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*Short Communication*

# Tablet dissolution parameters: a statistical evaluation*

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## Introduction

The first model employed for dissolution curves was Higuchi's equation [1]:

$$Q = k \cdot t^{1/2}, \qquad (1)$$

which correlates the amount of drug dissolved $Q$ and the square-root of time (a lag-time $t_0$ may be subtracted from time $t$). From the studies of Gibaldi and Wagner [2] a conventional representation of dissolution curves on a logarithmic scale was derived. Relatively large distortions can be found by these methods. The application of the Weibull equation, proposed first by Langenbücher in 1972 [3], allows a very much better estimation of the process characteristics, through the determination of $t_0$:

$$Q = Q_{max}\,(1 - e^{-[(t-t_0)/T_d]\beta}), \qquad (2)$$

where $Q_{max}$ is the amount of active substance in the tablet, $t$ is the time, $t_0$ the lag time, $T_d$ is the time required to dissolve 63.2% of the active substance, and $\beta$ characterizes the sigmoidicity factor. However, this function sometimes presents strong deviations from linearity, due mainly to the very long dissolution times, as in the case of prolonged-release dosage forms. In these cases, the beginning and the tail of the curves are distorted, at values below 20% and over 80% [4].

A non-linear regression obtained by several methods (Gauss–Newton, Marquardt, Simplex) tends to eliminate this type of distortion. Different models have been recently proposed for the treatment of dissolution data: Hill's equation, proposed firstly by Peña Romero *et al.* [5]:

$$Q = Q_{max}\left(\frac{t^{\beta}}{T_{d50}^{\beta} + t^{\beta}}\right), \qquad (3)$$

where $T_{d50}$ is the time required to dissolve 50% of the active substance. Another is Gompertz model [6]:

$$Q = Q_{max} \cdot e^{(-\beta \cdot e^{-kt})}, \qquad (4)$$

where $k$ is the first-order constant of dissolution. $T_{d50}$ can be deduced from the formula:

$$T_{d50} = (0.367 + \ln \beta)/k. \qquad (5)$$

For the Hill and Gompertz models, the lag-time $t_0$ can be subtracted from $t$.

In this paper, results obtained from a dissolution study on conventional tablets of methyldopa are treated by COMSTAT-W, a

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non-linear regression package based on the Steepest Descent method [7]. This package is available from CIRIC (175, rue F. Vervloet 1180-B, Brussels, Belgium).

In Brazil, methyldopa is one of the essential drugs which are distributed free of charge by the Pharmaceutical Products National Central (CEME). The dissolution tests carried out at Fundação Oswaldo Cruz, Rio de Janeiro, showed poorer results compared with a commercial product ALDOMET® (Merck, Sharp & Dohme, São Paulo, Brazil). Both the formulations are shown in Table 1. Experimental formulations were prepared with the purpose of determining the origin of these deficiencies.

**Table 1**
Tablet formulations for CEME (Brazil) and ALDOMET® (Merck, Sharp & Dohme)

| Formulaton component | CEME (%) | ALDOMET (%) |
|---|---|---|
| Methyldopa | 76.7 | 68.5 |
| Microcel® | 10 | — |
| Lactose | — | 16.5 |
| Encompress® | — | 5 |
| Explosol® | 5.85 | — |
| Corn starch | — | 4.5 |
| Eudragit® L-100 | 0.95 | — |
| Polivinylpyrrolidone | — | 1.75 |
| Movital® | 2.75 | — |
| Guar gum | — | 2.2 |
| EDTA | 0.4 | 0.35 |
| Tartaric acid | 1 | — |
| Dibutylphthalate | 0.1 | — |
| Magnesium stearate | 2.15 | 0.63 |
| Aerosil® | — | 0.55 |

Microcel®: microcrystalline cellulose. Explosol®: sodium amylglycolate. Movital®: polyvinylbutyral.

## Experimental

Eight formulations were prepared according to a $2^3$ factorial plan. Among the differences between the two formulations (tablets CEME and MSD), three factors were chosen.

Factor 1: Microcel (microcrystalline cellulose, Trinca, São Paulo, Brazil) at 2%, (−) and 4% (+) (by weight of granulate).

Factor 2: type of binding — polyvinylpyrrolidone (GAF, São Paulo, Brazil), (+); and Movital (polyvinylbutyral, MEDIMPEX, Budapest, Hungary), (−).

Factor 3: disintegrant concentration Explosol (sodium amylglycolate, Trinca, São Paulo, Brazil) 1%, (−) and 4%, (+).

In this design, the factors were combined in all eight possible ways.

*Equipment*

Tablets were made using the single punch Fabbe press and the dissolution tests performed using the Erweka DT6R apparatus, with the paddle method at 50 rpm, according to the USP method. The apparatus was validated as regards the geometry, stirring rate, vibrations and the use of 0.1 M HCl dissolution medium (volume, temperature, pH and de-aeration conditions). Standard tablets Prednisone–Lactose USP were used for a calibration test, the results being an average of 51.0%, with RSD = 2.44% [8]. Analytical determinations were performed using a Micronal B-20 spectrophotometer (Micronal, São Paulo, Brazil), at $\lambda$ = 242 nm for prednisone and $\lambda$ = 280 nm for methyldopa, slit-width 7 nm with reference to a calibration curve based on methyldopa and Prednisone Reference Standards (National Institute for Health Control Quality, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil).

**Table 2**
Factorial design of experimental formulation

| | Formulations (per 100 g) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| Intra-granular | | | | | | | | |
| Methyldopa | 71.4 | 71.4 | 71.4 | 71.4 | 71.4 | 71.4 | 71.4 | 71.4 |
| Microcel | 2.0 | 4.0 | 2.0 | 4.0 | 2.0 | 4.0 | 2.0 | 4.0 |
| Corn starch | 9.85 | 7.85 | 9.85 | 7.85 | 9.85 | 7.85 | 9.85 | 7.85 |
| EDTA | 0.45 | 0.45 | 0.45 | 0.45 | 0.45 | 0.45 | 0.45 | 0.45 |
| Extra-granular | | | | | | | | |
| PVP or Movital (2%) | Mov | Mov | PVP | PVP | Mov | Mov | PVP | PVP |
| Microcel | 5.7 | 5.7 | 5.7 | 5.7 | 5.7 | 5.7 | 5.7 | 5.7 |
| Corn starch | 6.3 | 6.3 | 6.3 | 6.3 | 3.3 | 3.3 | 3.3 | 3.3 |
| Explosal | 1.0 | 1.0 | 1.0 | 1.0 | 4.0 | 4.0 | 4.0 | 4.0 |
| Aerosol | 0.55 | 0.55 | 0.55 | 0.55 | 0.55 | 0.55 | 0.55 | 0.55 |
| Magnesium stearate | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 |

*Tablet preparation*

Methyldopa (MSD), Microcel and corn starch (Refinações de Milho Brazil, Rio de Janeiro) were wetted with polivinylpyrrolidone or Movital in alcoholic solution and granulated through a sieve of 12 mesh; after drying, granules were standardized at 16 mesh and mixed with corn starch, Explosol®, Aerosil (GAF, São Paulo, Brazil) and magnesium stearate (Frama, Rio de Janeiro, Brazil). Tablets were obtained at a constant compression force of 130 MPa (Table 2).

**Table 3**
Comparison of variance for different models

| Formulation | Higuchi | Hill | Weibull | Gompertz |
|---|---|---|---|---|
| $F_1$ | 3.93* | 1.75 | 1.52 | 3.34 |
| $F_2$ | 100† | 1.57 | 0.83 | 0.75 |
| $F_3$ | 59.3† | 3.56† | 0.83 | 1.07 |
| $F_4$ | 27.6*† | 4.23 | 1.52 | 1.37 |
| $F_5$ | 161*† | 2.97† | 1.16 | 0.26 |
| $F_6$ | 158*† | 2.07† | 1.07 | 0.28 |
| $F_7$ | 99.1† | 8.11† | 1.58 | 1.37 |
| $F_8$ | 82.8† | 6.66† | 1.30 | 1.18 |
| Aldomet | 107*† | 3.93 | 6.26 | 3.13 |
| CEME | 1.54* | 0.76 | 0.52 | 0.52 |

*Presence of a latency time.
†Model discarded on the basis of *F*-test comparison between variances.

## Results and Discussion

Dissolution parameters were obtained using the statistical package COMSTAT-W. A significant lag-time is detected only for the Higuchi model in formulations $F_1$, $F_4$, $F_5$, *Aldomet* and CEME. The first analysis concerns the comparison of variance (Table 3) based on the *F*-test. This analysis discards the Higuchi model (eight cases out of 10) and the Hill model (five cases out of 10).

Tables 4 and 5 summarize the results obtained by the Weibull [9] and by the Gompertz [6] models. No significant difference between the models is detected on the basis of an *F*-test in terms of variance or with a *t*-test as regards mean precision.

**Table 4**
Results obtained by the Weibull model

| Formulation | $T_d$ | RSD (%) | β | RSD (%) | $Q_{max}$ (%) | RSD (%) | $T_{d50}$ | RSD (%) | Fitting time (min) |
|---|---|---|---|---|---|---|---|---|---|
| $F_1$ | 14.2 | 17 | 0.82 | 5.1 | 117 | 6.7 | 9.1 | 22.5 | 2.1 |
| $F_2$ | 4.90 | 4.1 | 0.75 | 3.6 | 99 | 1.2 | 3.0 | 6.3 | 1.2 |
| $F_3$ | 5.62 | 1.6 | 1.33 | 2.6 | 100 | 0.7 | 4.3 | 1.3 | 0.4 |
| $F_4$ | 6.08 | 2.9 | 1.34 | 3.8 | 101 | 1.4 | 4.6 | 2.2 | 0.4 |
| $F_5$ | 2.82 | 3.2 | 0.92 | 4.7 | 98 | 0.9 | 1.9 | 4.3 | 0.5 |
| $F_6$ | 2.53 | 6.7 | 0.79 | 5.9 | 101 | 1.8 | 1.6 | 9.8 | 0.6 |
| $F_7$ | 4.80 | 1.8 | 1.44 | 3.4 | 100 | 0.7 | 3.7 | 1.5 | 0.4 |
| $F_8$ | 4.03 | 2.0 | 1.43 | 3.5 | 100 | 0.7 | 3.1 | 1.8 | 0.3 |
| Aldomet | 2.50 | 2.9 | 2.32 | 7.7 | 99 | 1.5 | 2.1 | 4.6 | 0.2 |
| CEME | 21.5 | 20 | 0.93 | 4.9 | 108 | 7.8 | 14.5 | 23 | 0.5 |
| Mean precision | | 6.2 | | 4.5 | | 2.3 | | 7.7 | |

*Expressed in minutes for processing time on a PC-486 personal computer.

**Table 5**
Results obtained by the Gompertz model

| Formulation | $k$ | RSD (%) | β | RSD (%) | $Q_{max}$ (%) | RSD (%) | $T_{d50}$ | RSD (%) | Fitting time (min) |
|---|---|---|---|---|---|---|---|---|---|
| $F_1$ | 0.14 | 7.6 | 1.84 | 4.8 | 96 | 2.4 | 7.0 | 9.0 | 0.7 |
| $F_2$ | 1.27 | 3.4 | 1.27 | 3.4 | 95 | 0.5 | 2.8 | 6.8 | 0.7 |
| $F_3$ | 0.31 | 3.3 | 2.74 | 4.2 | 100 | 0.7 | 4.4 | 4.5 | 0.5 |
| $F_4$ | 0.30 | 4.0 | 2.78 | 4.8 | 100 | 1.0 | 4.7 | 5.3 | 0.5 |
| $F_5$ | 0.39 | 2.5 | 1.39 | 3.2 | 97 | 0.3 | 1.8 | 5.3 | 0.6 |
| $F_6$ | 0.36 | 3.3 | 1.13 | 3.7 | 99 | 0.4 | 1.3 | 8.2 | 0.5 |
| $F_7$ | 0.38 | 3.4 | 2.97 | 5.3 | 100 | 0.6 | 3.8 | 5.0 | 0.5 |
| $F_8$ | 0.45 | 3.8 | 2.89 | 5.8 | 101 | 0.7 | 3.2 | 5.5 | 0.4 |
| Aldomet | 1.13 | 5.6 | 7.49 | 13.1 | 101 | 1.1 | 2.1 | 7.8 | 0.4 |
| CEME | 0.096 | 5.3 | 2.04 | 3.4 | 90 | 2.1 | 11.2 | 6.2 | 0.1 |
| Mean precision | | 4.2 | | 5.2 | | 1.0 | | 6.4 | |

*Expressed in minutes for processing time on a PC-486 personal computer.

**Table 6**
Correlation between dissolution parameters and formulation factors

| | Weibull model | | | Gompertz model | | |
|---|---|---|---|---|---|---|
| Factors | $T_d$ | β | $T_{d50}$ | $k$ | β | $T_{d50}$ |
| Binder | −0.14 | 0.98* | 0.006 | −0.28 | 0.96* | 0.23 |
| Microcell | −0.36 | −0.087 | −0.38 | 0.45 | −0.15 | −0.15 |
| Explosol | −0.60 | 0.15 | −0.61† | −0.17 | −0.04 | −0.65† |

*Highly significant correlation ($P < 1\%$).
†Weak correlation ($P < 10\%$).

Correlation analysis detects a highly significant correlation between the sigmoidicity factor β and the nature of the binder, both by the Weibull and by the Gompertz models. Values of β are enhanced when utilizing polyvinylpyrrolidone, from 1.4 to 2.8 in the Gompertz model and from 0.8 to 1.4 in the Weibull model. No significant difference between these models is detected on the basis of the *F*-test or by a *t*-test on mean precision.

According to Gibassier *et al.* [9], values of $\beta < 1$ characterize slow kinetics while values of $\beta > 1$ characterize fast kinetics in the Weibull model. Thus from the present results polyvinylpyrrolidone produces fast kinetics and Movital produces slow kinetics of dissolution.

A weak negative correlation was detected between the concentrations of disintegrant Explosol (Table 6). An increase in Explosol from 1 to 4% decreased $T_{d50}$ values in the Weibull model (from 5.25 to 2.57 on average) and in the Gompertz model (from 4.72 to 2.52 on average). These results are in agreement with the conclusions obtained by Cid and Jaminet [10], who verified an increase in dissolution rates when increased amounts of Primogel (sodium amylglycolate) were used.

Formulations $F_1$ and the CEME product present a significantly enhanced $T_{d50}$ in the Weibull (14.2 and 12.5) and in the Gompertz (7.0 and 11.2) models. Both these formulations use Movital as binder. An important additional remark can be made about the CEME tablet formulation, with regard to its utilization of Eudragit L, which is insoluble between pH 2.0–5.0 [11], and therefore is not used for gastro-soluble tablets. Granules coated with Eudragit L offer considerable resistance to water uptake, and this is probably a significant factor which may account for the weaker performance of CEME tablets.

## Conclusions

Application of the program COMSTAT-W to data for the dissolution of methyldopa tablets allows the more adequate model (Gompertz and Weibull) to be chosen, in order both to determine the parameters with precision and an assurance of validity, and to compare various formulations with regard to their dissolution efficiency. The parameters obtained by factorial design allow two phenomena to be shown: the sigmoidicity factor is increased according to the type of binder used, and $T_{d50}$ values are decreased if larger quantities of Explosol are used. On the basis of these parameters it is possible to identify the factors which are responsible for the variations in dissolution rate of the various formulations examined.

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