Comparison of dissolution profiles of Ibuprofen pellets

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Abstract

In this work we use both model dependent and independent techniques to assess the difference between dissolution profiles in which ibuprofen, in the form of uncoated pellets, is used as a model drug. The choice of a proper regression function, the relevance of the estimated parameters and the influence of the choice of dissolution points in the assessment of differences is discussed. The results obtained via mean dissolution times (MDT) and fit-factors (f_1 and f_2) are also discussed and a non-quantitative method based on profiles correlation with graphical representation (concentration vs. concentration and rate vs. rate) presented. The tested methods discriminate similarly between curves, although not in all cases, but those based on modeling, MDT and fit-factors have shown to be less informative than the correlation approach.
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1. Introduction

In vitro dissolution has been recognized for the past four decades as an important element both in drug development and quality assessment [1–8], especially in controlled release formulations. Release and further dissolution of the drug from the solid dosage forms often constitute a determining step in the in vivo absorption process and is thus used in conjunction with in vivo/in vitro correlations to establish quality control parameters. This is especial-

ly relevant in checking batch to batch consistency in clinical trials, bioavailability and routine production. In the development of a new product, dissolution testing can thus aid in drug release modeling, e.g. through selection of excipients, optimization of the manufacturing process and scale-up, and formulation of test products matching required dissolution characteristics [9,10]. It may also be used to determine the long term stability of a dosage form and assess the impact of post-approval changes in the manufacturing process.

The methods for the comparison of dissolution profiles may be classified into two main groups according to whether or not they resort to a regression model. The model independent approaches encompass the calculation of mean dissolution times (MDT) or related characteristic values [2,8,11,12],

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ANOVA-based methods [3,13] and similarity criteria based on various indexes for pairwise comparison procedures [14–19]. It should also be pointed out that some of the methods rely on the individual characterization of each curve (MDT, modeling), while others go directly into pairwise comparison (fit-factors and other similarity measures). MDT values are strongly dependent on the upper limit of the dissolution interval, while fit-factors provide exclusively a measure of absolute value discrepancy. These topics will be discussed in detail later.

In procedures requiring an underlying functional form for the description of each dissolution profile, the usual approach for the determination of the relevant parameters involves performing either ordinary linear (OLS) or non-linear least-squares (NLLS) using a limited number of typical functions [13,20–22]. In the case of OLS, a preliminary linearization step is often performed. Inspection of residuals, weighting taking account of heterocedasticity and parsimony verification are frequently absent. The problem is thus reduced to the comparison of confidence intervals for the determined fitting parameters, which requires an accurate estimation of the corresponding uncertainty. In most cases, modeling does not contemplate estimation of the predicted asymptotic value of concentration (which is not necessarily equivalent to the total dissolved amount), and results often in very poor fits. Alternative procedures for the latter task, such as the use of calibration curves in each relevant matrix, are also seldom perceived and imply the independent determination of the dose and batch consistency. However, this determination has frequently broad error ranges that should not be, in some cases, introduced in assessing profile differences. The use of qualitative (i.e. in which each profile is auto-normalised) methods, based on correlation, may circumvent this difficulty. So, in this work we have applied several profile comparison methods, including correlation as a non-quantitative approach, to the dissolution data of different uncoated pellets formulations containing ibuprofen, aiming to contribute to its evaluation and identification of eventual advantages or disadvantages.

In summary, we have employed modeling resorting to some of the most popular functions for the purpose, but using weighted least squares to account

for heterocedasticy, absent in previous approaches. Also introduced was an additional parameter to describe the asymptotic value of the dissolution profile. These changes not only increase the reliability of the fitting parameters but drastically reduce the sum of squares and avoids dosage determination. We have also introduced a correlation approach, complemented with the graphical representation of profiles and their time variations for assessing the respective differences and their evolution as dissolution proceeds. Comparison with traditional methods, such as those based in fit-factors and MDT values is made, and their shortcomings pinpointed.

2. Experimental procedure

2.1. Materials

In this work, we have used Ibuprofen (Shasun, batch IBU 0001097, shelf-life 12/04), as a model drug with pH-dependent solubility and pK_a of ca. 4.4 [23], microcrystalline cellulose (Microcel PH 101, Sagran, Milan, Italy), monohydrate lactose and tricalcium phosphate, as soluble and insoluble fillers respectively, and citric acid as a pH adjuster. Sodium hydroxide and kallium dihydrogenophosphate, analytical grade (Merck), were used in a pH 7.2±0.05 phosphate buffer preparation. Ibuprofen solubility is increased at this pH, when compared to more acidic ones, which facilitates the comparison of profiles.

2.2. Preparation of pellets

Pellets (200 g) were prepared by the extrusion/spheronization method. Four different formulations with 20% of ibuprofen were prepared as shown in Table 1. Demineralysed water was used as the wetting liquid. The powders were mixed for 5 min (Kenwood, UK) before the water was added (130 ml). The masses were extruded in an extruder with cylinders fitted with a die of 1 mm diameter (Caleva Process, Ltd., UK). The extrudate was spheronized in a spheronizer (G. B. Caleva, Ltd, UK) fitted with a radial plate, 250 mm diameter at 1020 rev./min for 4 min. The obtained pellets were dried in a fluidized bed dryer (Glatt), for 15 min at 50 °C. Pellets were

Table 1
Pellets formulations containing 20% (w/w) of ibuprofen

I		II		III		IV	
Lactose	30.00%	Lactose	25.00%	Tricalcium phosphate	30.00%	Tricalcium phosphate	25.00%
Microcel	50.00%	Citric acid	5.00%	Microcel	50.00%	Citric acid	5.00%
		Microcel	50.00%			Microcel	50.00%

then submitted to sieve analysis using a mechanical sieve shaker for 10 min.

2.3. In vitro dissolution studies

Dissolution of the size fraction 1.0–1.4 mm of each formulation was conducted in a USP Method 1 (rotating basket) apparatus, at a speed of 100 rev./min, in 6×900 ml of dissolution media (phosphate buffer at pH 7.2 ± 0.05), maintained at 37 ± 0.5 °C, using an automated assembly which consisted of a Fujitsu Ergo Proe PC, with the UV-1601PC software, a peristaltic pump (Watson Marlow 205S), a UV spectrophotometer (Shimadzu UV-1603), a cell positioner (Shimadzu CPS-Controller), a water bath fitted with a variable-speed stirrer (Vankel UK 7000) and a heater (Vankel VK750D). The released ibuprofen absorbance was recorded automatically each 5 min for 8 h, at a wavelength of 264 nm. Triplicates were obtained for each experiment, with a total of 18 dissolution curves for each formulation. Profile comparison methods were applied to the mean profile obtained from these 18 curves, which were previously normalized with the pellets weighted mass. Tests

conducted with pellets in which the active substance is absent have shown negligible absorption in the wavelength considered.

3. Release modeling

Mathematical models have been used extensively for the parametric representation of the dissolution data [3,4,13,20–22,24,25], which may be followed by the statistical comparison of the estimated parameters employing a t-test. In this work we have employed several models to compare the various profiles and also attempted to identify the nature of drug release. Several common models were analyzed (see Table 2) in a manner that slightly differs from the most common approaches. First, when the total amount released is present in the regression function, it is used as an additional parameter. Also, non-linear weighted least squares, based on the Marquardt algorithm, was employed so as to take into consideration the heterocedastic nature of the data.

In some previous approaches, the final released amount is established from the stated dose [3,13].

Table 2
Release models tested

Zero order	$c_1 t$	Constant release rate
Higuchi	$c_1 t^{0.5}$	Fickian diffusion mechanism
Korsmeyer–Peppas	$c_2 t^{c_1}$	Diffusion based mechanisms
Hixson–Crowell	$c_2 (1 - (1 - c_1 t))^3$	Erosion release mechanism
First order	$c_2 (1 - \exp(-c_1 t))$	First order mass balance
Weibull	$c_3 \left(1 - \exp\left(-\frac{t}{c_1} \right)^{c_2} \right)$	Life-time distribution function
Logistic	$c_3 \times \dfrac{\exp(c_1 + c_2 \log t)}{1 + \exp(c_1 + c_2 \log t)}$	S-shaped model

This is common practice when commercial drug products are employed. However, the value of the dose may be affected with a systematic error of up to 5 or 10%, depending on the substance. Having in view the comparison of dissolution profiles, dose errors may thus be an important part of the discrepancies found. This type of error may be simply discarded if the total released amount is used as an additional fitting parameter, which corresponds to an extrapolation based on the prevailing mechanisms for the period considered and thus do not necessarily point to the actual asymptotic value of the dissolution profile. Its inclusion, apart from minimizing the referred dose errors, has an additional consequence, i.e. drastically improving the quality of the fit. This parameter acts also as a normalising constant, and should not therefore be considered in the t-test comparison of profiles.

Apart from comparing profiles, modeling may also provide some insight into the drug release mechanisms. We note, however, that in some cases, a single functional form is not capable of describing the whole profile. Excipients, e.g. which promote controlled release have an effect that tends to vary during the dissolution process. In these cases we obtain information that essentially describes the dominant mechanism, which is often not the same for the profiles for which a comparison is intended.

3.1. Results and discussion

We have fitted the various functions for dissolution times up to 60, 120 and 480 min. In the first case, only the ascending part of the curve is considered, for 120 min the curves are approaching the plateau and 480 min correspond to the whole set of points determined. In the latter case, a significant number of points in this plateau are present in the curve (Figs. 1 and 2).

We first look at our results for 60 min, presented in Table 3. These indicate, based on the Akaike Information Criterion (AIC) [26], that the best overall function is undoubtedly the logistic (Fig. 3), although the Weibull function also presents good fits. For formulation II, unlike the others, the best fit is obtained with the first order equation. The remaining functions are not adequate for the dissolution curves corresponding to our formulations (see, e.g. Fig. 4). Thus, the best regression functions rely more on the description of shape, having not a direct connection
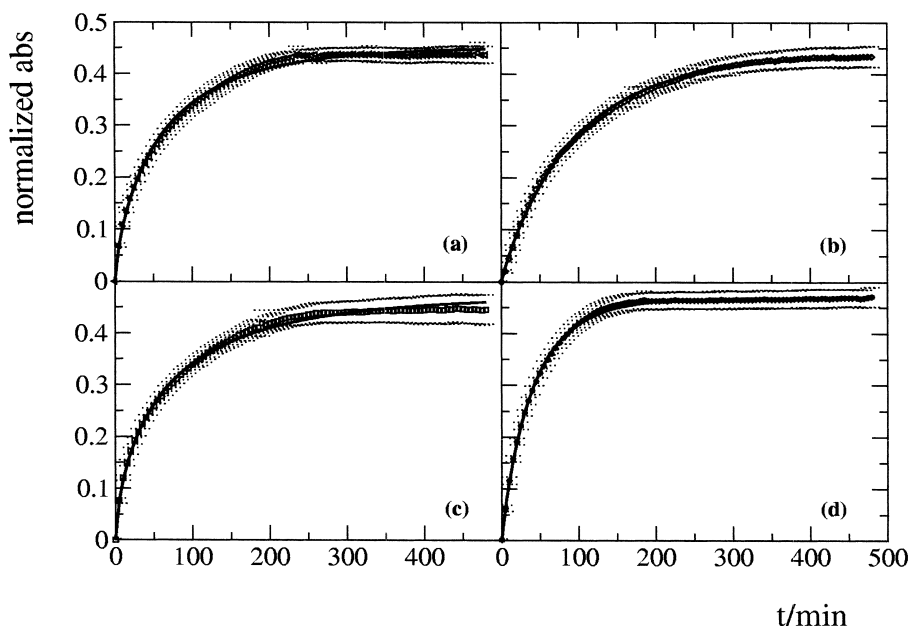

Fig. 1. Dissolution profiles of formulations I (a), II (b), III (c) and IV (d) fitted with the Weibull function (solid line).
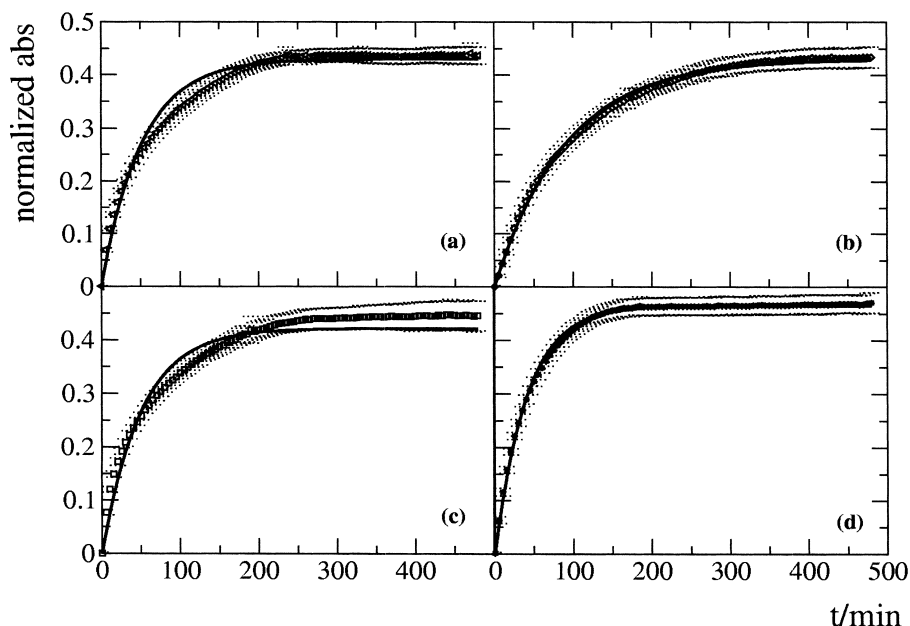
Fig. 2. As in Fig. 1 for the first order function.

with mechanism. Results for 120 min are similar to those reported before and stress the fact that the logistic function is more reliable for the description of the ensemble of curves (see Table 4). These findings are in agreement with some previous determinations, irrespective of the formulations under study [13].

The full curve was employed to check the prediction capabilities of functions in what concerns the asymptotic values (see Table 5). This is relevant for those functions, such as the first order one, in which this limit is built-in. Our conclusion is that the asymptotic value cannot be accurately estimated from the points corresponding to the 60 min period and that a substantial deviation is found even for 120 min. This may be ascribed to the way in which the mechanism evolves along the dissolution process as stated before. Also, the fact that this functions do not directly incorporate mass balance results means that they are not capable of accurately describing the plateau value which is reached after total consumption of the active substance, no matter which mechanism (or set of mechanisms) has been followed during dissolution.

Considering thus the parameters estimated from the logistic function (see Table 6 for a summary of the t-test results) we conclude that formulations I and III are similar, while formulation II and IV differ from reference I. Formulation IV differs significantly in both parameters for 120 min, although for 60 min this difference is apparent in only one of the parameters. The other regression functions were not considered, once they fail to give a good description of the original data.

When the full curve is considered, the best fit acordding to AIC is obtained with the Weibull function (Fig. 1). The correspondent t-test results present, however, differences in one of the function parameters for formulations I and III. This stems from deviations between the fitted and the actual asymptotic dissolution values along the extended plateau.

4. Model independent approaches

Model independent approaches promote direct comparison of the dissolution data, and do not rely in the choice of model functions that sometimes may prove artificial. The objective is essentially to trans-

Table 3
Model parameters and AIC values for $t = 60$ min

Function	Formulation	c_1	c_2	c_3	AIC
Zero order	I	$5.45 \times 10^{-3} \pm 5.74 \times 10^{-5}$	–	–	24.81
	II	$3.52 \times 10^{-3} \pm 5.68 \times 10^{-5}$	–	–	7.86
	III	$4.94 \times 10^{-3} \pm 5.51 \times 10^{-4}$	–	–	22.75
	IV	$7.00 \times 10^{-3} \pm 6.50 \times 10^{-5}$	–	–	23.42
Higuchi	I	$3.24 \times 10^{-2} \pm 3.34 \times 10^{-4}$	–	–	8.94
	II	$1.99 \times 10^{-2} \pm 3.35 \times 10^{-4}$	–	–	23.27
	III	$3.14 \times 10^{-2} \pm 3.45 \times 10^{-4}$	–	–	9.24
	IV	$4.28 \times 10^{-2} \pm 3.93 \times 10^{-4}$	–	–	14.35
Korsmeyer–Peppas	I	$0.59 \pm 1.83 \times 10^{-2}$	$2.4 \times 10^{-2} \pm 1.54 \times 10^{-3}$	–	3.1
	II	$1.02 \pm 3.85 \times 10^{-2}$	$3.26 \times 10^{-3} \pm 4.64 \times 10^{-4}$	–	10.35
	III	$0.59 \pm 2.13 \times 10^{-2}$	$2.27 - 10^{-2} \pm 1.76 \times 10^{-3}$	–	6.21
	IV	$0.63 \pm 1.91 \times 10^{-2}$	$6.9 \times 10^{-3} \pm 1.82 \times 10^{-3}$	–	8.2
First order	I	$3.87 \times 10^{-2} \pm 2.42 \times 10^{-3}$	$0.27 \pm 8.81 \times 10^{-3}$	–	2.5
	II	$1.99 \times 10^{-3} \pm 2.44 \times 10^{-3}$	$1.84 \pm 2.13 \times 10^{-3}$	–	-5.5
	III	$3.65 \times 10^{-2} \pm 2.59 \times 10^{-3}$	$0.27 \pm 9.29 \times 10^{-3}$	–	-3.63
	IV	$3.04 \times 10^{-2} \pm 2.05 \times 10^{-3}$	$0.40 \pm 1.52 \times 10^{-3}$	–	13.36
Hixson-Crowell	I	$1.32 \times 10^{-2} \pm 6.18 \times 10^{-4}$	$0.24 \pm 5.90 \times 10^{-3}$	–	6.37
	II	$1.02 \times 10^{-3} \pm 1.14 \times 10^{-3}$	$1.21 \pm 1.29 \times 10^{-3}$	–	10.25
	III	$1.25 \times 10^{-2} \pm 6.56 \times 10^{-4}$	$0.24 \pm 5.94 \times 10^{-3}$	–	2.61
	IV	$1.10 \times 10^{-2} \pm 5.60 \times 10^{-4}$	$0.35 \pm 9.76 \times 10^{-3}$	–	-3.8
Weibull	I	43.9 ± 15.65	$0.81 \pm 7.09 \times 10^{-2}$	$0.35 \pm 5.98 \times 10^{-2}$	-10.72
	II	35.2 ± 3.69	1.59 ± 0.13	$0.21 \pm 1.75 \times 10^{-2}$	-1.31
	III	33.2 ± 7.677	$0.91 \pm 8.11 \times 10^{-2}$	$0.30 \pm 3.32 \times 10^{-2}$	-4.32
	IV	34.9 ± 6.21	$0.97 \pm 7.12 \times 10^{-2}$	$0.42 \pm 3.93 \times 10^{-2}$	-12.10
Logistic	I	-3.48 ± 0.11	$0.87 \pm 9.58 \times 10^{-2}$	0.49 ± 0.11	-12.29
	II	-6.33 ± 0.42	1.78 ± 0.19	$0.27 \pm 3.32 \times 10^{-2}$	-5.09
	III	-3.58 ± 0.14	1.01 ± 0.12	$0.39 \pm 6.10 \times 10^{-2}$	-6.26
	IV	-3.88 ± 0.13	1.06 ± 0.10	$0.55 \pm 7.55 \times 10^{-2}$	-18.50

late either the profile or profile differences into a single value.

4.1. Moments of the dissolution profiles

The mean in vitro dissolution times (MDT) are given from a release $M(t)$ by [2]

$$\text{MDT} = \frac{\int_0^\infty t \, dM(t)}{\int_0^\infty dM(t)} \quad (1)$$

where the denominator corresponds to the total amount dissolved, $M(\infty)$. A fraction of drug release, $M(t)/M(\infty)$ is related to the number of molecules of drug substance released from the dosage form up to the time t and can be regarded as a cumulative function $F(t)$ in the statistical sense [12]. In practice, the integrals in the above equation are computed numerically, yielding,

$$\text{MDT} = \frac{\sum_i \bar{t}_i \, \Delta M_i}{\sum_i \Delta M_i} \quad (2)$$

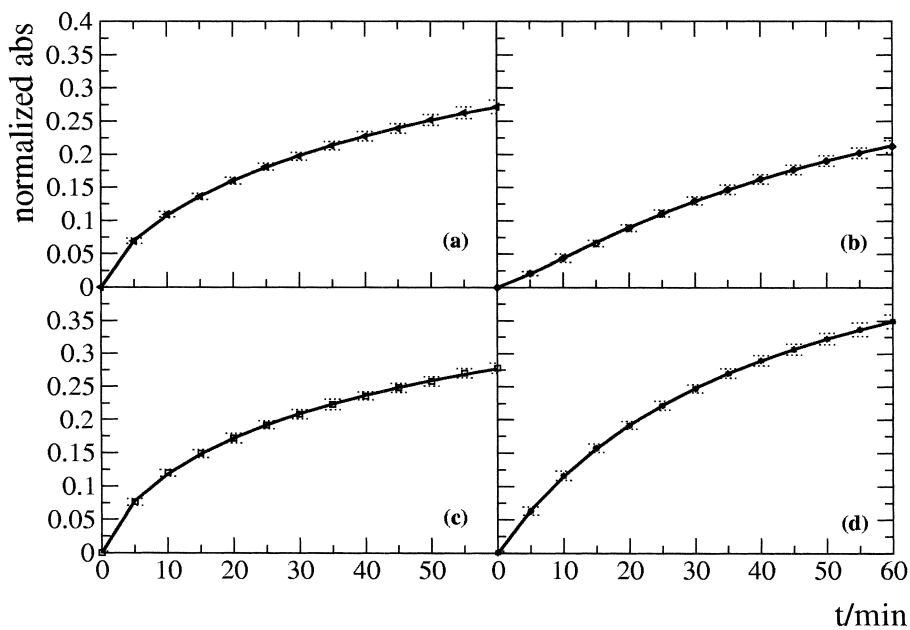where $\bar{t}_i$ is the midpoint of the time period during

Fig. 3. Dissolution profiles up to 60 min fitted with the Logistic function (solid line).
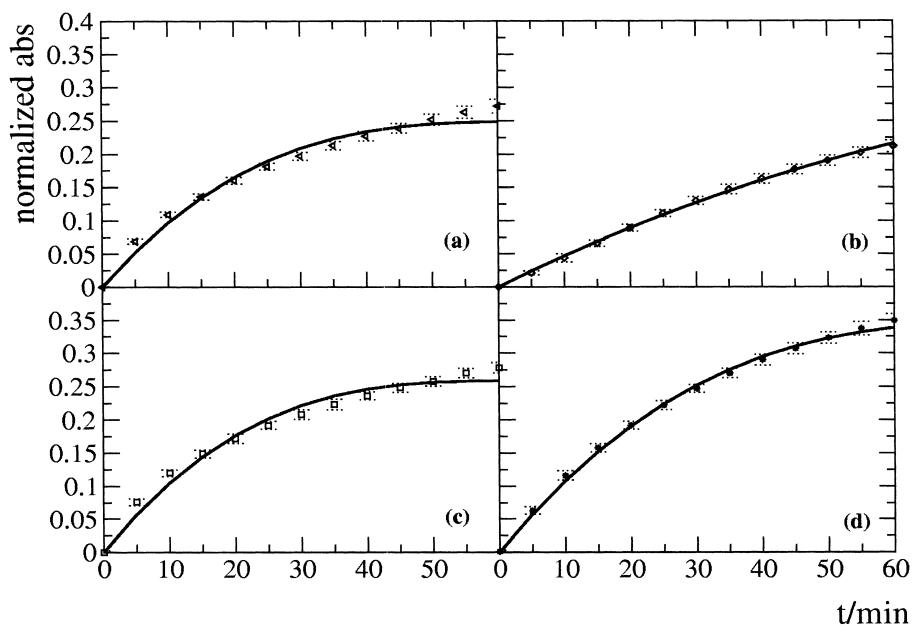
Fig. 4. As in Fig. 3 for the Hixson–Crowell function.

Table 4
Model parameters and AIC values for $t = 120$ min

Function	Formulation	c_1	c_2	c_3	AIC
Zero order	I	$4.02 \times 10^{-3} \pm 3.26 \times 10^{-5}$	–	–	52.85
	II	$2.93 \times 10^{-3} \pm 2.86 \times 10^{-5}$	–	–	29.8
	III	$3.62 \times 10^{-3} \pm 2.75 \times 10^{-5}$	–	–	50.66
	IV	$4.97 \times 10^{-3} \pm 3.17 \times 10^{-5}$	–	–	56.31
Higuchi	I	$3.23 \times 10^{-2} \pm 2.51 \times 10^{-4}$	–	–	7.55
	II	$2.33 \times 10^{-2} \pm 2.31 \times 10^{-4}$	–	–	40.68
	III	$3.11 \times 10^{-2} \pm 2.29 \times 10^{-4}$	–	–	8.87
	IV	$4.22 \times 10^{-2} \pm 2.60 \times 10^{-4}$	–	–	19.87
Korsmeyer–Peppas	I	$0.53 \pm 1.09 \times 10^{-3}$	$2.90 \times 10^{-3} \pm 1.25 \times 10^{-3}$	–	7.49
	II	$0.80 \pm 1.78 \times 10^{-3}$	$6.89 \times 10^{-3} \pm 5.20 \times 10^{-4}$	–	22.32
	III	$0.52 \pm 1.20 \times 10^{-3}$	$2.92 \times 10^{-3} \pm 1.46 \times 10^{-3}$	–	10.86
	IV	$0.52 \pm 9.95 \times 10^{-3}$	$3.93 \times 10^{-3} \pm 1.61 \times 10^{-3}$	–	21.96
First order	I	$2.78 \times 10^{-3} 2.75 \times 10^{-4}$	$0.42 \pm 1.76 \times 10^{-3}$	–	11.72
	II	$9.94 \times 10^{-3} \pm 8.43 \times 10^{-4}$	$0.42.50 \times 10^{-3}$	–	11.48
	III	$2.63 \times 10^{-3} \pm 1.05 \times 10^{-3}$	$0.32 \pm 5.56 \times 10^{-3}$	–	7.55
	IV	$2.62 \times 10^{-3} 8.34 \times 10^{-4}$	$0.46 \pm 6.29 \times 10^{-3}$	–	-9.03
Hixson–Crowell	I	$8.84 \times 10^{-3} \pm 2.47 \times 10^{-4}$	$0.31 \pm 4.34 \times 10^{-3}$	–	21.24
	II	$4.12 \times 10^{-3} \pm 2.80 \times 10^{-4}$	$0.34 \pm 1.55 \times 10^{-3}$	–	10.33
	III	$8.24 \times 10^{-3} \pm 2.38 \times 10^{-4}$	$0.30 \pm 3.89 \times 10^{-3}$	–	18.06
	IV	$8.42 \times 10^{-3} \pm 1.95 \times 10^{-4}$	$0.41 \pm 4.31 \times 10^{-3}$	–	11.07
Weibull	I	67.5 ± 14.19	$0.75 \pm 3.98 \times 10^{-3}$	$0.43 \pm 3.88 \times 10^{-3}$	-25.10
	II	55.5 ± 3.80	$1.29 \pm 5.92 \times 10^{-3}$	$0.30 \pm 1.26 \times 10^{-3}$	-0.29
	III	58.8 ± 10.04	$0.78 \pm 4.40 \times 10^{-3}$	$0.39 \pm 2.84 \times 10^{-3}$	-11.55
	IV	43.5 ± 3.36	$0.91 \pm 3.83 \times 10^{-3}$	$0.47 \pm 1.61 \times 10^{-3}$	-24.03
Logistic	I	$-3.56 \pm 6.61 \times 10^{-3}$	$0.81 \pm 5.44 \times 10^{-3}$	$0.59 \pm 7.38 \times 10^{-3}$	-31.29
	II	-5.85 ± 0.23	$1.48 \pm 8.88 \times 10^{-3}$	$0.37 \pm 2.32 \times 10^{-3}$	-7.09
	III	$-3.60 \pm 8.75 \times 10^{-3}$	$0.87 \pm 6.24 \times 10^{-3}$	$0.51 \pm 5.19 \times 10^{-3}$	-16.35
	IV	-3.87 ± 0.11	$1.04 \pm 5.82 \times 10^{-3}$	$0.58 \pm 3.13 \times 10^{-3}$	-44.64

which the fraction ΔM_i of the drug as been released from the dosage form [2]. Other similar formula gives the moments of dissolution times of order k

$$m_k = \frac{\sum_i \bar{t}_i^{\,k} \, \Delta M_i}{\sum_i \Delta M_i} \qquad (3)$$

One of the advantages of this method is that the comparison is based on a physically significant quantity, of widespread use for establishing in vitro/in vivo correlations. It is also possible to characterize the profiles with statistical moments such as MDT, its relative dispersion (RD) and the variance associated with the MDT (VT) [12]. An additional advantage is that Eqs. (1)–(3) are self-normalized, i.e. they are amenable to direct treatment of signal data. The method may require, however, the knowledge of the time at which the plateau, i.e. full dissolution, is attained (see below).

Variance of dissolution times are estimated from

$$VT = \frac{\sum_i (\bar{t}_i - MDT)^2 \, \Delta M_i}{\sum_i \Delta M_i} \qquad (4)$$

The relative dispersion of dissolution times (RD) is given by [27]

Table 5
Model parameters and AIC values for $t = 480$ min

Function	Formulation	c_1	c_2	c_3	AIC
Zero order	I	$1.36 \times 10^{-3} \pm 3.26 \times 10^{-5}$	–	–	244.03
	II	$1.33 \times 10^{-3} \pm 6.19 \times 10^{-6}$	–	–	205.83
	III	$1.55 \times 10^{-3} \pm 7.89 \times 10^{-6}$	–	–	229.26
	IV	$1.51 \times 10^{-3} \pm 6.13 \times 10^{-6}$	–	–	260.92
Higuchi	I	$2.50 \times 10^{-3} \pm 1.20 \times 10^{-4}$	–	–	157.13
	II	$2.29 \times 10^{-3} \pm 1.04 \times 10^{-4}$	–	–	112.93
	III	$2.61 \times 10^{-3} \pm 8.67 \times 10^{-5}$	–	–	126.97
	IV	$2.88 \times 10^{-3} \pm 1.00 \times 10^{-4}$	–	–	191.00
Korsmeyer–Peppas	I	$0.35 \pm 3.75 \times 10^{-3}$	$5.7 \times 10^{-3} \pm 1.15 \times 10^{-3}$	–	114.06
	II	$0.50 \pm 5.42 \times 10^{-3}$	$2.34 \times 10^{-3} \pm 6.86 \times 10^{-4}$	–	115.4
	III	$0.36 \pm 4.88 \times 10^{-3}$	$5.34 \times 10^{-3} \pm 1.32 \times 10^{-3}$	–	80.91
	IV	$0.27 \pm 3.58 \times 10^{-3}$	$9.96 \times 10^{-3} \pm 1.87 \times 10^{-3}$	–	134.23
First order	I	$1.78 \times 10^{-3} \pm 2.74 \times 10^{-4}$	$0.42 \pm 1.76 \times 10^{-3}$	–	36.17
	II	$1.00 \times 10^{-3} \pm 1.92 \times 10^{-4}$	$0.42 \pm 3.02 \times 10^{-3}$	–	-31.44
	III	$1.70 \times 10^{-3} \pm 3.22 \times 10^{-4}$	$0.40 \pm 2.27 \times 10^{-3}$	–	28.43
	IV	$2.42 \times 10^{-3} \pm 3.85 \times 10^{-4}$	$0.46 \pm 1.98 \times 10^{-3}$	–	-80.62
Hixson–Crowell	I	$3.38 \times 10^{-3} \pm 3.04 \times 10^{-5}$	$0.42 \pm 2.09 \times 10^{-3}$	–	137.59
	II	$3.13 \times 10^{-3} \pm 4.72 \times 10^{-5}$	$0.39 \pm 2.75 \times 10^{-3}$	–	8.78
	III	$3.55 \times 10^{-3} \pm 3.93 \times 10^{-5}$	$0.41 \pm 2.93 \times 10^{-3}$	–	113.13
	IV	$3.44 \times 10^{-3} \pm 2.82 \times 10^{-5}$	$0.49 \pm 2.61 \times 10^{-3}$	–	174.57
Weibull	I	65.1 ± 1.76	$0.79 \pm 1.57 \times 10^{-3}$	$0.43 \pm 3.14 \times 10^{-3}$	-50.44
	II	98.1 ± 2.41	$1.02 \pm 2.05 \times 10^{-3}$	$0.42 \pm 3.83 \times 10^{-3}$	-29.94
	III	72.5 ± 2.87	$0.76 \pm 1.90 \times 10^{-3}$	$0.43 \pm 5.66 \times 10^{-3}$	-89.12
	IV	42.1 ± 0.76	$0.93 \pm 2.07 \times 10^{-3}$	$0.46 \pm 2.26 \times 10^{-3}$	-142.36
Logistic	I	$-3.80 \pm 7.38 \times 10^{-3}$	$0.97 \pm 2.62 \times 10^{-3}$	$0.49 \pm 6.77 \times 10^{-3}$	-2.60
	II	-5.48 ± 0.12	$1.26 \pm 3.38 \times 10^{-3}$	$0.47 \pm 7.20 \times 10^{-3}$	-67.27
	III	$-3.71 \pm 8.44 \times 10^{-3}$	$0.91 \pm 3.09 \times 10^{-3}$	$0.50 \pm 1.12 \times 10^{-3}$	-60.4
	IV	-4.36 ± 0.11	$1.29 \pm 3.59 \times 10^{-3}$	$0.48 \pm 3.64 \times 10^{-3}$	-32.92

$$RD = \frac{VT}{MDT^2} \qquad (5)$$

In spite of the mentioned advantages, the use of mean dissolution times (or similar approaches) poses some problems. For zero order (or close to zero order) release mechanisms, Eq. (1) yields, in practice, $MDT = \frac{1}{2} t_{max}$ when infinite dissolution times are replaced by specific dissolution intervals between 0 and t_{max}. This means that when such curves are

Table 6
Results of the comparison of formulation I with test curves from modeling functions (*t*-test, $\alpha = 0.05$). Indicated is when difference is found for only one parameter

Formulation	Logistic ($t = 60$ min)	Logistic ($t = 120$ min)	Weibull ($t = 480$ min)
II	Different	Different	Different
III	Similar	Similar	Different (1 parameter)
IV	Different (1 parameter)	Different	Different

truncated before full dissolution, the result is in-dependent of the release rate, rendering impossible the discrimination between two curves. Of course, for other release mechanisms differences may arise, but the dependence on the upper integration limit is always present.

4.2. Results and discussion

Results obtained from our formulations are shown in Table 7, for $t = 60$, 120, and 480 min. With the obtained RD values it is not possible to conclude about release order or, more generally, mechanism, by comparison to those obtained for some common models (see description in Ref. [12]). This fact suggests the coexistence of different mechanisms. MDT values, naturally, tend to increase with time. The increase is much more evident when the formulation has some prolonged release as we can see with formulation II when compared to the reference (formulation I). The MDT value of formulation IV at $t = 60$ min is higher than that of the reference which reflects a lower dissolution rate, but this effect is lost and the dissolution of this formulation reaches the lowest MDT value, showing a modification in release rate or dissolution mechanism. Also, we see that these values are stable even when the plateau is taken into consideration, which allows for a characterization of the complete dissolution curve [12]. These findings are also illustrated in Fig. 5. This method, for our data, indicates the extension of an induced controlled release effect even when it is observed for a very short period of time, which is very useful in formula development and comparison of excipients.

4.3. Fit factors
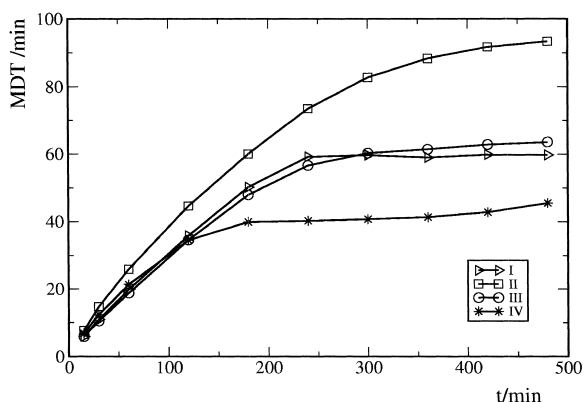
Recently a simple model independent approach

Fig. 5. MDT values for formulations I, II, III and IV at different cumulative time points.

that uses a difference factor (f_1) and a similarity factor (f_2) was proposed to compare dissolution profiles [14]. Fit factors were adopted by FDA Center for Drug Evaluation and Research (CDER) and the similarity factor was also adopted by the European Medicines Evaluation Agency (EMEA) Committee for Proprietary Medicinal Products (CPMP) as an assessment criterion of similarity between two in-vitro dissolution profiles [9,10]. The difference factor (f_1) calculates the percent difference between the two curves at each time point and is a measure of the relative error between the two curves,

$$f_1 = \frac{\sum\limits_{t=1}^{n} |R_t - T_t|}{\sum R_t} \times 100 \qquad (6)$$

where n is the number of time points, R_t is the dissolution value of the reference formulation at time t and T_t is the dissolution value of the test formulation at time t.

The similarity factor (f_2) is a logarithmic re-

Table 7
MDT and VT values for formulations I, II, III and IV at $t = 60$, 120 and 480 min (number of points considered $n = 13$, 25 and 97, respectively)

	60 min				120 min				480 min			
	I	II	III	IV	I	II	III	IV	I	II	III	IV
MDT/min	19.89	25.89	18.79	21.38	35.81	44.58	34.56	34.5	59.79	93.42	63.57	45.52
VT/min^2	1041	1256	988.9	768.4	3036	3469	3090	2119	8567	18684	11476	7265
RD	2.631	1.874	2.801	1.681	2.368	1.746	2.587	1.780	2.396	2.141	2.840	3.506

ciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the curves

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

(7)

For curves to be considered similar, f_1 values should be close to 0 and f_2 values should be close to 100. Generally, f_1 values up to 15 (0–15) and f_2 values greater than 50 (50–100), which means an average difference of no more than 10% at the sample time points [16], ensures equivalence of the two curves and thus of the performance of the test and reference products [10].

Fit factors are essentially a quantitative method, reflecting the differences between corresponding values in the two curves. They do not indicate the sense of the deviation, and yield the same value irrespectively of the test curve being placed below or above the reference [14]. Thus, they do not directly take into consideration the shape of the curve, and not allow for a variation in the spacing between sampling times [19,25]. Also, they do not take into account variability within test and references batches. Since fit factors are commulative functions they are sensitive to measurements obtained after either test or reference batch are dissolved more than 85% [16]. Thus it becomes apparent that the selection and determination of the dissolution end pull points plays a critical role in the calculation of fit factors and the subsequent decision as to whether the test and reference profiles resemble each other or not [13,15].

In spite of these limitations fit-factors have been very useful in comparing dissolution curves once

they present a great advantage of reducing complexity by providing a single number to describe two curves that consist of several points [14].

Results obtained from our formulations are shown in Table 8. The recommendations presented in the above mentioned guidelines were followed and we observe that the similarity factor f_2 is more sensitive in finding dissimilarity between dissolution curves than the difference factor f_1 and, also, that these values are dependent on the length of dissolution profile and number of time points chosen. These findings have been also mentioned by other authors [13,15]. Our results show clear differences between formulations I and II and a similitude between I and III. In what concerns formulations I and IV the difference appears for the largest dissolution interval considered (120 min). This might indicate that a large number of time points should be included in order to obtain a suitable discrimination.

4.4. Correlation coefficients and similarity criteria

In cluster analysis [28] euclidean distances (and their variants) and correlation coefficients are frequently used as measures of similarity. These measures can be applied in a straightforward manner to dissolution curves. The use of euclidean distances would have the same underlying philosophy as the use of fit-factors, also consisting of an essentially quantitative approach. The use of correlation coefficients in the comparison focus, for our analysis, on the shape of the curves, discarding the absolute value. It is thus, a valuable complement of some other approaches.

The correlation coefficient (ρ) measures the strength of the linear relationship between two variables, say X and Y:

Table 8
Fit factors values for formulations II, III and IV compared with formulation I

Fit factors	$t=10$, 40 and 120 min			up to $t=30$ min			up to $t=60$ min			up to $t=120$ min		
	I/II	I/III	I/IV	I/II	I/III	I/IV	I/II	I/III	I/IV	I/II	I/III	I/IV[a]
f_1	3.96	0.57	2.41	8.65	0.65	2.6	13.6	1.19	6.57	26.4	2.29	9.63
f_2	42.6	88.0	50.4	42.2	92.6	63.9	42.2	87.2	52.1	43.4	86.5	48.6

For the second heading, only the three points indicated have been considered, while in the remaining, and except where noted, all determined points have been included.

[a] Dissolution curve of formulation IV without time points from 90 to 115 min.

$$\rho = \frac{\sum (x - \bar{x})(y - \bar{y})}{\sqrt{\sum (x - \bar{x})^2 \sum (y - \bar{y})^2}} \qquad (8)$$

where x and y are the variables points and $\bar{x}$ and $\bar{y}$ are the respective means. Correlation coefficient ranges from -1 to $+1$. For $\rho = \pm 1$ there exists a functional relationship between X and Y and all points (x, y) lie on a straight line. If $\rho = 0$ then X and Y are uncorrelated; two random variables are the more strongly correlated the closer $|\rho|$ is to 1 [29].

4.4.1. Graphical representation

The use of correlation coefficients suggests the concomitant use of concentration vs. concentration or rate vs. rate plots. In fact, the linearity of these plots corresponds, using this criterium, to a high similitude between curves. These plots also provide information concerning the relative evolution of profiles and, for complete dissolution curves, pinpoint the times for which dissolution has come to a halt in certain formulation while continues in others.

4.4.2. Discussion

Our results are based on correlation coefficients calculated both from the normalized signals and the corresponding rates, respectively presented in Fig. 6 panels (a) and (b). While rate based coefficients emphasize differences, those related to concentration show the commulative behavior of the dissolution profiles, which is also shown in Fig. 7. Both co-

Fig. 7. Graphical representation of test formulations II, III and IV normalized absorbance signal as a function of that of formulation I (reference). Correlation coefficients ($t = 480$ min) also shown.

efficients clearly present a high degree of similitude for formulation III and the reference that decreases slightly for formulation IV and again, more markedly, for formulation II. This picture is present up to ca. 120 min, where a substantial portion the active substance is already in solution, and inverts for formulation II and IV when a large number of points in the asymptotic plateau is included. We note that, for our data, the choice of time at which the curve is truncated becomes irrelevant with rate coefficients.

In what concerns the concentration plots, Fig. 7, we see that the formulation IV is the first to attain complete dissolution, while formulation II is the slowest. It also patent the similitude between formulation I and III. We may also observe that the bulk concentration for formulation II is always below that of the other curves. For formulation IV, a slower start is compensated by an intermediate increase.

The rate vs. rate plots, Fig. 8, depict similar conclusions. The effects in the beginning of the curves are much more emphasized, due to drastic initial variations and in spite of our constant interval between time points. The initial zero order release present for formulation II is clearly represented as is the initially slow behavior of formulation IV and its subsequent increase.

5. Final remarks
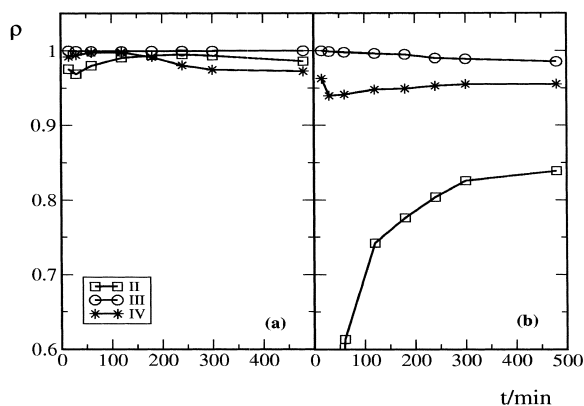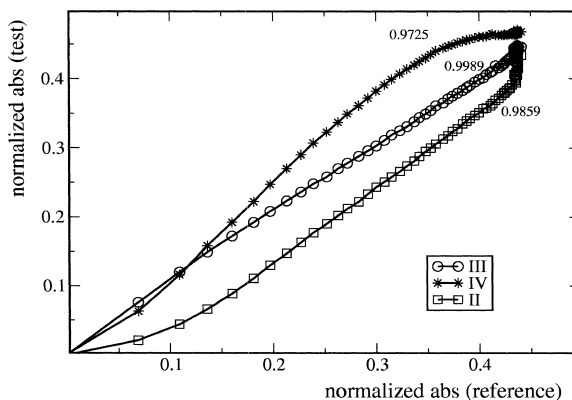
All methods considered here have given results

Fig. 6. Correlation coefficients between formulations pairs (reference/test) I/II, I/III and I/IV normalized absorbance signal (a) and respective time derivatives (b).
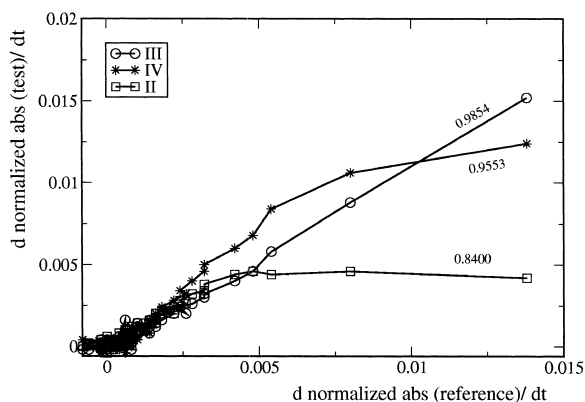
Fig. 8. Graphical representation of test formulations II, III and IV normalized signal time derivative as a function of the corresponding values for the reference. Correlation coefficients ($t = 480$ min) are also shown.

with some consistency, especially when dissolution percentages are typically below 80%. When points in the asymptotic plateau are considered, some differences may be found between methods. In this regards, MDT values and, especially, correlation coefficients based on signal time derivatives seem to be the more stable approaches.

The methods differ in complexity and user friendliness and the information provided on the dissolution profiles varies. Modeling is a useful characterization of mechanism, but poses some problems. Generally, good quality fits are obtained with shape rather than mechanism-based functions, mostly due to a change in mechanism as the dissolution proceeds or to a coexistence of concomitant mechanisms.

MDT values are an useful way to reduce each curve to a single number, which may be related in some cases to the dissolution rate constant. Mechanisms may also be inferred in favorable situations. However, its importance for practical use is somewhat diminished by the fact that discrimination is, formally, dependent on the final time point considered, i.e. their proper use requires a detailed knowledge of the dissolution end-point.

Fit-factors are both robust and reliable, but strongly focused in quantitative differences, mostly overlooking the similitude of shapes. Also, they do not take into consideration the variability within each curve.

Finally, the use of correlation coefficients and the corresponding graphical representation provides a useful way to emphasize non-quantitative differences, and their evolution along the profile. However, they lack a simple criterion for classification into 'similar' or 'different'.

In our view, the combination of fit-factors, in a quantitative perspective, with correlation coefficients, for spotting shape differences, provides a reliable way to assess differences between profiles.

If one is interested in an in-depth analysis of the release-control factors, the time extension of their action and its sense, then suitable graphical representations, such as those suggested here, should also be taken into consideration.

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