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Research paper

Biopharmaceutical characterization of oral controlled/modified-release drug products. In vitro/in vivo correlation of roxatidine

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Abstract

From the marketed drug product Roxane® 75 mg C/MR capsules (roxatidine controlled/modified-release capsules), an in vitro/in vivo comparison was performed to demonstrate a 1:1 correlation between in vitro and in vivo dissolution, and, furthermore, to ensure bioequivalence of the roxatidine controlled/modified-release (C/MR) capsules exhibiting dissolution profiles within the defined acceptance criteria. This 1:1 in vitro/in vivo comparison was calculated using a model independent numerical deconvolution method. The high degree of correlation is extremely rare, nevertheless it allows to omit the testing of clinical side batches for the setting of acceptance criteria for the in vitro dissolution of roxatidine controlled/modified-release (C/MR) capsules. The 1:1 in vitro/in vivo correlation can be explained by the biopharmaceutical characteristics of the drug substance as well as the drug product, that is, pH-independent high solubility of the drug substance as well as dissolution which is independent of pH and agitation. These facts lead to a controlled/modified-release formulation. Therefore, it is important to keep in mind that in most cases in which a pH-dependent solubility/dissolution as well as permeability characteristics can be found, a 1:1 in vitro/in vivo correlation could not be expected.

Keywords: Bioavailability; Oral controlled/modified-release drug product; In vitro/in vivo correlation; Dissolution; Level A correlation; Roxatidine acetate hydrochloride; Compendial recommendations

1. Introduction

Dissolution test methodology has been introduced to many pharmacopoeias and a number of regulations and guidelines on bioavailability, bioequivalence and in vitro dissolution testing have been used at national and international levels. The first guidelines for dissolution testing of solid oral products were published in 1981 [1]. As far as is reasonable for the purpose of these guidelines, technical terms and definitions have been adopted from other harmonized recommendations and mainly correspond to USP terminology [2]. One new term is 'in vitro/in vivo comparison', which by definition means the relationship between an in vitro property of an oral controlled/modified-release drug product (usually the rate or extent of drug dissolution) and a relevant in vivo response, e.g. plasma drug concentration or amount of drug absorbed.

Regarding oral controlled/modified-release drug products, the United States Pharmacopeia (USP) [2] has categorized correlative methods, harmonized in a wide international consensus, as correlation level A, correlation level B and correlation level C.

This work shows the development of a 1:1 in vitro/in vivo comparison (level A correlation) according to compendial requirements [2,3] for the marketed drug product Roxane® 75 mg C/MR capsules (roxatidine controlled/modified-release capsules) using a model independent numerical deconvolution technique. This level A correlation is predictive for the relationship between the entire in vitro dissolution time course and the entire in vivo response time course of plasma drug concentration in contrast to level B or level C correlations, which characterize the in vitro/in vivo time

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course using statistical moment analysis and a single-point correlation, respectively. In the case of a level A correlation, manufacturing site changes, minor formulation modifications, scale-up considerations and setting of acceptance criteria for in vitro dissolution testing can be based and justified without further in vivo studies [4].

2. Materials/test conditions

The active ingredient roxatidine acetate hydrochloride is very soluble in aqueous media regardless of pH. The release kinetics of the drug product are achieved by using a pellet base as a vehicle which is coated with a mixture of the drug substance and the coating material. The coated pellets are filled into hard gelatine capsules corresponding to the intended dosage of 75 mg (Roxane® 75 mg C/MR capsules).

In vitro dissolution of roxatidine controlled/modified-release capsules is tested by the paddle method (Ph.Eur., USP Apparatus 2) at 100 rpm using 900 ml of 0.1 N hydrochloric acid as dissolution medium. The amount of dissolved drug substance is determined after testing for 1, 2, 3 and 12 h.

3. Development of dissolution tests

The dissolution of a controlled/modified-release (C/MR) drug product is known as being an essential parameter with regard to bioavailability. In principle, the same apparatus and factors which are described for immediate-release drug products [5] may be applicable to C/MR drug products. However, the testing conditions such as the pH of the dissolution media and duration of the test are more critical for developing dissolution tests for C/MR drug products.

The significance of pH dependency is considered by the EC Note for Guidance [3] and USP XXIII [2]. Recommendations concerning physico-chemical properties, test conditions, equipment and analytical method are also given with both compendia.

4. Compendial recommendations for in vitro/in vivo comparison

In vitro dissolution testing is important for (1) providing process control and quality assurance, (2) determining stable release characteristics of the product over time, and (3) facilitating certain regulatory determinations such as absence of minor formulation changes or of change in manufacturing site on performance. Especially in the case of C/MR formulations, the dissolution test can serve not only as a quality control for the manufacturing process but also as an indicator of how the formulation will perform in vivo. Thus, a major objective of developing and evaluating an in vitro/in vivo correlation is to establish the dissolution test as a surrogate for human bioequivalence studies, which may reduce the number of bioequivalence studies performed during the initial approval process as well as with certain scale-up and post-approval changes. However, the complete process of developing an in vitro/in vivo correlation with high quality and predictability and identifying specific applications for such correlations has still not been well defined [6].

The justification of the acceptance criteria set for in vitro dissolution of a C/MR drug product should be performed on the basis of a meaningful comparison between in vitro release characteristics and bioavailability parameters [2,3]. The correlations – a better wording may be ‘comparison’ – are categorized into three levels, A, B and C, in order of decreasing predictive quality.

For level A (Table 1) which is the highest level of comparison, a 1:1 relationship between in vitro and in vivo dissolution exists. In this procedure, the in vitro dissolution profile of the drug product corresponds to the in vivo dissolution profile generated by deconvolution of plasma concentration data. The deconvolution may involve the model depending on mathematical procedures according to Wagner–Nelson or Loo–Riegelmann, or direct mathematical deconvolution [7].

At level B the mean in vitro dissolution time of the drug product is compared with the mean residence time or the mean in vivo dissolution time determined by using the principles of statistical moment analysis. Although a level B

Table 1
In vitro and in vivo comparison

USP (Level A)	EC (3.3.3.a)[a]
In vivo evaluation Deconvolution of plasma concentrations or model-dependent methods	*In vivo evaluation* Deconvolution of plasma concentrations or other appropriate methods
In vivo–in vitro –1:1 Correlation –Prediction for quality control –Justification of specifications –No further human studies after a change of manufacturing site, method of manufacture, raw material supplier, minor formulation modification, different strengths of the same formulation	*In vivo–in vitro* –Prediction for quality control – ±10% –No further human studies after minor change to the composition, method and site of manufacture or manufacturing equipment

[a]EC Note for Guidance: Quality of Prolonged Release Oral Solid Dosage Forms [3].

comparison is performed on the basis of all in vitro and in vivo data, no 1:1 comparison may be deduced as it does not reflect the plasma concentration–time curve of the drug product. Level C represents a single point correlation. It relates the mean in vitro dissolution time, i.e. expressed as $t_{50\%}$, $t_{90\%}$ to the mean of one pharmacokinetic parameter (e.g. area under the curve, C_{max}, T_{max}).

5. Results

5.1. In vitro dissolution

C/MR drug products should be characterized primarily with respect to their effect on pH and agitation [4]. As shown in Figs. 1 and 2, in vitro dissolution of roxatidine controlled/modified-release capsules may be characterized as controlled. The similarity of the dissolution profiles was confirmed by calculating the model independent approach using the similarity factor f_2 [4], which is a logarithmic reciprocal square root transformation of the sum of the squared error. For roxatidine controlled/modified-release capsules similarity factors between 60 to 90 were determined, which suggests that the dissolution profiles are similar.

5.2. In vivo dissolution

The in vivo dissolution of roxatidine controlled/modified-release capsules (Fig. 4) was calculated by model independent numerical deconvolution of the mean plasma concentration–time profiles of roxatidine controlled/modified-release capsules (Fig. 3) and roxatidine 75 mg immediate release capsules, as proposed by several investigators and the FIP Working Group [7].

The bioavailability study [8] was performed as an open, single-dose, crossover study. Eight subjects were studied on two study days which were separated by a period of at least 1 week. Each of the subjects received the following drug products:

roxatidine controlled/modified-release capsules containing 75 mg of roxatidine acetate hydrochloride;
roxatidine immediate release (IR) capsules containing 75 mg of roxatidine acetate hydrochloride.

Blood samples for the determination of roxatidine were collected at the following times: pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12 and 24 h after dosing.

5.3. In vitro/in vivo comparison

In vitro and in vivo dissolution of roxatidine controlled/modified-release capsules show practically identical profiles (Fig. 4). This suggests a 1:1 in vitro/in vivo relationship for dissolution according to level A.

Following the concept of the establishment of acceptance criteria for dissolution given in Table 2, the in vitro and in vivo comparison was performed taking into consideration

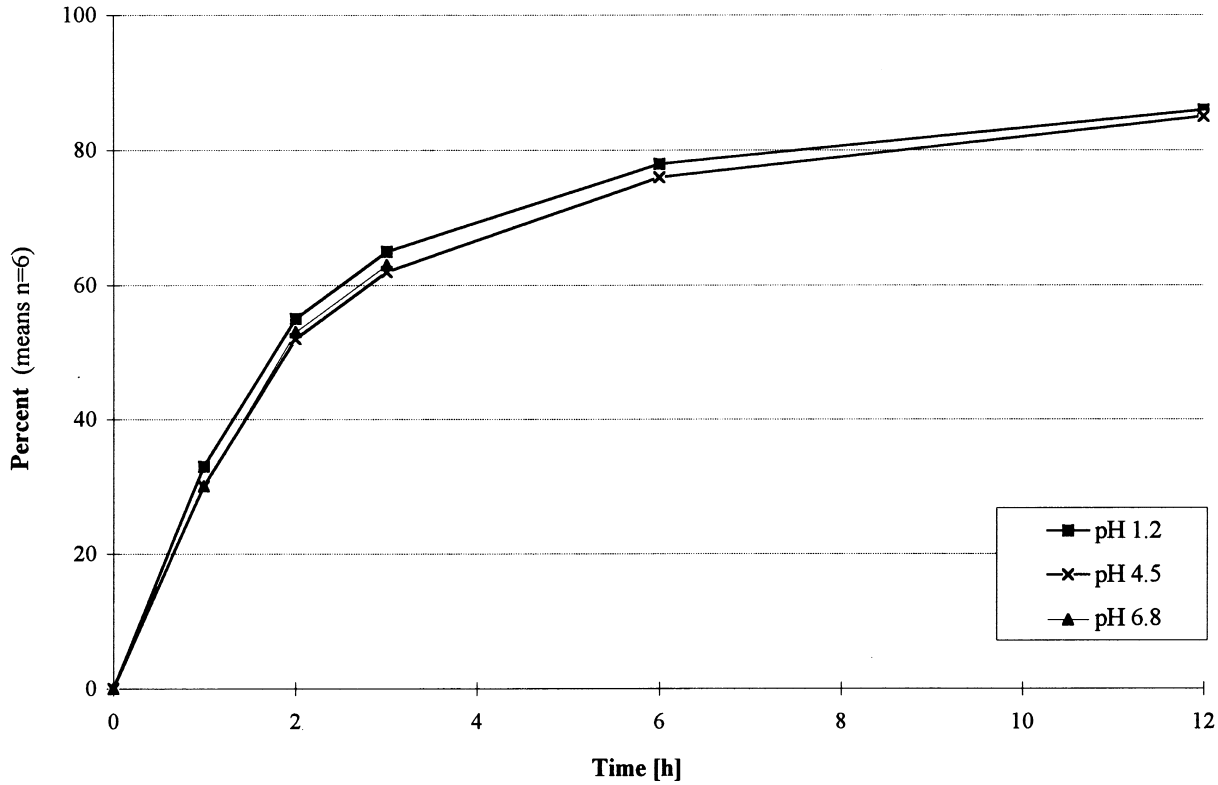

Fig. 1. In vitro dissolution of roxatidine C/MR capsules at different pH values.

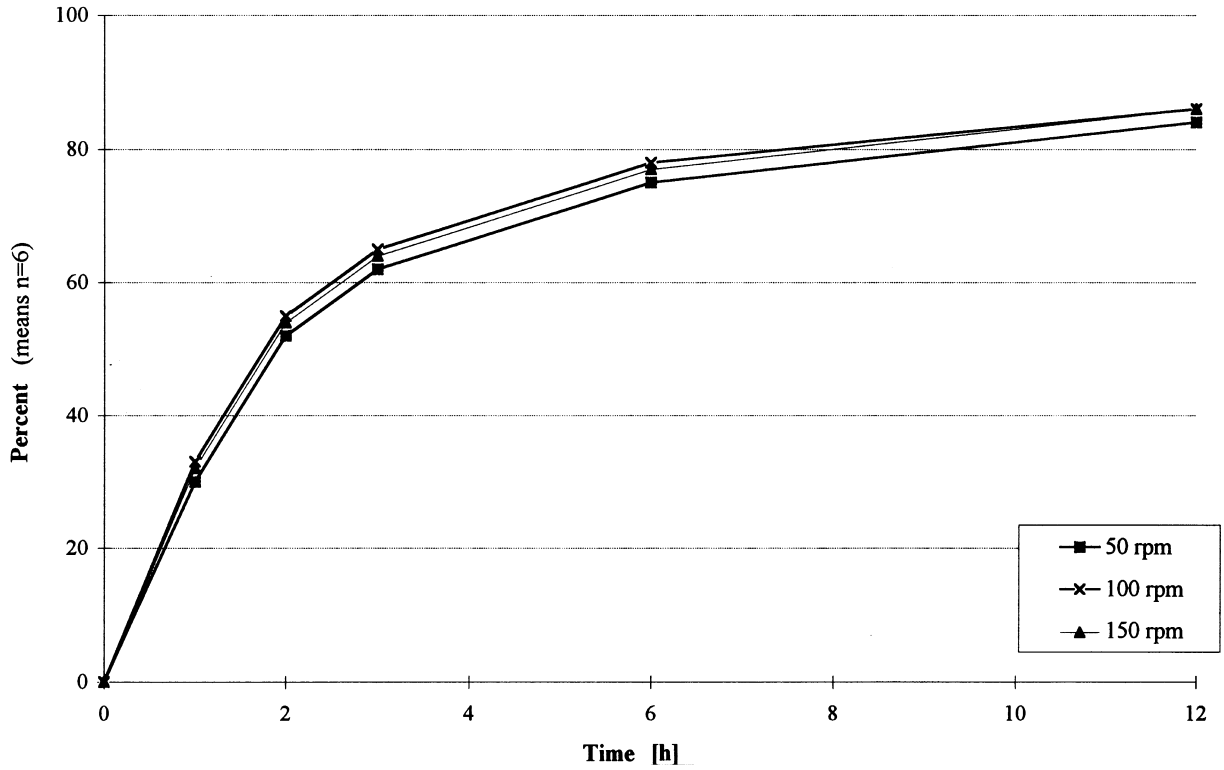

Fig. 2. In vitro dissolution of roxatidine C/MR capsules at different agitation.

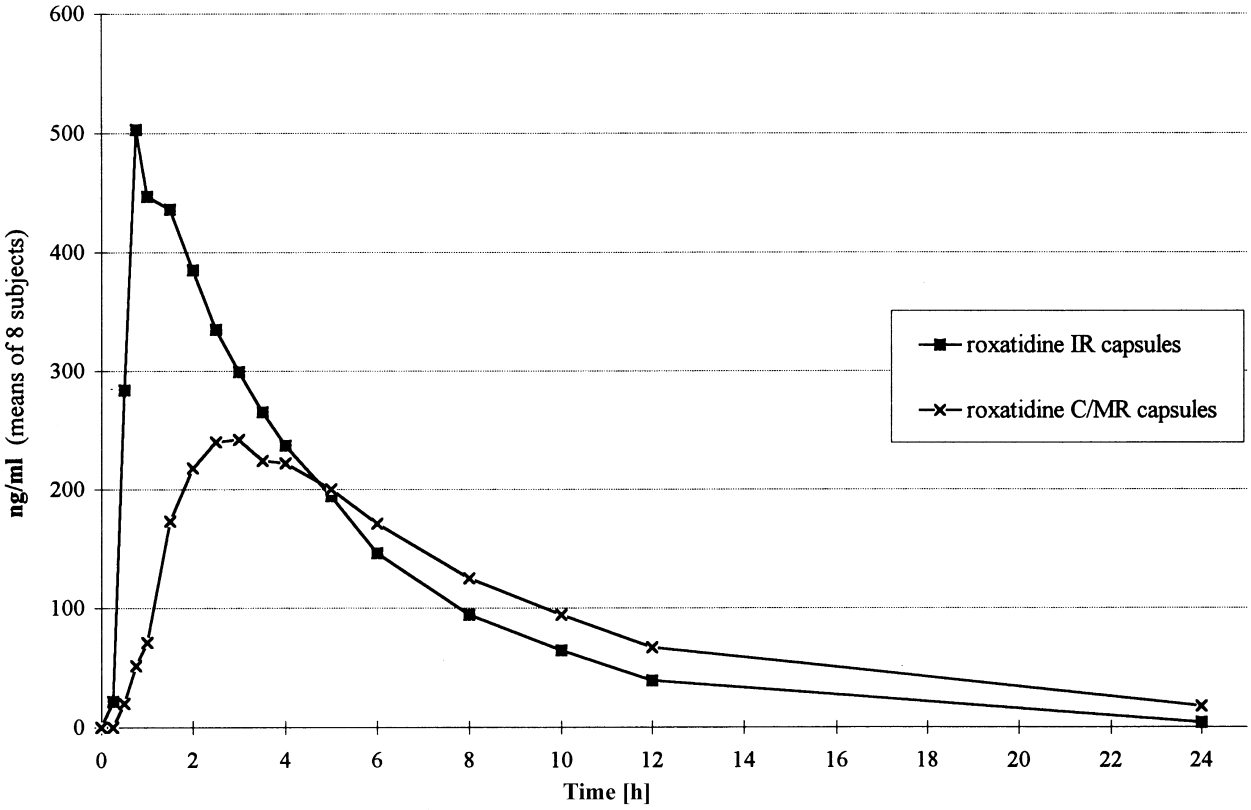

Fig. 3. Plasma concentration of roxatidine C/MR capsules and roxatidine immediate release (IR) capsules.

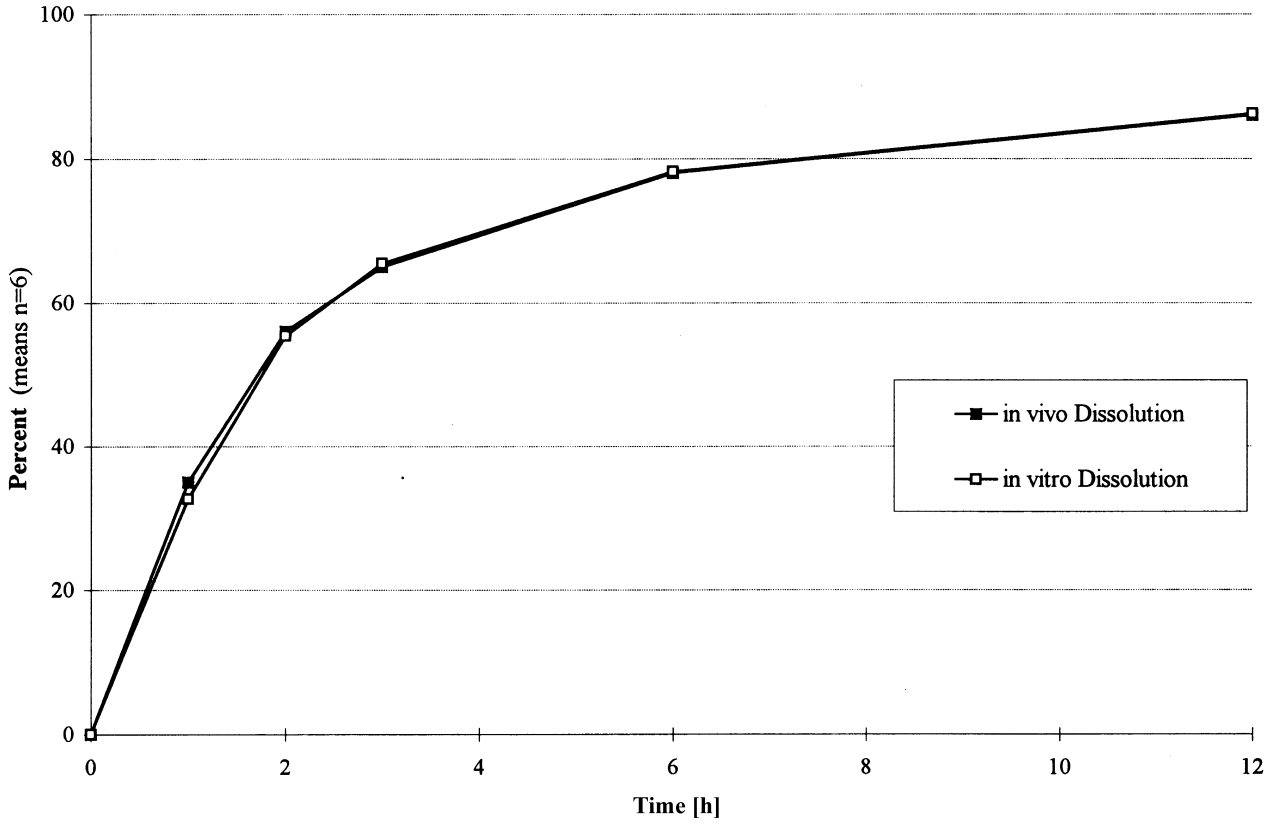

Fig. 4. In vitro dissolution and in vivo dissolution of roxatidine C/MR capsules.

the USP approach [2] and the European recommendation [3].

Due to the highest degree of correlation, the target in vitro dissolution profile should correspond to that calculated from the plasma concentrations in the bioavailability study. To define the lower and upper dissolution limits, the extremes of the 95% confidence intervals (Fig. 5) and ±1 standard deviation (Fig. 6) of the mean plasma concentrations were deconvoluted [7]. The resulting input rate curves are comparable with the acceptance criteria for in vitro dissolution (±10% of target dissolution profile) at each time point. As a consequence, the plasma concentrations calculated by convolution from the specified extremes of the in vitro dissolution are similar to the 95% confidence limits of the plasma concentrations determined in the bioavailability study (Fig. 7).

These estimations lead to the 1:1 in vitro/in vivo comparison for the marketed drug product Roxane® 75 mg C/MR capsules (roxatidine controlled/modified-release capsules).

Table 2

Establishment of acceptance criteria for dissolution level A (USP) [2], considering European requirements (EC) [3]

Convolution	–Define the lower and upper limits of dissolution (biobatch) within the range of ± 2.5 to 3 standard deviations [2] –EC recommends a range of 20% at each time point [3] –Convolute the lower and upper limits –The results fall within the 95% confidence intervals obtained in bioavailability–bioequivalence study (biobatch)
Deconvolution	–Deconvolute the individual plasma concentrations and select the extremes of the 95% confidence intervals or ± 1 standard deviation of the mean plasma concentrations –Compare the results with dissolution of biobatch and set specifications at each time point

6. Conclusions

On the basis of the in vitro/in vivo comparison, the acceptance criteria for in vitro dissolution of roxatidine controlled/modified-release capsules are specified as follows:

Time (h)	Target (%)	Acceptance criteria (%)
1	35	25–45
2	55	45–65
3	65	55–75
12	>80	>80

These values are based on the extremes of the in vitro

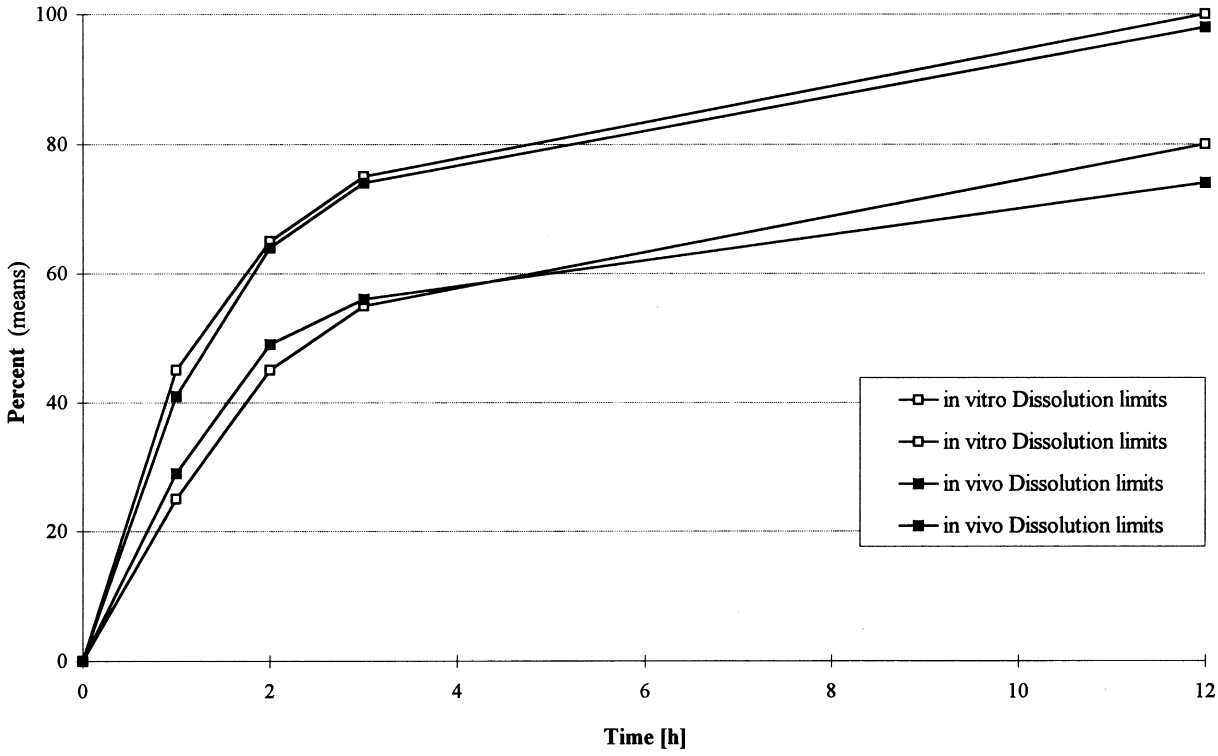

Fig. 5. In vitro and in vivo dissolution limits of roxatidine C/MR capsules. Lower and upper limits of in vitro dissolution. In vivo dissolution (95% confidence limits of mean plasma concentrations).

dissolution, which lie within the ranges given by the in vivo data (Fig. 7).

The main objective of developing and evaluating this in vitro/in vivo correlation was to establish a dissolution test

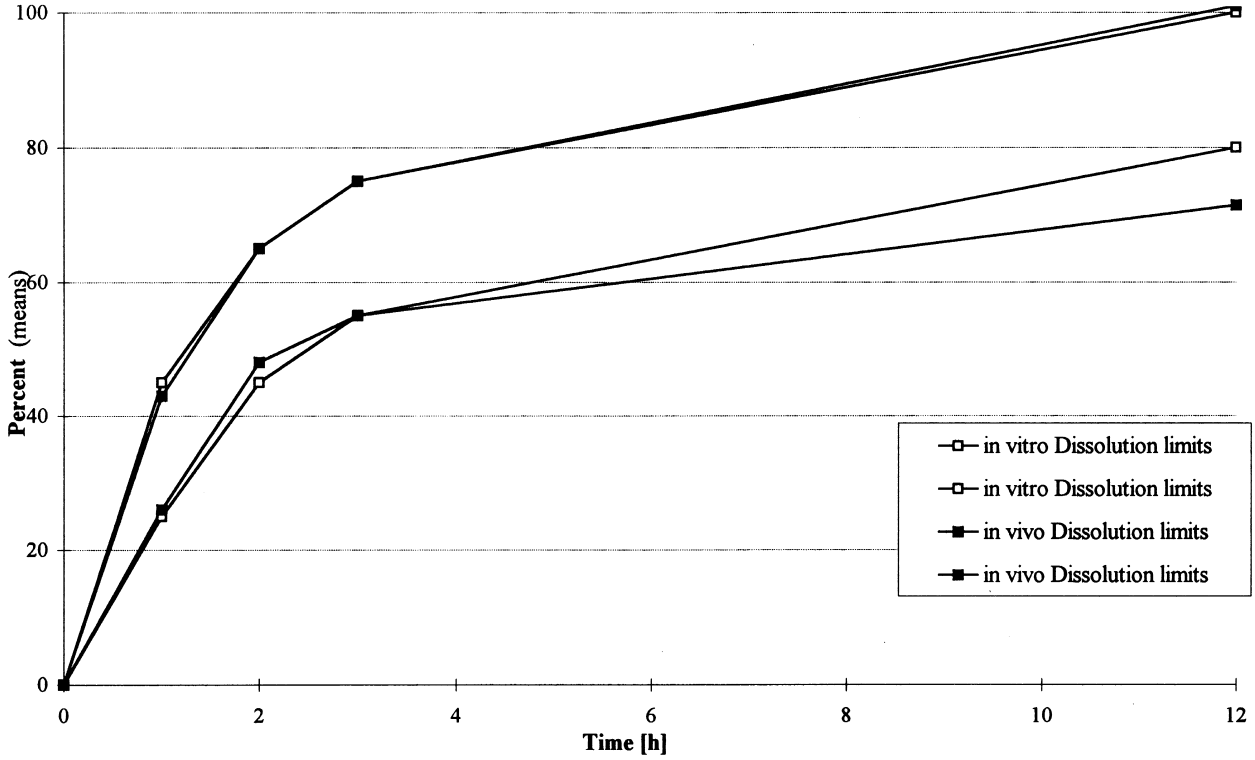

Fig. 6. In vitro and in vivo dissolution limits of roxatidine C/MR capsules. Lower and upper limits of in vitro dissolution. In vivo dissolution (deconvolution of (± 1%SD) mean plasma concentrations.

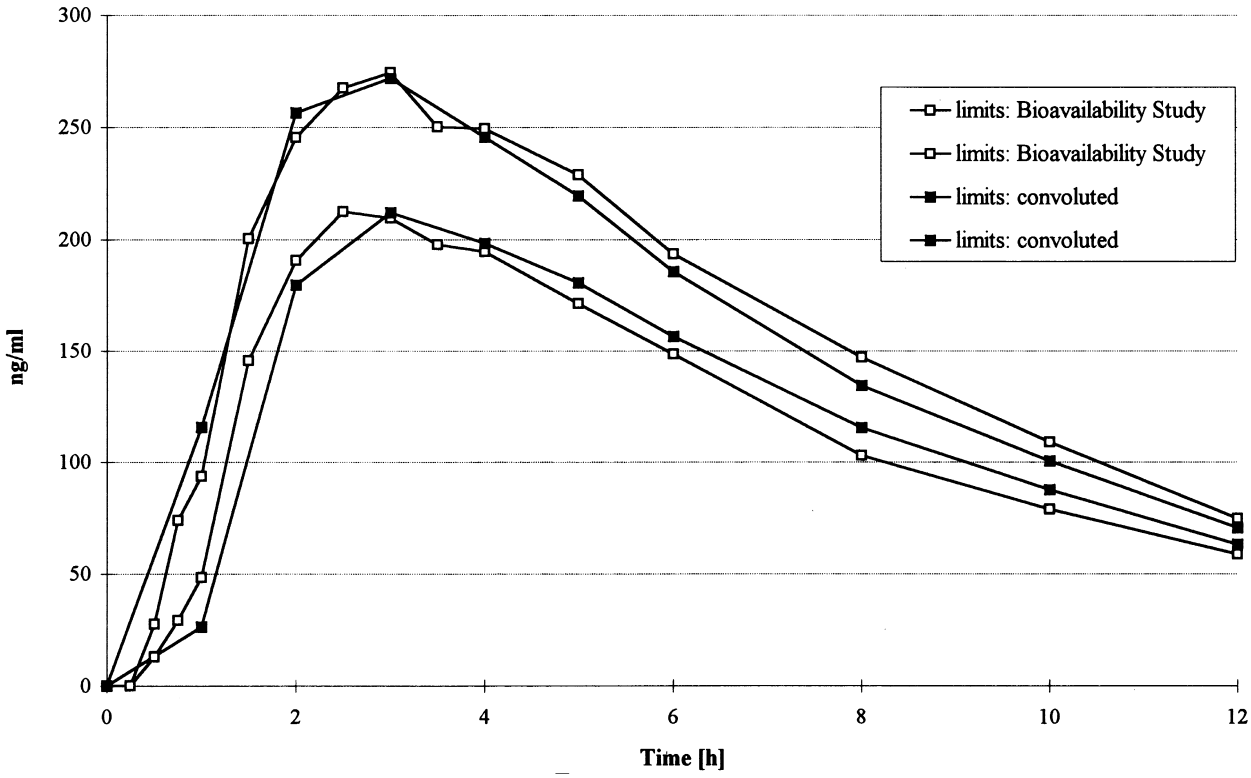

Fig. 7. Plasma concentration of roxatidine: 95% confidence limits of plasma concentration (bioavailability study), convoluted from upper and lower dissolution limits by setting ranges of 20% at each time point.

method for roxatidine controlled/modified-release capsules as a surrogate for human bioequivalence studies, which may reduce the number of bioequivalence studies performed during the initial approval process as well as with certain scale-up and post-approval changes.

The presented high degree of correlation is extremely rare, nevertheless it allows one to omit the testing of clinical side batches for the setting of acceptance criteria for the in vitro dissolution testing. The 1:1 in vitro/in vivo correlation can be explained by the biopharmaceutical characteristics of the drug substance roxatidine and the drug product itself, that is, pH-independent high solubility of the drug substance as well as dissolution which is independent of pH and agitation. These facts lead to a controlled release formulation. However, in most of the cases in which a pH-dependent solubility/dissolution as well as permeability characteristics can be found, a 1:1 in vitro/in vivo correlation cannot be expected [9]. This should be kept in mind when presenting a 1:1 in vitro/in vivo correlation for a certain drug product; moreover, the complete process of developing an in vitro/in vivo correlation with high quality and predictability, and identifying specific applications for such correlations, has still not been well defined [6].

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