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The effect of solubilization on the oral bioavailability of three benzimidazole carbamate drugs

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Abstract

The effect of solubilization by complexation with povidone on the oral bioavailability of three anthelmintic benzimidazole carbamate drugs: mebendazole (MBZ), albendazole (ABZ) and ricobendazole (RBZ), was studied in mice. The following in vitro characteristics of the initial raw materials and the drug–povidone complexes were evaluated: melting point (MP); mean dissolution time (MDT); solubility constants (Cs) in *n*-octanol, acid (pH 1.2) and neutral (pH 7.4) aqueous media; apparent partition coefficients (P) and capacity factors (k'_w) determined by HPLC. The following in vivo parameters were also evaluated: $AUC_{0-\infty}$, C_{max}, T_{max} and MRT. The possible relationship between in vitro characteristics and in vivo parameters was explored and it was found that an increase in solubility, especially in acidic medium, leads to an increase in AUC and C_{max} and a decrease in T_{max}. Therefore, dissolution seems to be the absorption limiting step for these drugs. For the in vivo parameters related to the amount of absorbed drug (AUC and C_{max}), the best correlation was obtained with the in vitro characteristics related to solubility which are Cs, MP and MDT. On the other hand, there were good linear correlations between T_{max} which is an in vivo parameter related to the rate of drug absorption, and the *lipophilia*/*hydrophilia* ($\log P$ and $\log k'_w$) relation-parameters.

Keywords: Solubility; Complexation; Povidone; Bioavailability; Solid dispersion

1. Introduction

The absorption of most orally administered drugs in the intestinal tract can be related to their solubility and permeability properties. These two characteristics, especially solubility, can be modified by complexation of the drug with different excipients and through this process, the oral bioavailability of drugs with a low aqueous solubility can be greatly improved (Serajuddin, 1999). The knowledge of the solubility and permeability characteristics can be useful in predicting oral bioavailability of most of these drugs and is the basis of the actually well established Biopharmaceutics Classification System (BCS) (Amidon et al., 1995; Lipka and Amidon, 1999). For class II drugs of the BCS classification, which comprises of less soluble/high permeable drugs, an improvement in solubility could lead to an increase in bioavailability. As far as these drugs are concerned, it seems that there is a clear relationship between in vitro and in vivo

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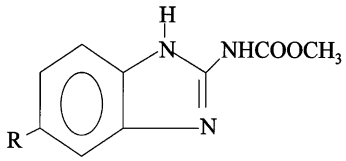

MBZ, R= -CO-C_6H_5

ABZ, R= -S-CH_2-CH_2-CH_3

RBZ, R= -SO-CH_2-CH_2-CH_3

Fig. 1. Structures of different anthelmintic benzimidazole carbamates: mebendazole (MBZ), albendazole (ABZ) and ricobendazole (RBZ).

properties and if some of their physicochemical characteristics are altered, for instance by complexation, it should be expected that their biopharmaceutical properties could also be proportionally modified.

The aim of this work is to study the effect of a complexation process with povidone in the solubility of three benzimidazole carbamate drugs and its consequences in their oral bioavailability. Furthermore, the relationship between their in vitro physicochemical characteristics and their in vivo pharmacokinetical parameters is also studied.

Three anthelmintic benzimidazole carbamate drugs: mebendazole (MBZ), albendazole (ABZ) and ricobendazole (RBZ), which chemical structures are shown in Fig. 1, were chosen as model drugs and formulated with povidone in order to prepare drug–povidone complexes. The following in vitro characteristics of the initial raw materials and the drug–povidone complexes were evaluated: melting point (MP); mean dissolution time (MDT); solubility constants (Cs) in *n*-octanol, acid (pH 1.2) and neutral (pH 7.4) aqueous media; apparent partition coefficients (P) and capacity factors (k'_w) were determined by HPLC as an alternative to $\log P$, and as a possible prediction tool for bioavailability characteristics (Hsieh and Dorsey, 1995).

Liquid formulations of these drugs, as a solution prepared with the povidone–drug complexes and as a suspension of crude/raw drug prepared with sodium carboxymethylcellulose, were orally administered to mice. Blood samples were taken at different times, assayed by HPLC and the following in vivo parameters were evaluated: $AUC_{0-\infty}$, C_{max}, T_{max} and MRT. The relationship between in vitro characteristics and in vivo parameters was explored.

2. Materials and methods

2.1. Elaboration of drug–povidone complexes

Drugs solubilization was performed by complexation with povidone K12 PF (Basf, USA) in the proportions of 1:20 (w:w) for MBZ (Sigma, USA) and 1:10 for both ABZ (SmithKline Beecham, England) and RBZ (Chemo Ibérica, Spain). The solvent evaporation method was used in preparation of solid complexes (Torrado et al., 1996). The melting temperatures (MP) of the assayed products were evaluated with a Buchi B-540 melting point apparatus.

2.2. Solubility studies

An excess amount of the different drugs were suspended in glass tubes containing *n*-octanol and USP 24 buffers at the following pHs 1.2 (HCl/KCl) and 7.4 (KH_2PO_4). The tubes were closed and kept at 37 °C under a one-week constant agitation. Then, the samples were taken out, filtered, diluted and assayed by HPLC to estimate the Cs. The quantitative analysis of the drugs is the same used for the assay of the biological samples and is described below. The apparent partition coefficients (P) were calculated as the ratios of the different solubility constants.

2.3. Dissolution rate studies

Dissolution rate profiles of the MBZ, ABZ and RBZ suspensions were studied under sink conditions with 0.1N HCl at 37 °C and stirred at 50 rpm in an USP 24 apparatus, method II. Samples were taken at the following intervals: 5, 10, 15, 30, 45, 60, 90, 120, 180, 240 and 360 min. They were then filtered and assayed by UV analysis at 291 nm. The MDT was calculated according to the following equation:

$$\mathrm{MDT} = \frac{Q_{360} \times 360\,\mathrm{min} - \mathrm{AUC}_{0-360}}{\mathrm{Dose}}$$

where Q_{360} was the amount of drug dissolved at 360 min and AUC_{0-360} was estimated by the trapezoidal rule method.

2.4. Chromatographic retention

Various drugs retention times were determined from mobile phases containing different proportions

of methanol:water at 1.5 ml/min with a C_{18} column (Hypersil® 250 mm × 4.6 mm). The effect of povidone on the retention times, as an additive at a 3% (w/v) proportion in the mobile phase, was also evaluated and interpreted as the retention time for the povidone:drug complex. The logarithm of the capacity factor with a mobile phase of 100% water ($\log k'_w$) was used as descriptor of lipophilicity in accordance with the method described by Hsieh and Dorsey (1995). This capacity factor was estimated by extrapolating a linear plot of $\log k'$ versus percentage of organic modifier volume (methanol proportion) to the interception point with 0% organic modifier, representing retention in a 100% aqueous phase:

$$\log k' = \log k'_w - s\,(\text{vol.}\%).$$

2.5. Bioavailability studies

The povidone:drug complexes were dissolved in deionized water and then orally administered to NMRI mice by a bucco-gastric tube at a dose of 100 mg/kg. The reference formulations were prepared using a 1% (w/v) sodium-carboxymethylcellulose 30–70 cS (BDH, England) suspension as vehicle. The drug concentration for each formulation was 0.6% (w/v). After the drugs administration, blood samples were collected from at least three mice at different time-intervals (0.25, 0.5, 0.75, 1, 1.5, 3, 6 and 9 h), individually heparinized and centrifuged. Then, the resulting plasma samples were frozen until HPLC analysis.

2.6. HPLC quantitative analysis of the drugs

MBZ assay was performed in a 5 μm C_{18} (Hypersil®) 250 mm × 4.6 mm column and a mobile phase containing 400 ml of 0.05 M ammonium phosphate buffer and 600 ml of methanol at a flow rate of 1 ml/min. Afterwards, the samples were assayed at 291 nm. ABZ assay was conducted according to the HPLC method described in USP 24 (2000). RBZ was assayed in accordance with the method previously described by García et al. (1999).

2.7. Bioavailability parameters

T_{max}, C_{max}, $AUC_{0-\infty}$ and MRT were estimated according to the non-compartmental approach described by Shargel and Yu (1993) and applied before (García et al., 2003). The comparative statistical studies between in vitro and in vivo parameters were performed by linear regression analysis (Excel, Office 97) and the significance level was set at $P < 0.05$.

3. Results and discussion

Table 1 shows the physicochemical properties of the drugs and their corresponding drug–povidone complexes. The meltings points were only determined for the pure drug due to the typical amorphous characteristics structure of the three drug–povidone complexes of the solid dispersion systems. A clear relationship between drugs melting points and the apparent solubility constant was found. MBZ and ABZ have higher MP values but lower solubility constants, in each of the three studied liquid media, compared to RBZ. This correlation between solubility and melting points can be an indication of the intermolecular interactions in the solid phases as it has been depicted in previous works (Florence and Atwood, 1998; Stella et al., 1998; Ihnat et al., 2000).

It is also clear that drug solubility is significantly improved by complexation with povidone and this effect is more prominent for the less soluble drugs like MBZ and ABZ than for RBZ. Solubility was related to the medium pH and due to the basic-nature of these drugs an ionization effect and hence increasing their solubility was observed in an acidic medium compared to a neutral pH medium (Jung et al., 1998; Castillo et al., 1999).

From the use of HPLC, a partition constant expressed as $\log k'_w$, was determined. Interestingly, it was observed that when povidone was used as mobile phase additive there was a decrease in the retention times, which is an indicatory sign of its good complexing agent characteristics and confirms the improvement on solubility observed with the Cs values.

On the other hand, the MDT is an indicator of the dissolution rate for the different suspension formulations. Table 1 shows the inverse relationship between the solubility coefficients and the MDT. The higher the solubility, the lower the MDT values, as it happens with RBZ. Contrary for MBZ, the lower the solubility, the higher the MDT values.

Table 1
In vitro properties of the different products

	MP (°C)	$Cs_{1.2}$ (μg/ml)	$Cs_{7.4}$ (μg/ml)	Cs_o (μg/ml)	$P_{o/w\,1.2}$	$P_{o/w\,7.4}$	Log k'_w [b]	MDT (min)
MBZ	288.5	15.7 ± 3.1	1.1 ± 0.1	95 ± 15	6.1	89.6	3.69, $n = 5$ (0.98)	59.9
MBZ-SD	–[a]	64.8 ± 3.0	6.1 ± 0.7	550 ± 41	8.5	90.2	2.93, $n = 4$ (0.97)	–[c]
ABZ	209	183.7 ± 24.3	0.75 ± 0.2	765 ± 21	4.2	1020.7	3.89, $n = 4$ (0.98)	17.1
ABZ-SD	–[a]	255.2 ± 12.9	2.0 ± 0.3	1028 ± 103	4	514	3.5, $n = 4$ (0.96)	–[c]
RBZ	94.1	1520 ± 73	308 ± 95	2086 ± 130	1.4	6.8	2.24, $n = 5$ (0.98)	7.3
RBZ-SD	–[a]	1575 ± 194	967 ± 325	8452 ± 387	5.4	8.7	1.1, $n = 5$ (0.80)	–[c]

Key: SD, solid dispersion, MP, melting point; Cs, solubility constants in *n*-octanol (Cs_o), acid ($Cs_{1.2}$) and neutral ($Cs_{7.4}$) aqueous media; *P*, apparent partition coefficients at different pHs; k'_w, capacity factors determined by HPLC and MDT is mean dissolution time.
[a] Amorphous structures without a clear MP.
[b] *n*: number of points used to estimate linearity, and in parenthesis, the correlation coefficients values.
[c] Instantaneous dissolution.

Figs. 2–5 show the mean drug plasma concentration after oral administration of the two liquid formulations (solution and suspension) of each drug. It is clear that the highest bioavailability enhancement effect is obtained for MBZ which is the least soluble of the studied benzimidazole carbamate drugs. The ABZ bioavailability is also limited by its fast in vivo oxidation yielding albendazole sulphoxide (ABZSO), which is a more polar molecule than ABZ. This metabolite of ABZ has anthelmintic activity and for this reason, it has been marketed with the generic name of RBZ. Due to the fast ABZ metabolization to its active metabolite, the biopharmaceutical characteristics of the ABZ formulations with respect to the ABZSO formation were also studied and are shown in Fig. 4. The biopharmaceutical characteristics of the six formulations are summarized in Table 2.

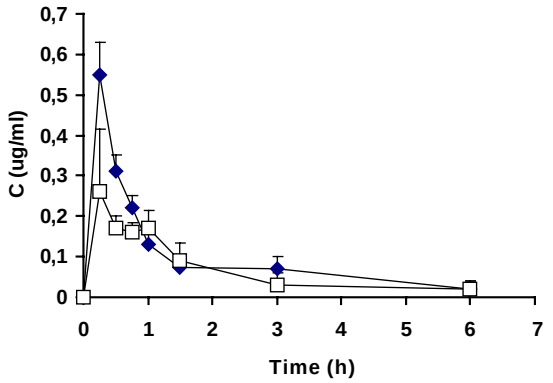

Fig. 3. Mean plasma concentration–time profiles of ABZ after oral administration of two ABZ formulations. Key: (◆), ABZ-SD solution and (□), ABZ suspension. Error bars indicate standard deviation.

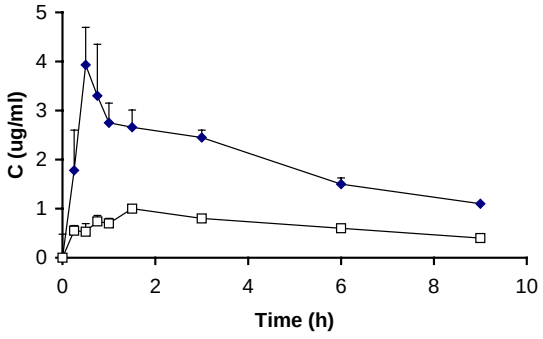

Fig. 2. Mean plasma concentration–time profiles of MBZ after oral administration of two MBZ formulations. Key: (◆), MBZ-SD solution and (□), MBZ suspension. Error bars indicate standard deviation.

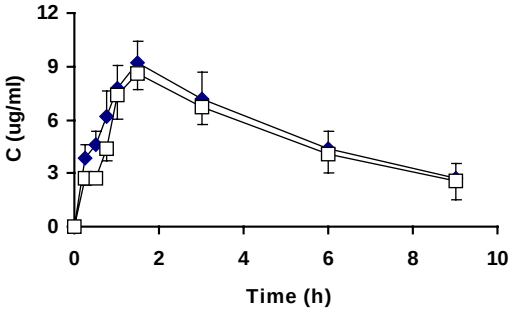

Fig. 4. Mean plasma concentration–time profiles of ABZSO after oral administration of two ABZ formulations. Key: (◆), ABZ-SD solution and (□), ABZ suspension. Error bars indicate standard deviation.

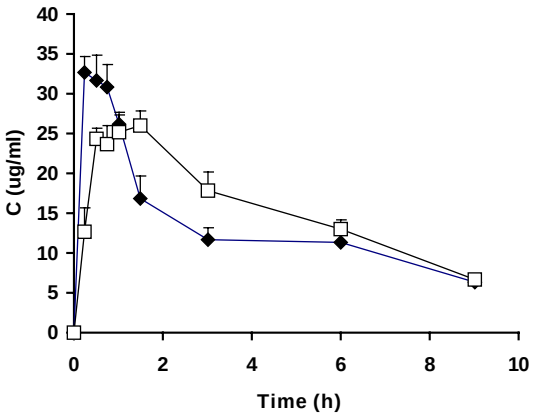

Fig. 5. Mean plasma concentration–time profiles of RBZ after oral administration of two RBZ formulations. Key: (◆), RBZ-SD solution and (□), RBZ suspension. Error bars indicate standard deviation.

From these results, it is clear that the bioavailability properties change depending on the drug nature. For instance, MBZ which is the least soluble drug in acidic medium, the use of a solution formulation with respect to the suspension, significantly improves the relative oral bioavailability, estimated either as $AUC_{0-\infty}$ or at C_{max}. The same applies for ABZ, although the effect is of less intensity, and it is not significant for RBZ which is the more soluble drug. The effect of povidone and other excipients such as cellulose and cyclodextrines compounds used as complexing agents to improve oral bioavailability of these two low soluble drugs namely MBZ and ABZ, have been previously reported (Chiba et al., 1991; Lopez et al., 1997; Castillo et al., 1999; Evrard et al., 2002; García et al., 2003) and those previous results coincide with the results reported in this paper. The novelty of this work is that three different drugs of the same chemical group have been used and compared this time.

Table 2 shows how both T_{max} and MRT change depending on whether the drug is administered as a solution or a suspension. As it was expected, solution formulations have both lower T_{max} and MRT values than the corresponding suspensions. This effect is less evident for ABZSO, the main metabolite of ABZ, probably because the variability in the metabolization rate can mask the effect of the different rate of absorption. The MRT values for the oral formulations administered as suspensions and solids can be useful in determination of the in vivo MDT values ($MDT_{in\ vivo}$). According to Shargel and Yu (1993), the $MDT_{in\ vivo} = MRT_{SUSP} - MRT_{SOL}$. The $MDT_{in\ vivo}$ values for MBZ, ABZ and RBZ are: 56.4, 21 and 6 min, respectively, which are very close to those calculated from the in vitro dissolution test and reported as MDT in Table 1. These results confirm the utility of the dissolution test conditions proposed in this work and that could adequately be used as a prediction tool for the oral absorption characteristics of this kind of drug formulations. The dissolution test conditions used in this work are similar to those previously proposed for the dissolution testing on ABZ oral solid formulations (Galia et al., 1999).

Table 3 shows the results of the in vitro/in vivo correlation studies. Due to the fact that the same procedures have been used with the three drugs it is possible to study possible in vitro/in vivo correlations. The correlation coefficient values higher than 0.7, are assumed to be an indicative of a linear correlation between the variables, and the sign expresses the type of relationship. For instance, the relative bioavailability, expressed as either $\log(AUC_{SUSP}/AUC_{SOL})$ or as $\log(C_{max\ SUSP}/C_{max\ SOL})$, was found be inversely

Table 2
In vivo characteristics of the different formulations

Formulations	$AUC_{0-\infty}$ (μg h/ml)	C_{max} (μg/ml)	T_{max} (h)	MRT (h)
MBZ_{SUSP}	9.3	1.1 ± 0.1	1.1 ± 0.4	8.8
$MBZ\text{-}SD_{SOL}$	25.9	6.1 ± 0.4	0.7 ± 0.25	7.8
ABZ_{SUSP}	0.5	0.3 ± 0.1	0.4 ± 0.4	2.1
$ABZ\text{-}SD_{SOL}$	0.8	0.7 ± 0.1	0.2 ± 0.1	1.8
$ABZSO_{SUSP}$[a]	61.4	11.9 ± 0.3	3.8 ± 4.5	6.8
$ABZSO\text{-}SD_{SOL}$[a]	65.7	12.6 ± 0.6	1.3 ± 0.3	6.7
RBZ_{SUSP}	216.5	28.5 ± 1.0	1.3 ± 0.3	5.4
$RBZ\text{-}SD_{SOL}$	188.9	37.1 ± 2.0	0.3 ± 0.1	5.3

[a] Pharmacokinetic characteristics of the ABZ formulations (suspension and solution) determined from the ABZSO concentrations.

Table 3
In vitro/in vivo linear correlation coefficients

In vivo/in vitro	MP	MDT	$Cs_{1.2}$	$Cs_{7.4}$	Cs_o	$\log P_{o/w\,1.2}$	$\log P_{o/w\,7.4}$	$\log k'_w Z$
$\log(AUC_{SUSP}/AUC_{SOL})$	−0.891* ($n = 4$)	−0.917* ($n = 4$)	0.72* ($n = 4$)	0.646 ($n = 4$)	0.857* ($n = 4$)	−0.81* ($n = 4$)	−0.238 ($n = 4$)	−0.562 ($n = 4$)
$\log(C_{max\,SUSP}/C_{max\,SOL})$	−0.735* ($n = 4$)	−0.869* ($n = 4$)	0.514 ($n = 4$)	0.431 ($n = 4$)	0.686 ($n = 4$)	−0.622 ($n = 4$)	−0.016 ($n = 4$)	−0.341 ($n = 4$)
T_{max}	−0.343 ($n = 3$)	0.101 ($n = 3$)	0.619 ($n = 3$)	0.696 ($n = 3$)	0.419 ($n = 3$)	−0.501 ($n = 3$)	−0.958* ($n = 3$)	−0.771* ($n = 3$)
MRT	0.414 ($n = 3$)	0.770* ($n = 3$)	−0.110 ($n = 3$)	−0.01 ($n = 3$)	−0.338 ($n = 3$)	0.249 ($n = 3$)	−0.482 ($n = 3$)	−0.103 ($n = 3$)

In parenthesis, the number of molecules or formulations considered for the linearity studies. Asterisks (*) indicate significant correlation ($P < 0.05$). Key: MP, melting point of raw material; MDT, mean dissolution time of the suspension drug form; Cs, solubility constants in acid ($Cs_{1.2}$) and neutral ($Cs_{7.4}$) aqueous media and in *n*-octanol (Cs_o); *P*, apparent partition coefficients at different pHs and k'_w, capacity factors determined by HPLC.

proportional to MP and MDT, which means that, the lower the drug initial raw material MP, the lower the drug suspension formulation MDT, thus this may lead to an increase in the relative bioavailability. It is also clear that the relative bioavailability expressed as $\log(AUC_{SUSP}/AUC_{SOL})$ is also directly related to the $Cs_{1.2}$, Cs_o and inversely to $\log P_{o/w\,1.2}$. Therefore, an increase in drugs solubility coefficients and a decrease in $\log P_{o/w\,1.2}$ will result in an increase in relative bioavailability. These data support the facts that aqueous solubility is the limiting step for the drugs oral absorption. Interestingly, a linear relationship were observed between the T_{max}, which is an in vivo parameter related to the rate of absorption, and both the $\log P_{o/w\,7.4}$ and $\log k'_w$. None of these two in vitro characteristics could be correlated with the $\log(AUC_{SUSP}/AUC_{SOL})$ and $\log(C_{max\,SUSP}/C_{max\,SOL})$. Therefore, it seems that the in vivo parameters related to the amount of absorbed drug (AUC and C_{max}) are strongly correlated with the in vitro characteristics related to solubility, namely Cs, MP and MDT but not to the partition coefficients expressed as $\log P_{o/w\,7.4}$ and $\log k'_w$. Besides, there is a linear correlation between the T_{max}, which is the in vivo parameter related to the rate of drug absorption and the $\log P_{o/w\,7.4}$ and $\log k'_w$. This means that an increase on both $\log P_{o/w\,7.4}$ and $\log k'_w$ values, both indicating an increase in the quotient *lipophilia*/*hydrophilia*, will speed up the rate of absorption of these drugs. With respect to MRT, only a slight linear relationship with MDT could be established. According to the USP 24 (2000), the in vitro/in vivo correlation between MDT and MRT is a *B* correlation level. The obtained slight correlation coefficient value ($r = 0.770$), is probably due to the relatively high analytical errors that is obtained when low ABZ plasma concentrations are assayed. A very important first-pass effect and fast metabolization rate has been described for ABZ (Galtier et al., 1991). Thereupon, the bioavailability of ABZ formulations have been studied mainly basing on its main active metabolite—ABZSO, instead of ABZ only (López-García et al., 1997, 1998; Torrado et al., 1997). When the MRT of ABZSO was used instead of that of ABZ, a better correlation coefficient of 0.969 was obtained, reflecting a good linear relationship between the MDT values obtained from the in vitro dissolution test and the in vivo MRT values.

Table 3 shows the correlation between the in vivo parameters and direct in vitro characteristics, but another kind of relationship can be explored between the changes obtained from the in vitro properties by complexation, with respect to the initial raw material and the changes produced in the in vivo parameters. Thus, the proportional increase in Cs and log *P* of the solid dispersion form and the initial raw material can be estimated as the quotient between the two drug systems or forms. For instance, $\Delta Cs_{1.2}$ is calculated as the quotient between the $Cs_{1.2}$ values of the solid dispersion and that of the initial raw material. The changes on the in vivo parameters with respect to solution and suspension formulations can be studied directly (as the quotation between the characteristic of the solution and the suspension) or relatively (as the difference between the characteristic of the suspension and solution divided by the parameters of the suspension formulations). Table 4 shows the possible relationship between the changes in the in vitro physicochemical characteristics and the ones observed in the in vivo bioavailability studies. As it was previously depicted in Table 3, the data reported in Table 4, elucidate the relative bioavailability, expressed as log quotient of either AUC or C_{max}, and the former directly depends on the solubility of the two aqueous media (at pH 1.2 and 7.4). So, when the solubility constants increase, also the relative bioavailability increases. In addition to that, the logarithmic relative changes of T_{max} for the solution and the suspension preparations, also become linearly correlated as a consequence of variations in the logarithmic partition coefficients. Besides, the variations in the rate of absorption, expressed as changes in T_{max}, implies that there is a decrease in solubility ($Cs_{1.2}$ and MP) and the dissolution rate (MDT), which in turn may delay the rate of absorption. Table 4 also shows how the quotient *lipophilia*/*hydrophilia* (log of partition coefficients) is directly and inversely proportional to T_{max} and the rate of absorption, respectively.

Consequently, we can concluded that the increased relative bioavailability estimated by both AUC and C_{max} values, is inversely proportional to the melting points and MDT. Moreover, the increased relative bioavailability calculated in terms of AUC values, is also directly proportional to the Cs in *n*-octanol and the aqueous media at pH 1.2 but inverse to $\log P_{o/w\,1.2}$. The best correlation for the in vivo parameters T_{max} and MRT was observed for the in vitro characteristics

Table 4
In vitro/in vivo linear correlation coefficients

In vivo/in vitro	MP	MDT	$\Delta Cs_{1.2}$	$\Delta Cs_{7.4}$	ΔCs_o	$\Delta(\log P_{o/w\,1.2})$	$\Delta(\log P_{o/w\,7.4})$
$\mathrm{Log}(AUC_{SOL}/AUC_{SUSP})$	0.891* ($n = 4$)	0.917* ($n = 4$)	0.897* ($n = 4$)	0.786* ($n = 4$)	0.473 ($n = 4$)	−0.613 ($n = 4$)	−0.298 ($n = 4$)
$\mathrm{Log}(C_{max\,SOL}/C_{max\,SUSP})$	0.735* ($n = 4$)	0.869* ($n = 4$)	0.867* ($n = 4$)	0.819* ($n = 4$)	0.602 ($n = 4$)	−0.396 ($n = 4$)	−0.07 ($n = 4$)
$\mathrm{Log}((T_{max\,SUSP} - T_{max\,SOL})/T_{max\,SUSP})$	−0.99* ($n = 3$)	−0.831* ($n = 3$)	−0.79* ($n = 3$)	−0.607 ($n = 3$)	−0.156 ($n = 3$)	0.947* ($n = 3$)	0.752* ($n = 3$)

In parenthesis the number of molecules or formulations used in the linearity studies. Asterisks (*) indicate significant correlation ($P < 0.05$). Key: MP, melting point of raw material; MDT, mean dissolution time of the suspension drug form; ΔCs, increment of the solubility constants in acid ($\Delta Cs_{1.2}$) and neutral ($\Delta Cs_{7.4}$) aqueous media and in *n*-octanol (ΔCs_o); ΔP, increment of the apparent partition coefficients at different pHs.

of $\log P_{o/w\,7.4}$ and MDT values, respectively. Therefore, for these drugs, an increase in solubility, especially in acidic media, leads to an increase in AUC and C_{max} and a decrease in T_{max}. For that case, dissolution might be the drug absorption limiting step. It also seems that the in vivo parameters related to the amount of absorbed drug (AUC and C_{max}), are also well correlated with the in vitro characteristics related to solubility such as Cs, MP and MDT. For T_{max}, which is the in vivo parameter related to the rate of drug absorption, the better correlations were obtained with the in vitro characteristics of $\log P_{o/w\,7.4}$ and $\log k'_w$.

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