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Research paper

In vitro/in vivo correlations of dissolution data of carbamazepine immediate release tablets with pharmacokinetic data obtained in healthy volunteers ☆

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Abstract

The aim of the study was to select a dissolution test method for carbamazepine (CBZ) immediate release tablets, giving the best in vitro/in vivo correlations (IVIVC) and to determine the potential of this method as an estimate for bioequivalence testing. Four 200 mg CBZ products which are sold on the Dutch market, covering the innovator and three generic products, were selected. They had been tested in a randomised, fourway cross-over bioavailability study in healthy volunteers. Their dissolution rate behaviour in vitro was investigated in two dissolution media: (1) 1% sodium lauryl sulphate in water (SLS), in accordance with the United States Pharmacopeia (USP); (2) 0.1 mol/l Hydrochloric acid in water (HC). In the bioavailability study these products had shown no large differences in the extent of absorption ($AUC_{0-\infty}$;) but large differences in absorption rate. The products now also showed large differences in dissolution rate in vitro in both dissolution media, the rank order being the same as for the absorption rate. It was concluded that the absorption rate in vivo depends on the dissolution rate in vivo. 'Level C' IVIVC according to the USP were optimised by plotting percentages dissolved on selected time points (D values) or their reciprocals ($1/D$ values), against several pharmacokinetic parameters primarily related to the absorption phase and against $AUC_{0-\infty}$. In this way for each IVIVC the optimum D or $1/D$ value, was calculated. For both media no meaningful IVIVC were obtained with $AUC_{0-\infty}$, but favourable IVIVC were obtained with the parameters primarily related to the absorption phase. In the bioavailability study indicated above it was found that, among the pharmacokinetic characteristics primarily related to the absorption phase, C_{max} is the most promising in expressing rate of absorption in bioequivalence testing in single dose studies with CBZ immediate release tablets. Consequently, C_{max} was selected for expressing rate of absorption. The most favourable IVIVC were obtained with D_{20} in SLS versus C_{max}. From this IVIVC and the requirements for bioequivalence ($AUC_{0-\infty}$: 0.8–1.25 and C_{max} : 0.75–1.35; 90% confidence interval), a specification for dissolution testing in SLS was calculated as follows: 'after 20 minutes, 34–99% dissolved'. Owing to the fact that the rate of absorption *in vivo* depends on i.a. the dissolution rate in vivo, it can be concluded that with this specification bioequivalence with respect to both rate of absorption and extent of absorption is ensured. As this specification is comparable with the USP specification: 'not less than 75% dissolved after 1 h', it is concluded that the USP specification is suitable to ensure bioequivalence of CBZ immediate release tablets.

Keywords: Carbamazepine; Dissolution; Bioequivalence; Pharmacokinetics; In vitro/in vivo correlation

1. Introduction

Carbamazepine (CBZ) is a widely used anti-epileptic drug. Large fluctuations in blood levels should be avoided in view of the narrow therapeutic range. Recently, a number of cases have been reported about the loss of seizure control and occurrence of side effects when one CBZ immediate release product is exchanged for another [1–4]. Also several studies on the dissolution rate of CBZ immediate release tablets have been published, reporting significant differences in dissolution rate [5,6,2]. Davidson [5] reported the results of a world-wide study of the pharmaceutical quality of CBZ immediate release tablets, in this study differences were observed in dissolution rate even within a single brand. According to the literature, carbamazepine is highly sensitive to moisture and this property is the cause of rearrangement of the polymorphic form in tablets, resulting in a change in the dissolution rate in vitro and in vivo [4,7–16].

☆ This paper does not necessarily reflect the opinion of the Medicines Evaluation Board in the Netherlands.

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This raised the question whether the occurrence of side effects was a result of differences in the rate of absorption, and, if so, was this a result of differences in dissolution rate in vivo. For this reason, a pharmacokinetic and bioavailability study was performed with four brands of CBZ immediate release tablets on the Dutch market (including the innovator), in a randomised fourway cross-over, single dose study in healthy volunteers [17]. In that study no large differences were observed in the extent of absorption ($AUC_{0-\infty}$), but the products showed large differences in pharmacokinetic characteristics primarily related to the absorption phase (C_{max}, $C_{max}/AUC_{0-\infty}$, $AUC_{0-12\ h}$, t_{max}, $t_{1/2\ abs}$, MRT_{abs} and AUC_{0-tmax}).

A follow-up clinical study was also performed, three of the four products were administered to patients in a steady-state situation [18]. In steady state no significant differences were found in the pharmacokinetic properties of the products (i.e. mean plasma levels), and also no significant differences were observed in the occurrence of side-effects. So, no evidence was found that differences in absorption rate of CBZ tablets had clinical significance.

However, the EU registration rules require different brands of a product on the market to be bioequivalent. The authors define bioequivalence as follows: 'the extent of absorption ($AUC_{0-\infty}$) should range from 0.8 to 1.25 of the reference product, and C_{max} from 0.75 to 1.35 (both with 90% confidence interval)' [17]. (Within the EU requirements for bioequivalence now under reconsideration [19,20].)

In the present study, dissolution testing as a means to predict $AUC_{0-\infty}$ and C_{max} was explored using in vitro/in vivo correlations (IVIVC).

In the literature only two media for the dissolution testing of CBZ immediate release tablets have been documented, on the basis of IVIVC: 1% sodium lauryl sulphate in water (SLS) [21]and 0.1 mol/l hydrochloric acid in water (HC).

Antilla et al. [22] found differences between two commercially available brands of CBZ immediate release tablets in the in vitro dissolution test with HC as the dissolution medium. These differences were also found with respect to the pharmacokinetic parameters primarily related to the absorption phase in a comparative bioavailability study. Neuvonen [3] reported central side effects to be significantly more common when a brand of tablets with fast absorption was used. These tablets were characterised by fast dissolution in vitro with HC. Shaheen et al. [23] performed a comparative bioavailablity study with two commercially available brands. No differences were found with respect to the pharmacokinetic parameters; this finding was reflected by the in vitro dissolution study with HC as dissolution medium. In contrast, differences in dissolution rate were found if water was used as a medium. So, the in vitro results in water did not correlate with the pharmacokinetic results.

Dissolution testing of CBZ immediate release tablets in SLS is included in the USP [21]. Dissolution testing in SLS was also shown to give good IVIVC by Meyer et al. [2], favourable IVIVC were found between, amongst others, the C_{max} results and dissolution results in SLS. However, no other media were considered in this study.

The two dissolution media described above were subjected to a direct comparison in an experimental study to find the dissolution method that produces the best IVIVC. Objectives were, to select a suitable dissolution test, also to establish a dissolution specification which ensures bioequivalence with the innovator with respect to both $AUC_{0-\infty}$ and C_{max}.

2. Materials and methods

2.1. In vitro study procedures

The tablets of four different brands of CBZ (200 mg immediate release) tablets were subjected to pharmaceutical quality control according to the British Pharmacopeia (BP) with respect to uniformity of tablet weight and content of active drug substance. The UV absorbance apparatus used for the assay of the active substance was a Perkin Elmer Lambda 16 UV 5. All batches were in compliance with the BP.

After having passed the quality control the tablets were stored according to their recommended storage conditions given on the label, and used before the expiry date.

The batches included were: Carbamazepine 200 mg Pharmachemie® lot no. 92 A 21 NF (product A); Carbamazepine 200 mg Centrafarm® lot no. 92 E 18 A (product B); Carbamazepine 200 mg Pharbita® lot no. 920401 (product C) and Tegretol Ciba Geigy® 200 mg lot no. 92 F 22 (product D, innovator).

The dissolution of the tablets was studied with two methods.

The first was the USP method [21], i.e. the paddle apparatus, operated at 75 rev./min, in 1% sodium lauryl sulphate in water (SLS) as the dissolution medium, at 37 ± 0.5°C. UV absorbance was measured at 285 nm. The dissolution apparatus used was a Pharmatest dissolution semi-automatic Diss 2, the UV absorbance was measured with a Perkin–Elmer Lambda 16 UV 5.

For each dissolution profile, one tablet was added to the medium and samples of the medium were drawn at 5, 10, 15, 20, 25, 30, 40, 50, 60, 80, 100 and 120 min ($n = 9$/product). The second dissolution method was identical to the first method, however instead of SLS, 0.1 mol/l hydrochloric acid in water (HC) was used as the dissolution medium.

The solubility of CBZ in the two media was studied by subjecting carbamazepine as pure substance to dissolution testing with the two dissolution methods described above. The concentrations of carbamazepine dissolved in the two dissolution media were measured until they remained

Table 1
Qualitative composition of the products

Product A	Product B	Product C	Product D
Carbamazepine	Carbamazepine	Carbamazepine	Carbamazepine
Potato starch	Maize starch	Maize starch	Microcrystalline cellulose
Povidone	Methylcellulose	Lactose	Carboxymethyl-cellulose sodium
Silica colloidal	Talc	Pregelatinised starch	Silica colloidal
Magnesium stearate	Magnesium stearate	Polysorbate 80	Magnesium stearate
Microcrystalline cellulose	Pregelatinised starch	Formaldehyde caseine	–
–	–	Microcryst. cellulose	–
–	–	Povidone	–

constant. For each of the two dissolution media, sink conditions were assumed to prevail if the amounts of substance dissolved in the dissolution media at the end of the dissolution test did not exceed 30% of the saturation concentrations [25].

The dissolution characteristics selected for the IVIVIC calculations were, mean percentages of the unit dose dissolved at given time points in minutes, expressed as D values. For instance D_{20} means, the mean percentage dissolved after 20 min. To avoid inverse correlations for certain pharmacokinetic characteristics selected such as t_{max}, the reciprocal value of the mean percentage of the unit dose dissolved at given time points was expressed as $1/D$ values.

2.2. IVIVC

IVIVC were computed using linear regression analysis ('LINREG-AAS' and 'Microsoft Excel 5.0'). For each relationship a linear plot was generated between the in vitro dissolution D values and $1/D$ values respectively (mean values) in both media and the in vivo pharmacokinetic variables (mean values). In vitro and in-vivo results were taken as independent (x) and dependent (y) variables, respectively. The correlation coefficient (r) and unexplained variance ($\sum d^2$) were calculated.

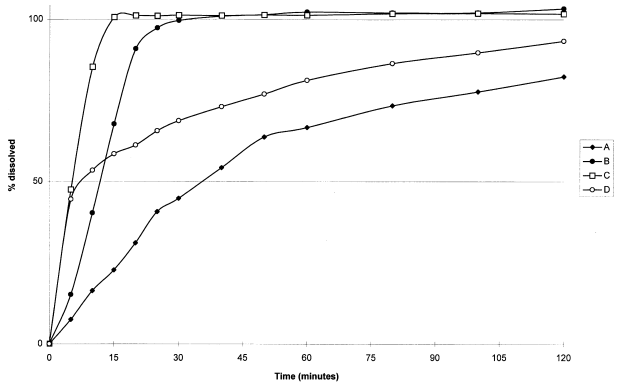

Fig. 1. Mean dissolution profiles ($n = 9$) of the four screened batches (products A, B, C and D) with SLS as dissolution medium.

3. Results

The qualitative compositions of the four products A, B, C and D (innovator) investigated are presented in Table 1.

The solubilities of carbamazepine in the two dissolution media were found to be 2.04 mg/ml in SLS and 0.34 mg/ml in HC.

Taking into account the total volume of the dissolution apparatus and the dose unit (200 mg) it is concluded that for SLS complete dissolution corresponded to 11% of the maximum solubility and for HC to 64% of the maximum solubility. So, with SLS as dissolution medium, sink conditions as defined before prevailed, and with HC this was not the case.

The average dissolution curves of the four products in the two dissolution media are shown in Figs. 1 and 2, respectively. These curves show that after 15 min and before 40 min the dissolution rate rank order is the same in the two media, i.e. C-B-D-A. Before 15 min there are differences in the rank order, and also after 40 min but these are almost negligible.

The relevant pharmacokinetic data of these four products are shown in Table 2. Further details (S.D. etc.) are given in reference [17]. The differences found in the characteristics C_{max}, $C_{max}/AUC_{0-\infty}$, t_{max}, $t_{1/2abs}$, $AUC_{0-12\ h}$, AUC_{0-tmax}, and MRT_{abs} were reflected by the in vitro dissolution rates between 15 and 40 min: the rank order of D or $1/D$ in this time period is identical to the rank order of either C_{max}, $C_{max}/AUC_{0-\infty}$, $AUC_{0-12\ h}$ and AUC_{0-tmax}, (C-B-D-A) or of tmax, $t_{1/2\ abs}$ and MRT_{abs} (A-D-B-C).

IVIVC results were obtained with a range of D (mean) values, respectively. $1/D$ values, against C_{max}, $C_{max}/AUC_{0-\infty}$, $AUC_{0-12\ h}$, t_{max}, $t_{1/2\ abs}$, $MRT_{abs.}$ and AUC_{0-tmax}, for both the SLS and the HC dissolution media.

No useful correlations were obtained with $AUC_{0-\infty}$ (r ranging from approximately 0.5–0.8). For the other pharmacokinetic characteristics the D value or $1/D$ value, giving the highest correlation coefficient and lowest unexplained variance, was established for each IVIVC. An example of establishing the optimum D value for C_{max} is shown in Table 3 and Fig. 3. In Fig. 4a&a–c the relationships between D_{20}, D_{40} and D_{50} in SLS and C_{max} are presented graphically (program, Microsoft Excel 5.0). In Table 4, the best correla-

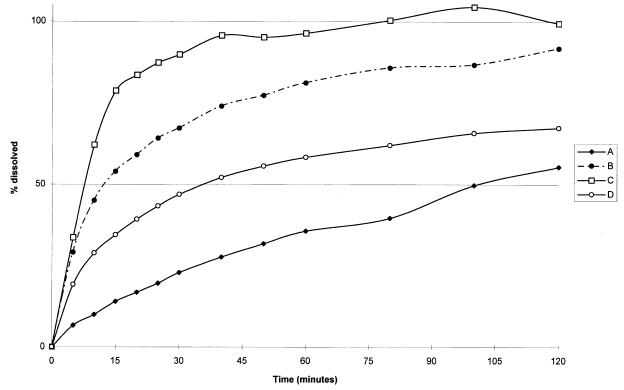

Fig. 2. Mean dissolution profiles ($n = 9$) of the four screened batches (products A, B, C and D) with HC as dissolution medium.

tion results for each pharmacokinetic characteristic are presented (program, LINREG-AAS).

4. Discussion

C_{max}, $C_{max}/AUC_{0-\infty}$, $AUC_{0-12\ h}$, t_{max}, $t_{1/2\ abs}$, MRT_{abs} and $AUC_{0-tmax,}$, which are pharmacokinetic parameters primarily related to the absorption phase, all showed large differences within the four products, with product C exhibiting the fastest absorption, followed by B, D and A: see Ref. [17]. When Figs. 1 and 2 are studied more closely, it appears that this rank order is also reflected in the dissolution rates in the two dissolution media, however, there are a few exceptions, as follows.

In SLS product D shows a faster dissolution rate than batch B during the first 15 min of the test whereas the dissolution of product D shown after 15 min is slower (Fig. 1). We consider this initial dissolution phase not relevant considering the physiological situation in the stomach and will therefore consider only the dissolution after 15 min. From 40 to 120 min the rank order for dissolution of the batches B and C in SLS varies but the differences are negligible. The differences in absorption rate are thus reflected in the differences of the in vitro dissolution rate between 15 min and 40 min in SLS and in those of the entire dissolution profiles in HC (Fig. 2). This indicates that the power of the two dissolution media to predict the in vivo absorption rate is roughly the same.

In selecting a dissolution test method it is generally considered advisable to use dissolution media with sink conditions [24,25]. In the SLS medium sink conditions prevailed, as complete dissolution corresponded with 11% of the maximum solubility: see the results. In the HC medium, sink conditions were absent, complete dissolution corresponded with 64% of the maximum solubility. However, considering the dissolution profiles in HC (Fig. 2) it can be concluded that non-sink conditions as defined here may in some cases provide better discriminatory power than sink conditions, and therefore, dissolution media with non-sink conditions may be acceptable as well.

A choice between the two dissolution media must be based on the results of IVIVC.

The USP [24] describes three levels of IVIVC: level A; level B; level C. In level C correlations one single in vitro dissolution time point is related to one single pharmacokinetic parameter. It is most applicable to immediate release tablets. In the literature several level C correlations are described [2,26–28].

In selecting the characteristics to be correlated in the present study, it was considered that dissolution testing will only be predictive for the absorption rate if the absorption rate depends on the dissolution rate in vivo, and this dissolution rate in vivo in its turn is predicted by the dissolution test method in vitro. This is apparent from the results of the IVIVC for CBZ immediate release tablets; the extent of absorption ($AUC_{0-\infty}$) does not correlate well with the dissolution rate and meaningful correlations were only found between dissolution data and pharmacokinetic data that are related primarily to the absorption phase, i.e. the above mentioned seven pharmacokinetic characteristics.

As was shown before, D values as in vitro data appear to be good estimates of the rate of dissolution [2,26–28], thus, D values were correlated with the pharmacokinetic parameters given above.

To optimise each of the in vitro/in vivo relationships the D and $1/D$ values were selected that gave the best correlation, i.e. the highest correlation coefficient.

An example is shown in Table 3 and Fig. 3 for the dissolution in SLS and HC versus C_{max}. The optimum values of these IVIVC are given in Table 4.

From Table 4 it appears that, at the optimum D value dissolution testing in SLS in general gave slightly better correlations than testing in HC. So, dissolution testing in

Table 2
Mean relevant pharmacokinetic characteristics of the four screened batches (products A–D) after administration of 400 mg as a single dose to 16 volunteers. Parameters were calculated compartment-independently, with the exception of $t_{1/2abs}$ and MRT_{abs} (open two-compartment model). For more details and examples of SD refer to the pharmacokinetic study [17]

Product	$AUC_{0-\infty}$ (mg h/l)	$AUC_{0-12\ h}$ (mg h/l)	$AUC_{0-\ tmax}$ (mg h/l)	C_{max} (mg/l)	$C_{max}/AUC_{0-\infty}$ (h^{-1})	t_{max} (h)	$t_{1/2\ abs}$ (h)	MRT_{abs} (h)
A	246.18	29.3	44.7	3.29	13.36×10^{-3}	18.9	15.7	23.0
B	294.32	56.2	20.1	5.90	20.05×10^{-3}	5.7	3.8	5.9
C	292.15	58.2	13.5	6.15	21.05×10^{-3}	3.9	1.9	3.1
D	295.86	42.7	39.3	4.54	15.35×10^{-3}	11.6	13.1	19.0

Table 3
An example of IVIVC calculations concerning D values in the range D_5–D_{120} and a selected pharmacokinetic characteristic: C_{max}, with SLS and HC respectively as dissolution medium.

D value	r[a] SLS	a[b] SLS	b[c] SLS	$\sum d^{2d}$ SLS	r HC	a HC	b HC	$\sum d^2$ HC
D_5	0.4807	4.07695	0.03123	4.048	0.9955	2.53582	0.11027	0.047
D_{10}	0.7670	3.24152	0.03537	2.168	0.9708	2.86971	0.05762	0.303
D_{15}	0.9298	2.56774	0.03845	0.713	0.9537	2.90576	0.04562	0.476
D_{20}	0.9984	1.99239	0.04186	0.017	0.9592	2.75656	0.04460	0.420
D_{30}	0.9983	1.12840	0.04884	0.018	0.9680	2.42983	0.04480	0.332
D_{40}	0.9959	0.22689	0.05756	0.044	0.9730	2.21905	0.04412	0.280
D_{50}	0.9914	−1.05842	0.07016	0.090	0.9814	1.89396	0.04736	0.194
D_{60}	0.9940	−1.78091	0.07682	0.064	0.9871	1.63498	0.04913	0.135
D_{80}	0.9963	−3.73032	0.09569	0.039	0.9884	1.44823	0.04895	0.121
D_{100}	0.9958	−5.54650	0.11326	0.045	0.9684	0.86154	0.05362	0.328
D_{120}	0.9855	−7.93673	0.13565	0.152	0.9855	0.00317	0.06333	0.152

[a] Correlation coefficient.
[b] Intercept.
[c] Slope.
[d] Unexplained variance.

SLS, i.e. the testing conditions in the USP, which are also accepted world-wide for dissolution testing of CBZ immediate release tablets, was found to give the best performance.

Of the pharmacokinetic parameters primarily related to the absorption phase, C_{max} is selected as the pharmacokinetic parameter of choice in bio-equivalence testing; the discussion on this topic is given in the former publication [17]; so, the correlation of C_{max} versus D values in SLS deserves special attention.

It appears from Tables 3 and 4, also Fig. 4 that in SLS C_{max} is best predicted at D_{20} as judged from both correlation coefficient and unexplained variance ($r = 0.998$, $\sum d^2 = 0.017$). The overall conclusion is that the USP method, using D_{20} in SLS under the experimental conditions used in this study (paddle, rotation speed 75 rev./min) is the best dissolution method, providing favourable IVIVC with C_{max}.

On the basis of the IVIVC results between D_{20} and C_{max} found (see Table 3), and the requirements for C_{max} (0.75–1.35) the following dissolution rate specification is set 'after 20 min, 34–99% dissolved'.

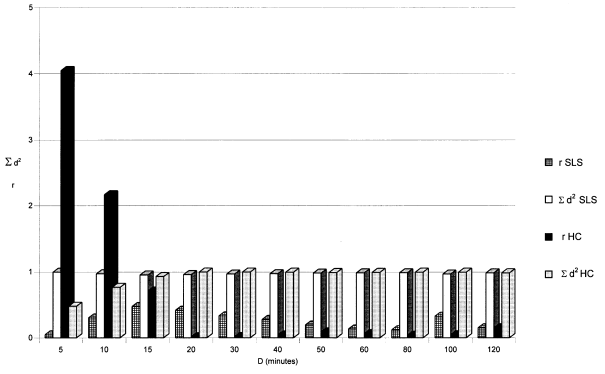

Fig. 3. IVIVC results of D values versus C_{max}, with SLS and HC respectively, as dissolution medium.

As no meaningful IVIVC correlations were obtained with $AUC_{0-\infty}$, no dissolution specification can be deduced to ensure extent of absorption. However, $AUC_{0-\infty}$, appeared to be nearly invariant between the four products [17], and owing to the fact that the rate of absorption in vivo depends i.a. on the dissolution rate in vivo, also bio-equivalence with respect to extent of absorption is ensured with this dissolution specification.

Taking into account the dissolution results after 20 min (see Fig. 1), it can be deduced that the dissolution results of all products in this experiment except those of product A fall within the specification. When considering the dissolution specification in the USP monograph for CBZ immediate release tablets, 'not less than 75% dissolved after 1 h', therefore a conclusion may be drawn: the dissolution results of product A after 1 h do not comply with the specification in the USP, but the results for the other products do. The specification proposed above is thus comparable with the specification in the USP, both this specification and the USP specification are considered suitable to ensure bioequivalence, if tested according to the testing conditions in the USP.

So, when the dissolution of a CBZ immediate release batch/product is tested and the mean dissolution results are within the USP specification, bio-equivalence of the batch/product as defined before is ensured, including batch to batch and between brands bioavailability. With this specification it is also possible to estimate a possible influence on the bioavailability of changes within one brand in manufacturing site, storage time, storage condition and changes in the composition.

5. Conclusion

It can be concluded that within the range of CBZ immedi-

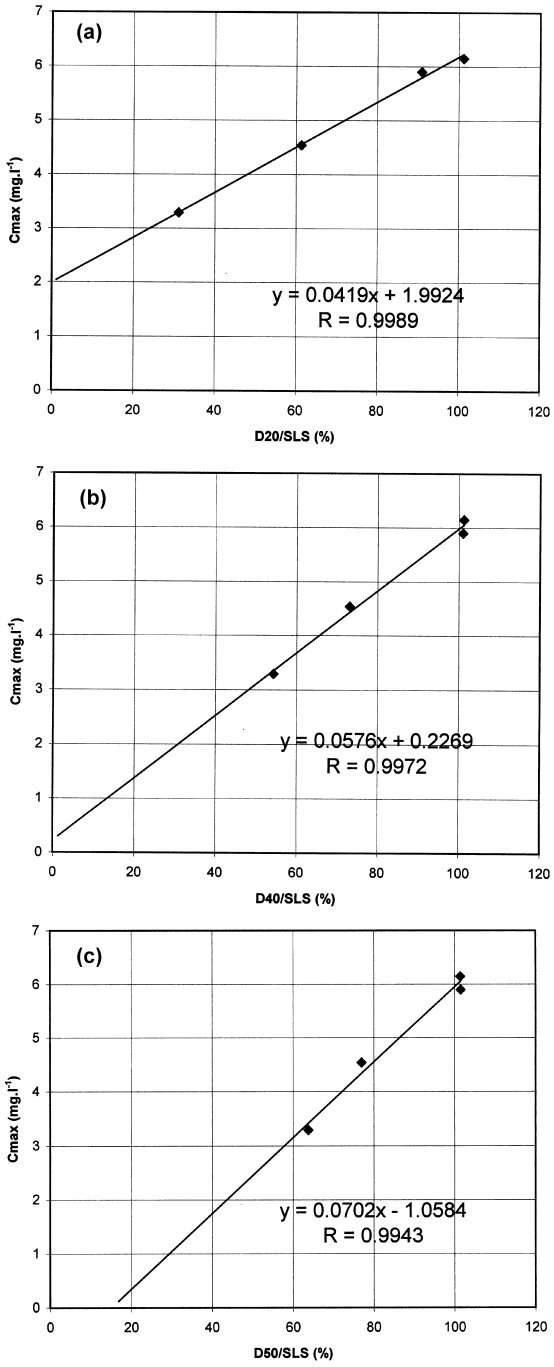

Fig. 4. Relationship between C_{max} and the percentage dissolved in vitro in SLS, at 20, 40 and 50 min.

ate release tablets that have a qualitative composition comparable to the products studied (Table 1), dissolution testing according to the USP method and specification is a reliable predictor of bioequivalence. Thus, this method and specification can be used to evaluate bioequivalence between brands and within one brand, and also changes in manufacturing site, storage time, storage condition, and composition of products, without performing in vivo studies.

Table 4
Best IVIVC of *D* values or 1/*D* values versus several pharmacokinetic characteristics with SLS and HC, respectively, as dissolution medium

Parameter	Method	Optimum D or 1/D	r[a]	$\sum d^{2b}$
C_{max}	SLS	D20	0.9984	1.7×10^{-2}
	HC	D 5	0.9955	4.7×10^{-2}
$C_{max}/AUC_{0--\infty}$	SLS	D50	0.9980	1.5×10^{-7}
	HC	D120	0.9941	4.5×10^{-7}
$AUC_{0-12\ h}$	SLS	D30	0.9981	2.1
	HC	D 5	0.9950	5.4
AUC_{0-tmax}	SLS	1/D60	0.9778	29
	HC	1/D100	0.9530	62
MRT_{abs}	SLS	1/D30	0.9880	6.7
	HC	1/D100	0.9530	26
$T_{1/2\ abs}$	SLS	1/D60	0.9868	3.6
	HC	1/D60	0.8982	27
T_{max}	SLS	1/D30	0.9954	1.3
	HC	1/D80	0.9970	8.4×10^{-1}

[a] Correlation coefficient.
[a] Unexplained variance.

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