classes are characterized as below:

Category I: $P_{eff,rat} > 5 \times 10^{-5}$ (cm/s) or $P_{eff,human} > 4.7 \times 10^{-5}$ (cm/s), IDR > 2 (mg/min/cm^2).

Examples of the compounds of this category include propranolol, metoprolol, verapamil and antipyrin which exhibit high dissolution and absorption. However, according to intestinal permeability estimates in rat, metoprolol is assigned to class III.

Category II: $P_{eff,rat} > 5 \times 10^{-5}$ (cm/s) or $P_{eff,human} > 4.7 \times 10^{-5}$ (cm/s), IDR < 1 (mg/min/cm^2).

Drugs like ketoprofen, naproxen, piroxicam, ibuprofen and carbamazepine are included in this category. Class II drugs have a high absorption but a low dissolution rate; therefore, absorption is limited primarily by drug dissolution in the gastrointestinal tract [26].

Category III: $P_{eff,rat} < 5 \times 10^{-5}$ (cm/s) or $P_{eff,human} < 4.7 \times 10^{-5}$ (cm/s), IDR > 2 (mg/min/cm^2).

Class III drugs have high dissolution and low absorption. In vivo permeability is a rate-limiting step for drug absorption [26]. Examples are atenolol, ranitidine and cimetidine.

Category IV: $P_{eff,rat} < 5 \times 10^{-5}$ (cm/s) or $P_{eff,human} < 4.7 \times 10^{-5}$ (cm/s), IDR < 1 (mg/min/cm^2).

Furosemide is an example of drugs in this category which exhibit a lot of problems for effective oral administration.

From the obtained results, it is provided that the presented classification based on IDR and human intestinal permeability of drugs is in high agreement with previously introduced classification, and most of the compounds are placed in correct categories they belong to [26]. Although when using the rat intestinal permeability values instead of human intestinal permeability, metoprolol was almost misclassified, considering non-feasibility of using human in intestinal perfusion studies, which is the major difficulty in assigning drugs to BCS classes, it may be suggested that determined intestinal permeability of drugs in rats could be used as a criterion for biopharmaceutical classification of compounds.

On the other hand, it was proposed that a biopharmaceutics drug disposition classification system (BDDCS) based on the extent of drug metabolism could provide an simple alternative method to assign drugs in class I for a waiver of in vivo bioequivalence studies [33–35]. According to this classification, highly metabolized drugs exhibit high permeability. Therefore, a drug is considered to be class I if it is highly soluble and highly metabolized. However, this definition excludes drugs that have high absorption but are excreted unchanged in to bile and urine [33]. Comparison of our results with BDDCS classification ($\geqslant$50% being defined as extensive metabolism) of drugs [35] shows high agreement (92% and 85% using human and rat intestinal permeability, respectively) with the classification of tested compounds (Table 1).

Another classification system, namely dissolution-based classification, was developed by Papadopoulou et al. [36] using mean intestinal transit time (MITT), mean dissolution time (MDT) and mean absorption time (MAT). The comparison of this classification with our results is also shown in Table 1. However, in dissolution-based classification propranolol and carbamazepine are classified as classes II and IV drugs, respectively, which are expected to be assigned in classes I and II, respectively, as was shown in other classifications in Table 1.

It seems that the presented classification could be used to waive in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms, which allows pharmaceutical companies to forego clinical bioequivalence studies if their drug product meets the required specification. Moreover, it may also be applied to new drug application (NDA) and abbreviated new drug application (ANDA) approvals as well as to scale-up and post-approval changes in drug manufacturing. BCS classification

can therefore save pharmaceutical companies a significant amount in development time and reduce costs.

5. Conclusion

In this study, a biopharmaceutical classification system was developed based on two principal properties, intrinsic dissolution rate at pH 6.8 and rat/human intestinal permeability of passively absorbed drugs. This classification is almost in agreement with previously introduced classification system on the basis of drug's solubility and human intestinal permeability.

References

[1] N. Laihanen, E. Muttonen, M. Laaksonen, Solubility and intrinsic dissolution rate of alprazolam crystal modifications, Pharm. Dev. Technol. 1 (1996) 373–380.

[2] S. Dastmalchi, A. Garjani, N. Maleki, G. Sheikhee, V. Baghchevan, P. Jafari-Azad, H. Valizadeh, M. Barzegar-Jalali, Enhancing dissolution, serum concentrations and hypoglycemic effect of glibenclamide using solvent deposition technique, J. Pharm. Pharm. Sci. 8 (2005) 175–181.

[3] M. Barzegar-Jalali, A.M. Nayebi, H. Valizadeh, J. Hanaee, A. Barzegar-Jalali, K. Adibkia, M. Anoush, M. Sistanizad, Evaluation of in vitro–in vivo correlation and anticonvulsive effect of carbamazepine after cogrinding with microcrystalline cellulose, J. Pharm. Pharm. Sci. 9 (2006) 307–316.

[4] M. Barzegar-Jalali, H. Valizadeh, S. Dastmalchi, M.R.S. Shadbad, A. Barzegar-Jalali, K. Adibkia, G. Mohammadi, Enhancing dissolution rate of carbamazepine via cogrinding with crospovidone and hydroxypropylmethylcellulose, Iran. J. Pharm. Res. 6 (2007) 159–165.

[5] H. Valizadeh, A. Nokhodchi, N. Qarakhani, P. Zakeri-Milani, S. Azarmi, D. Hassanzadeh, R. Lobenberg, Physicochemical characterization of solid dispersions of indomethacin with PEG 6000, Myrj 52, lactose, sorbitol, dextrin, and Eudragit E100, Drug Dev. Ind. Pharm. 30 (2004) 303–317.

[6] H. Valizadeh, P. Zakeri-Milani, M. Barzegar-Jalali, G. Mohammadi, M.A. Danesh-Bahreini, K. Adibkia, A. Nokhodchi, Preparation and characterization of solid dispersions of piroxicam with hydrophilic carriers, Drug Dev. Ind. Pharm. 33 (2007) 45–56.

[7] J. Haleblian, W. McCrone, Pharmaceutical applications of polymorphism, J. Pharm. Sci. 58 (1969) 911–929.

[8] G.E. Amidon, W.I. Higuchi, N.F. Ho, Theoretical and experimental studies of transport of micelle-solubilized solutes, J. Pharm. Sci. 71 (1982) 77–84.

[9] L.X. Yu, A.S. Carlin, G.L. Amidon, A.S. Hussain, Feasibility studies of utilizing disk intrinsic dissolution rate to classify drugs, Int. J. Pharm. 270 (2004) 221–227.

[10] J. Jinno, D. Oh, J.R. Crison, G.L. Amidon, Dissolution of ionizable water-insoluble drugs: the combined effect of pH and surfactant, J. Pharm. Sci. 89 (2000) 268–274.

[11] R. Dahlan, C. McDonald, V.B. Sunderland, Solubilities and intrinsic dissolution rates of sulphamethoxazole and trimethoprim, J. Pharm. Pharmacol. 39 (1987) 246–251.

[12] G. Levy, Effect of certain tablet formulation factors on dissolution rate of the active ingredient. I. Importance of using appropriate agitation intensities for in vitro dissolution rate measurements to reflect in vivo conditions, J. Pharm. Sci. 52 (1963) 1039–1046.

[13] E. Nelson, Comparative dissolution rates of weak acids and their sodium salts, J. Am. Pharm. Assoc. Am. Pharm. Assoc. (Baltim) 47 (1958) 297–299.

[14] J. Wood, J. Syarto, H. Letterman, Improved holder for intrinsic dissolution rate studies, J. Pharm. Sci. 54 (1965) 1068.

[15] K.M. Hillgren, A. Kato, R.T. Borchardt, In vitro systems for studying intestinal drug absorption, Med. Res. Rev. 15 (1995) 83–109.

[16] P. Zakeri-Milani, H. Valizadeh, H. Tajerzadeh, Y. Azarmi, Z. Islambolchilar, S. Barzegar, M. Barzegar-Jalali, Predicting human intestinal permeability using single-pass intestinal perfusion in rat, J. Pharm. Pharm. Sci. 10 (2007) 368–379.

[17] P.J. Sinko, P. Hu, A.P. Waclawski, N.R. Patel, Oral absorption of anti-AIDS nucleoside analogues. 1. Intestinal transport of didanosine in rat and rabbit preparations, J. Pharm. Sci. 84 (1995) 959–965.

[18] P. Zakeri-Milani, H. Valizadeh, Y. Yadollah Azarmi, M. Barzegar Jalali, H. Tajerzadeh, Simultaneous determination of metoprolol, propranolol and phenol red in samples from rat in situ intestinal perfusion studies, DARU 14 (2006) 102–108.

[19] P. Zakeri-Milani, M. Barzegar-Jalali, H. Tajerzadeh, Y. Azarmi, H. Valizadeh, Simultaneous determination of naproxen, ketoprofen and phenol red in samples from rat intestinal permeability studies: HPLC method development and validation, J. Pharm. Biomed. Anal. 39 (2005) 624–630.

[20] D. Ernest, E. Alfert, M. Brenda, B.M. Cross, A.A.E. McWilliam, CCAC, guide to the care and use of experimental animals, Can. Council Animal Care 1 (1993) 1–150.

[21] H. Valizadeh, P. Zakeri-Milani, Z. Islambulchilar, H. Tajerzadeh, A simple and rapid high-performance liquid chromatography method for determining furosemide, hydrochlorothiazide, and phenol red: applicability to intestinal permeability studies, J. AOAC Int. 89 (2006) 88–93.

[22] E. Gupta, D.M. Barends, E. Yamashita, K.A. Lentz, A.M. Harmsze, V.P. Shah, J.B. Dressman, R.A. Lipper, Review of global regulations concerning biowaivers for immediate release solid oral dosage forms, Eur. J. Pharm. Sci. 29 (2006) 315–324.

[23] G.E. Granero, M.R. Longhi, C. Becker, H.E. Junginger, S. Kopp, K.K. Midha, V.P. Shah, S. Stavchansky, J.B. Dressman, D.M. Barends, Biowaiver monographs for immediate release solid oral dosage forms: acetazolamide, J. Pharm. Sci. 97 (2008) 3691–3699.

[24] H. Kortejarvi, M. Yliperttula, J.B. Dressman, H.E. Junginger, K.K. Midha, V.P. Shah, D.M. Barends, Biowaiver monographs for immediate release solid oral dosage forms: ranitidine hydrochloride, J. Pharm. Sci. 94 (2005) 1617–1625.

[25] M. Nicklasson, A. Brodin, C. Graffner, Studies on a rotating disk method to determine drug dissolution rates from inert PVC matrices, Acta Pharm. Suec. 19 (1982) 211–222.

[26] G.L. Amidon, H. Lennernas, V.P. Shah, J.R. Crison, A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability, Pharm. Res. 12 (1995) 413–420.

[27] P. Parvin Zakeri-Milani, H. Valizadeh, H. Tajerzadeh, Z. Islambolchilar, The utility of rat jejunal permeability values for biopharmaceutics classification system, Drug Dev. Ind. Pharm., (2009), in press.

[28] N.A. Kasim, M. Whitehouse, C. Ramachandran, M. Bermejo, H. Lennernas, A.S. Hussain, H.E. Junginger, S.A. Stavchansky, K.K. Midha, V.P. Shah, G.L. Amidon, Molecular properties of WHO essential drugs and provisional biopharmaceutical classification, Mol. Pharm. 1 (2003) 85–96.

[29] WHO, Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability. Technical Report Series, No937, 40th Report, Annex7 <http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf>, 2006.

[30] FDA, Guidance for Industry: Waiver of in vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. US Food and Drug Administration, Center for Drug Evaluation and Research, USA, <http://www.fda.gov/cder/guidance/3618fnl.pdf>, 2000.

[31] EMEA, Note for Guidance on the Investigation of Bioavailability and Bioequivalence. European Agency for Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, <http://www.emea.eu.int/pdfs/human/ewp/140198en.pdf>., 2001.

[32] L.X. Yu, G.L. Amidon, J.E. Polli, H. Zhao, M.U. Mehta, D.P. Conner, V.P. Shah, L.J. Lesko, M.L. Chen, V.H. Lee, A.S. Hussain, Biopharmaceutics classification system: the scientific basis for biowaiver extensions, Pharm. Res. 19 (2002) 921–925.

[33] T. Takagi, C. Ramachandran, M. Bermejo, S. Yamashita, L.X. Yu, G.L. Amidon, A provisional biopharmaceutical classification of the top 200 oral drug products in the United States, Great Britain, Spain, and Japan, Mol. Pharm. 3 (2006) 631–643.

[34] L.Z. Benet, G.L. Amidon, D.M. Barends, H. Lennernas, J.E. Polli, V.P. Shah, S.A. Stavchansky, L.X. Yu, The use of BDDCS in classifying the permeability of marketed drugs, Pharm. Res. 25 (2008) 483–488.

[35] C.Y. Wu, L.Z. Benet, Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system, Pharm. Res. 22 (2005) 11–23.

[36] V. Papadopoulou, G. Valsami, A. Dokoumetzidis, P. Macheras, Biopharmaceutics classification systems for new molecular entities (BCS-NMEs) and marketed drugs (BCS-MD): theoretical basis and practical examples, Int. J. Pharm. 361 (2008) 70–77.

[37] H. Lennernas, Human intestinal permeability, J. Pharm. Sci. 87 (1998) 403–410.

[38] P. Modamio, C.F. Lastra, J. Maritto, Error structure for the HPLC analysis for atenolol, metoprolol and propranolol: a useful weighting method in parameter estimation, J. Pharm. Biomed. Anal. 17 (1998) 507–513.

[39] J.D. Irvine, L. Takahashi, K. Lockhart, J. Cheong, J.W. Tolan, H.E. Selick, J.R. Grove, MDCK cells: a tool for membrane permeability screening, J. Pharm. Sci. 88 (1998) 28–33.

[40] C.A. Phillips, B.B. Michniak, Transdermal delivery of drugs with differing lipophilicities using azone analogs as dermal penetration enhancers, J. Pharm. Sci. 84 (1995) 1427–1433.

[41] E. Walker, S. janich, B.J. Roessler, J.M. Hilfinger, G.L. Amidon, HT29-MTX/Caco-2 cocultures as an in vitro model for the intestinal epithelium: in vitro- in vivo correlation with permeability data from rats and humans, J. Pharm. Sci. 85 (1996) 1070–1076.

[42] M.D. Levitt, J.M. Kneip, D.G. Levitt, Use of laminar flow and unstirred layer models to predict intestinal absorption in the rat, J. Clin. Invest. 81 (1988) 1365–1369.

[43] H. Lennernäs, L. Knutson, A. Hussain, L. Lesko, T. Salmonson, G. Amidon, The human jejunal Peff-value for each enantiomet of (R,S)-verapamil, Pharm. Res. 13 (1996) 246.