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Computerized linearization test for tablet dissolution kinetics

P. Arnaud [2], C. Elkoubi [1], C. Renaux [1] and A. Le Hir [2]

[1] *Pharmacie Centrale des Hôpitaux de Paris, 13, rue Lavoisier, 92033 Nanterre Cedex*
and [2] *Faculté de Pharmacie de Paris, Laboratoire de Pharmacie Galénique, 4, avenue de l'Observatoire, 75006 Paris (France)*

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Summary

We have compared the linearization and computerized the dissolution rate of several commercially available tablets. Out of all the tested kinetic patterns, four have proved satisfactory (Higuchi, Hixson-Crowell, Kitazawa and Weibull). Considering the tablet characteristics, our research has been conducted according to the following criteria: tablets with low hardness and rapid release kinetics show Hixson-Crowell type linearization; tablets with a high rate of release of active substance display Higuchi-type linearization; tablets with high hardness but a short disintegration time show Kitazawa-type linearization, and finally, in the case of the rapid release of active substance in the dissolution medium, the curve was transformed into a straight line by using Weibull's equation.

Introduction

The dissolution kinetics of different tablets are represented by quite distinct curves. We were interested in performing comparisons between the main existing methods of linearization and in quantitation of the results according to the parameters of each form of tablet. The methods evaluated were as follows:

Square root law: Higuchi (1963) suggested that the dissolution rate should be calculated with reference to the square root of time in order to obtain a linear plot.

Correspondence: P. Arnaud, Faculté de Pharmacie de Paris, Laboratoire de Pharmacie Galénique, 4, avenue de l'Observatoire, 75006 Paris, France.

Cube root law: Hixon and Crowell (1931) defined a cube root law as follows:
$\sqrt[3]{100} - \sqrt[3]{\text{percent dissolved}} = f(t)$.

Gaussian law: Khan and Rhodes (1972) proposed representation of the rate of variation in the release of active substance vs time by a Gaussian curve.

Kitazawa's law: Kitazawa et al. (1975) suggested that, for the ordinary logarithmic type of dissolution, the amount dissolved as plotted on the y-axis (W) is linear with respect to the time plotted on a logarithmic scale on the x-axis:

$$\frac{\log[100(W^{\infty} - W)]}{W^{\infty}} = f(t)$$

The Rosin-Rammler, Sperling, Benett and Weibull distribution (RRSBW): this distribution

(Nelson and Wang, 1978) results in a straight line if the kinetics can be defined by the following equation:

$$M = 1 - \exp[-(T/T_d)]^B$$

where M represents the percent dissolved that is accumulated, t is the time, t_0 is the time at which $M \neq 0$, $T = t - t_0$, T_d is a constant, and B denotes the RRSBW parameter ($B < 1$, parabolic curve; $B > 1$, sigmoidal curve).

Our aim was to determine the parameters that were supposed to direct a formulation towards a specific method of linearization in preference to another type. Attention was focused on the dissolution kinetics of different active substances as well as of various formulations related to the same active substance, each being prepared at the Pharmacie Centrale des Hôpitaux de Paris (Nanterre, France).

Materials and Methods

The compositions of the various forms of drug substances used have been summarized in Table 1.

Measurements of tablet hardness were performed on six tablets using a Heberlein-Schleuninger apparatus (Frogerais, Vitry, France).

Disintegration times were also evaluated for six tablets with reference to the recommendations given in the French Pharmacopeia, 10th Edn, using an Erweka ZT6 instrument (Euraf, Courbevoie, France).

Dissolution tests were performed with a Sotax AT6 rotating paddle (OSI, Paris, France) on six tablets according to the French Pharmacopeia, 10th Edn. Operating conditions were: rotation speed, 60 rpm; dissolution medium, 1 l of gastric medium (USP XXII); samples, 5 ml medium removed manually at 5, 10, 15, 30, 45, 90 and 120 min. After taking each sample, 5 ml fresh medium was added in order to maintain a constant volume. Active substances were assayed using a UV spectrophotometer (Philips, Bobigny, France).

Agreement between curves and given patterns was determined using as software a BASIC program developed at our laboratory. Through linear regression analysis, we ascertained the best correlation factor (r^2) in relation to the theoretical pattern.

Results

Table 2 lists the results obtained. Tablet hardness measurements were generally low, being between 1.5 and 4.5 daN. The disintegration times

TABLE 1

Compositions of the dosage forms

DCI	Trade name	Dosage form	Auxiliary substance
Allopurinol	Zyloric®	100 mg	lactose, polyvidone, magnesium stearate, corn starch
	Allopurinol PCH	100 mg	lactose SD, polyvidone, corn starch, magnesium stearate
Furosemide	Lasilix®	40 mg	lactose, talc, corn starch, magnesium stearate
	Furosemide PCH	40 mg	corn starch, magnesium stearate, lactose, talc
Chlorothiazide	Diurilix®	500 mg	wheat starch, talc, magnesium stearate
	Chlorothiazide PCH	500 mg	Amigel, acacia gum, magnesium stearate
Nitrazepam	Mogadon®	5 mg	talc, magnesium stearate, starch, lactose
	Nitrazepam PCH	5 mg	Amigel, magnesium stearate, corn starch, lactose

TABLE 2

Galenic tests and linearization of dissolution curves

Trade name	Hardness (daN)	Disintegration time (min)	$T_{50\%}$ (min)	Linearization type
Zyloric	3.0	4	8.8	ϕ
Allopurinol	1.5	5	10.6	RRSBW
Lasilix	4.5	2	18.0	semi log
Furosemide (frusemide)	4.5	3	21.0	semi log
Diurilix	4.0	10	119.0	square root
Chlorothiazide	2.9	3	35.0	square root
Mogadon	2.6	2	2.7	cubic root
Nitrazepam	2.8	2	4.4	ϕ

were very short, namely, 2–5 min except for Diurilix® (10 min). The values were far smaller than the recommendations of the French Pharmacopeia 10th Edn (< 15 min). The $T_{50\%}$ values were between 2.7 and 35 min with the exception of Diurilix® which had a $T_{50\%}$ value of 119 min.

Using the linearization computer program described above, all the tablets, except Zyloric® and Nitrazepam® proved to be congruent with a straight line derived from modeling.

Discussion

On analysis of the results obtained, it was possible to classify the different patterns of linearization according to the particular parameters of each form of tablet. Hence, the type of kinetics could be established according to the kind of curve and the characteristics of the tablet.

Initially, the Higuchi law (Higuchi, 1963) was found to be suitable for matrix tablets only. However, Puisieux et al. (1980), Wall et al. (1985) and Costa et al. (1986) have given evidence of its applicability for tablets with a significant amount of active substance present and low solubility of the active substance.

This confirms the dissolution profiles of chlorothiazide PCH and Diurilix® tablets which showed a significant presence of active substance – 500 mg for a total weight of 550 mg – and with a solubility of approx. 500 mg per l.

The hypothesis was confirmed by the analysis of $T_{50\%}$ for Diurilix® which demonstrated its limited dissolution ability ($T_{50\%}$ = 119 min).

The studies of Wall et al. (1985) have been focused on lithium carbonate tablets showing Higuchi-type linearization. On the other hand, our research has indicated Kitazawa-type dissolution to occur in spite of the considerable amount of active substance present.

This difference can be accounted for by the relative calcium carbonate solubility as well as by the low hardness of the tested tablets (2.5 and 3.2 daN) which demonstrated their considerable difference from the matrix pattern.

The pattern suggested by Hixon and Crowell (1931) proved to be suitable for tablets produced by direct compression. During the disintegration process, small particles appeared in the medium, but no aggregates were found. Nelson (1962) has shown that this model could be used for tablets made via wet granulation if they were of low hardness because the compression force could alter the particles and create aggregates.

The investigations of Nelson and Wang (1977, 1978) as well as those of Rubinstein et al. (1986) appear to be confirmed by the analysis of the parameters of Mogadon® and Valium® – i.e., low hardness and short disintegration time.

The two formulas developed by the Pharmacie Centrale des Hôpitaux de Paris have not resulted in the same linearization pattern although they do exhibit comparable parameters except for the $T_{50\%}$ values and auxiliary substance composition.

Drug diffusion was retarded when using Amigel® as this product has the capacity of forming a gel around the tablet at the beginning of the dissolution process. It resulted in a greater $T_{50\%}$ value and linearization of the kinetics was not according to the cube root law.

Kitazawa et al. (1975) suggested a method where two straight lines with an inflexion point can be obtained from a dissolution curve (Levy et al., 1965). The first straight line represents the dissolution kinetics before disintegration, the second one corresponding to the case after disinte-

gration. This method resulted in a linearized curve only when disintegration had taken place before the initial 5 min, since this period of time corresponds precisely to our first sample-taking delay. In such a case, no disintegration took place and therefore only one straight line appeared.

Low tablet hardness and the use of an auxiliary substance facilitating the disintegration process were found to be beneficial factors in the case of Kitazawa-type log-linearization patterns. This was developed by Kitazawa et al. (1975) with caffeine tablets.

Joachim et al. (1987) demonstrated a major role to be played by the auxiliary substances in the rate of dissolution once the disintegration process has commenced.

During our assays, most of the tablets showing Kitazawa-type linearized kinetics had a disintegration time below 5 min and contained very soluble auxiliary substances or materials suitable for disintegration, e.g., corn starch in the cases of Lasilix® and furosemide PCH (Carstensen et al., 1983).

Optimum results were obtained when using Weibull's linearization method. The kinetic parameters, however, were not readily quantifiable nor easily determined.

Brossard (1976) demonstrated that the kinetics could be applied to rapidly released tablets and hard capsules with short disintegration times and $T_{50\%}$ values.

Langenbucher (1972) stated that: "Weibull's linearization method requires an asymptotic approach to the 100% dissolution steady state". Therefore, the curve must have a sigmoidal shape, reaching a plateau approximating 100% dissolution within a very short period of time.

The analysis performed on allopurinol PCH yielded a $T_{50\%}$ value after 20 min and a disintegration time of less than 5 min in both cases. This is due to the initial shape of the curve (sigmoidal) where a 'flattening' with time can be observed.

Within a short while, a significant increase in dissolution rate can be observed. Linearizations according to a Gaussian law or in the zero region were exceptions that cannot be quantified, since the results obtained show a substantial lack of congruency.

Conclusion

The current research has led to our identification of the three main parameters directing and orientating the dissolution kinetics of an active substance from a given type of dissolution curve to another preferred form. The parameters concerned are the rate of dissolution of active substance, tablet hardness and disintegration time.

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