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Statistical Comparison of Two Methods of Dissolution of Sustained-Release Theophylline Tablets

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ABSTRACT

A comparative study of two methods of dissolution (Simoons Apparatus and USP XXII Apparatus II) has been accomplished using sustained-release 50 mg anhydrous theophylline tablets. Sovic® 374 MB, Eudragit® RL PM, Aquacoat®, Methocel® K-15M, and Cutina® HR were some of the excipients used to elaborate inert, hydrophilic, and lipidic matrices. Theophylline release was prolonged in all cases, except when Aquacoat was used as matrix constituent. Simoons device was found to be more accurate for inert matrix tablets, whereas USP apparatus was advantageous for hydrophilic and lipidic matrix. ANOVA showed significant differences among all the factors analyzed. The drug release kinetics was adjusted better to Higuchi's kinetic model than to the Noyes–Whitney or Weibull models, from 10% to 70% release.

INTRODUCTION

In vitro dissolution tests are usually used to simulate the drug oral absorption reproducing the gastrointestinal tract physiological conditions. Numerous papers have been published comparing the different dissolution methods to determine the most reproducible test that confers better correlation between dissolution kinetics and bioavailability.

Due to the lack of an unique standardized dissolution test, we present in this paper a comparative study of two methods of dissolution: continuous flow device, described by Simoons (1), and the USP Apparatus II (2). The aim of this study was to investigate whether the method recommended by the USP is more reproducible, and also to investigate whether the release results obtained by both methods can be adjusted to the same kinetic process. Since a unique and universal norm for

interpreting the experimental results of the dissolution tests does not exist either, T_{50} and T_{90} of dissolution and areas under the dissolution curves or different types of statistical analyses are often compared. In this case, analysis of variance (ANOVA) and a study of regression of the data obtained with the dissolution tests have been accomplished.

MATERIALS

Six formulations of sustained-release theophylline tablets have been studied, these formulations correspond to three types of matrix tablets:

a. Inert matrix tablets: Three different excipients were used—polyvinyl chloride (Solvic® 374 MB: provided by Hispavic Industrial, SA, Madrid), an acrylic polymer (Eudragit® RLPM: Resinas acrílicas Röhm Pharma. Curtex Industrias Sintéticas, SA, Barcelona), and a polymeric aqueous dispersion containing 30% ethyl cellulose (Aquacoat®: FMC Corporation. Foret, SA, Barcelona).
b. Hydrophilic matrix tablets: These were formulated by means of hydroxypropylmethylcellulose (Methocel® K-15M: Dow Chemical International, SA, Madrid).
c. Lipidic matrix tablets: Hydrogenated castor oil (Cutina® HR: Henker International. Gmbd., Dusseldorf), was chosen to elaborate this formulation.

Anhydrous theophylline was provided by Knoll. Basf Española, SA, Lot 51163. The dosage of each tablet was 50 mg.

The quantitative composition of the tested tablets is shown in Table 1. Tablets I and V were obtained by direct compression, while tablets II, III, and IV were obtained by wet granulation. Tablets VI were achieved by fusion–pulverisation–compression. Compression was carried out by using a Bonals, model B, type MT/DM, eccentric tableting machine equipped with 5 mm concave punches.

METHODS

Dissolution Tests

Dissolution measurements were carried out by employing two different methods:

Continuous flow system (*method A*): The assays were carried out using an Erweka type AT 3 dissolution apparatus ("artificial intestine") connected to an ultraviolet (UV)–visible II (Vis) Perkin–Elmer 124 spectrophotometer provided with continuous flow cell and recorder.

Five tablets have been analyzed in triplicate in each test, as described in a previous paper (3). "Sink" conditions (5500 ml) were maintained using distilled water at 37 ± 0.5°C as dissolution medium.

USP Apparatus II (*method B*): The assays were performed using a SR2 Hanson Dissolution Test Station (4). The blade rotation was fixed at 75 rpm. Distilled

Table 1

Tablet Compositions

	Formula					
Composition	I	II	III	IV	V	VI
Anhydrous theophylline	50	50	50	50	50	50
Solvic 374 MB	50					
Eudragit RLPM		50				
Ethanol		98				
Aquacoat			40	40		
Methocel K-15M					26	
Cutina HR						20
Stearylic alcohol						20
Na lauryl sulfate						4
Talc		1				8
Magnesium stearate	3	1	2	2	5	2

water (4000 ml) was used as the dissolution medium and was maintained at 37° ± 0.5°C.

Three tablets were analyzed in each test and the analysis was accomplished six times. In each experience samples (5 ml) were taken over an 8 hr period and immediately replaced with an equal volume of dissolution medium. Samples were then filtered through 0.5 μm Millipore membranes and analyzed spectrophotometrically at 271 nm using a Perkin-Elmer Hitachi spectrophotometer.

In order to plot the corresponding dissolution curves, absorbance data were transformed into released concentrations (%).

Statistical Study

The statistical analysis of the obtained results makes it possible to complete the graphical or the mathematical methods of interpretation (5). In order to determine which method confers a higher accuracy, the standard deviations have been used to compare the variability of the dissolution percentages obtained in each point and formulation employing both devices.

In addition, results have been submitted to analysis of variance using the BMDP 2V program in order to determine significant differences in the individual behavior of the elaborated formulations according to the method. Independently of the used method, the differences between tablets release also were investigated. The interactions of this last parameter with the method, the type of tablet, and with the combination of both have been also studied.

The Statgraphic V6 program has been used to determine the release kinetics of each formulation utilizing both methods. The following equations have been applied to the experimental data:

Higuchi equation (6): defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$$Q = Kt^{1/2}$$

This law, fulfilled for matrix tablets with a low content of drug, has been verified also between 10% and 70% of release in tablets with a high-active substance rate in relation to their total weight (7,8). As this is the case, the equation has been applied to the release percentage intervals of the elaborated tablets.

Noyes-Whitney equation: considers the dissolution process at a first-order kinetics (9).

$$\ln(100 - Q) = -Kt + b$$

Q and t have the same meaning as in the previous equation, and K is the first-order dissolution rate constant.

Weibull equation: When the graphical representation of the dissolution process corresponds to a sigmoid, the interpretation of the kinetic of dissolution can be accomplished through the application of the equation of Weibull (10), modified by Langenbucher (11).

$$Q = Q_{max}\,(1 - e^{-(t-t_0/td)})^{\beta}$$

Q_{max} is the maximum quantity of drug dissolved in the process, td represents the "dissolution time" or the time required to dissolve 63.2% of the drug, β is a parameter of form whose value depends on the evolution of the dissolution kinetics, and t_0 is the period of latency.

RESULTS AND DISCUSSION

Dissolution Test

The dissolution curves of each formulation are represented individually (Figs. 1–3) in order to simplify the comparative study of the results. The figures represent the dissolution percentages (arithmetic mean) and their standard deviations.

The analysis of these plots proved the existence of a significant difference between the two methods for all the analyzed intervals.

A faster release was observed in the first moment when tablets were analyzed using the USP method. This phenomenon was difficult to explain due to the great number of different factors between both methods (liquid volume, agitation speed, automatic or manual samples extraction, etc.). However, once equilibrium has been reached, all tablets, except those of formulation II (Fig. 1), have shown a faster release kinetics with the continuous flow device than with the USP apparatus. This probably due to the higher agitation velocity of the continuous flow device provoking a higher dissolution and diffusion speed as the liquid surrounding the tablets was renewed faster.

The sustained release was achieved in all cases, except in those formulated with Aquacoat (Fig. 2). Those tablets released almost 70% of their content after 2 hr.

Statistical Analysis

The results of the dissolution tests of theophylline formulations (I, V, and VI) and their standard deviations (*SD*) are shown in Table 2.

Accuracy was lower during the first hour, probably due to the low sensitivity of the method of quantitation.

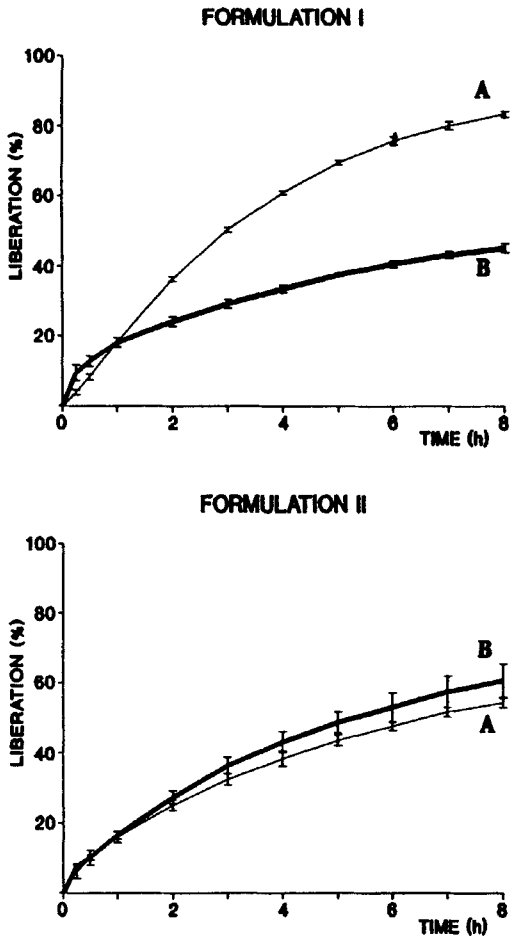

Figure 1. The dissolution curves of the tested formulations I and II. The figure represents the dissolution percentages (arithmetic mean) and the standard deviations.

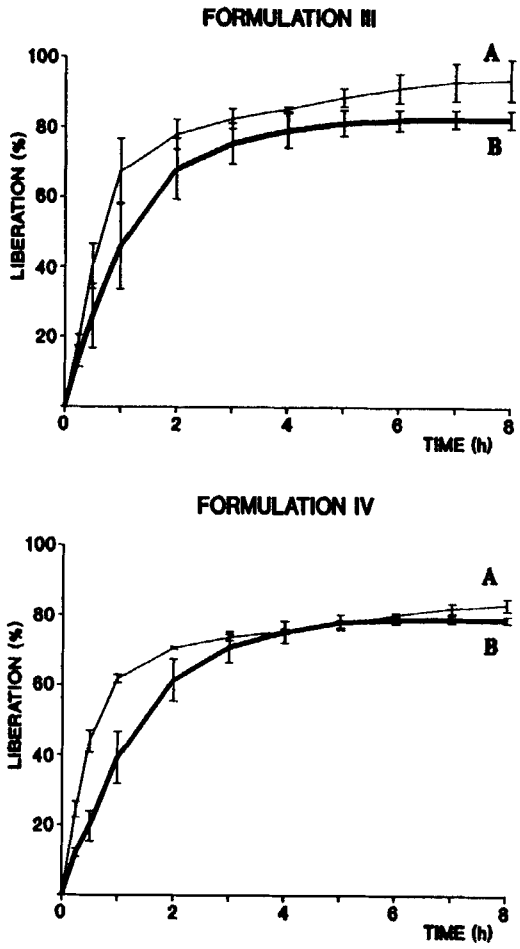

Figure 2. The dissolution curves of the tested formulations III and IV. The figure represents the dissolution percentages (arithmetic mean) and the standard deviations.

In general, method A was found to be more accurate for inert matrix tablets (formulations I, II, III, and IV), while method B was more reliable for hydrophilic and lipidic matrix tablets (formulations V and VI, respectively).

As five tablets were used for each experiment in method A, and spectrophotometric measurements were analyzed automatically in continuous flow, one could expect a higher accuracy of this method than the USP method, where three tablets were used for each experiment and samples extractions were carried out manually. This discrepancy can be attributed to the different form of drug release from each type of matrix.

The inert matrix tablets release the drug once this has been dissolved in the liquid that penetrates into the matrix; the drug then spreads outside. Once the matrix is exhausted of the drug, its "form" remains practically undisturbed; therefore the agitation speed does not exercise a considerable influence. However, the hydrophilic and lipidic matrix tablets release the drug once their components have jelled or they have been eroded, respectively. The less energetic agitation conditions using the USP device could favor more homogeneous gelation and erosion, making this method more accurate, even though fewer tablets were tested in each experiment.

The results of the analysis of variance are given in Table 3. All the factors studied (device, types of tablets, and device–tablet interaction) have a significant influence on the results obtained.

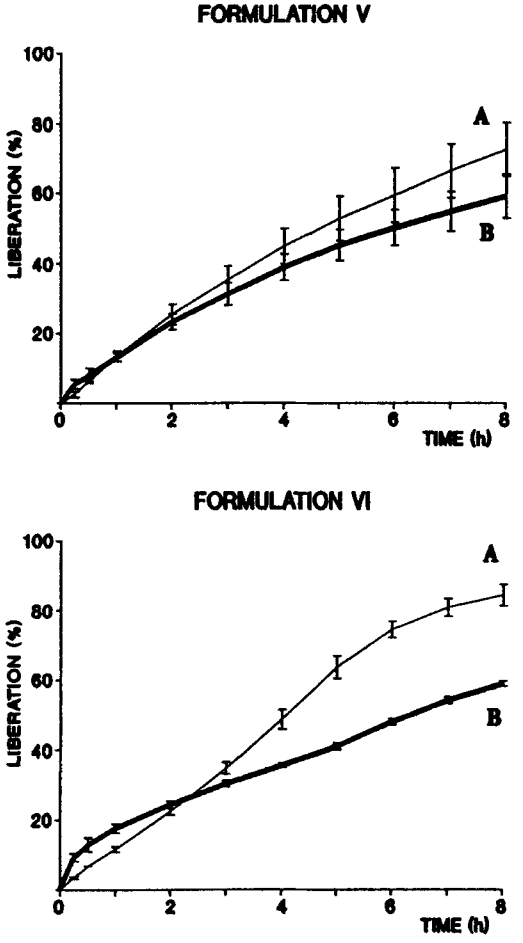

Figure 3. The dissolution curves of the tested formulations V and VI. The figure represents the dissolution percentages (arithmetic mean) and the standard deviations.

The type of device employed has an influence owing to the number of different factors between both devices (agitation speed, liquid volume, etc.). There were also differences between the types of tablets as for their dissolution behavior. This is probably due to the different release mechanism of each matrix, or even, due to the concrete excipient that has each formula.

The individual analysis of variance for each experimental time revealed that there was no significant difference between methods after 30 and 60 min, although this difference was detected between tablets and also in the method-tablet interaction.

There did not seem to be a significant difference in the quantity released after 7 hr; nor between methods, tablets, or in the method-tablet interaction. This phenomenon can be justified perhaps by the fact that tablets III and IV have been included in the analysis, whose dissolution curves showed absence of extended drug release; therefore the curves were asymptotic.

Regression Study

Dissolution percentages have been adjusted to the three kinetic equations indicated above. The maximum coefficient of determination (r^2) has been considered as statistical parameter to designate the function with better adjustment to the data. Tables 4 and 5 show the kinetic equations with better adjustment for each formulation and the coefficients of determination fitted to the degrees of freedom.

In all cases, the experimental data were fitted to the Higuchi equation from a 10% to 70% release. It was

Table 2

Theophylline Release Percentage: Formulas I, V, and VI

	Method A			Method B		
T (hr)	I: Average ± *SD*	V: Average ± *SD*	VI: Average ± *SD*	I: Average ± *SD*	V: Average ± *SD*	VI: Average ± *SD*
0.25	4.065 ± 0.828	2.576 ± 1.073	3.538 ± 0.437	9.477 ± 2.425	5.488 ± 1.397	9.315 ± 1.209
0.50	8.370 ± 1.096	6.558 ± 0.811	6.824 ± 0.000	12.837 ± 1.641	8.985 ± 0.909	12.949 ± 2.211
1.00	18.176 ± 1.657	13.585 ± 1.768	11.626 ± 0.875	18.179 ± 1.419	13.292 ± 1.241	17.658 ± 1.447
2.00	36.353 ± 0.829	25.531 ± 3.606	22.496 ± 1.158	24.159 ± 1.505	23.391 ± 2.468	24.450 ± 1.139
3.00	50.465 ± 0.828	35.369 ± 4.787	34.882 ± 2.006	29.262 ± 1.333	31.263 ± 3.490	30.427 ± 1.030
4.00	60.988 ± 0.717	44.973 ± 6.127	48.785 ± 3.420	33.568 ± 1.108	38.911 ± 4.041	35.588 ± 0.569
5.00	69.598 ± 0.717	52.938 ± 7.741	63.700 ± 4.013	37.554 ± 0.502	45.297 ± 4.845	41.022 ± 1.016
6.00	75.817 ± 1.493	59.497 ± 9.437	74.569 ± 2.871	40.664 ± 1.048	50.198 ± 5.605	47.995 ± 0.951
7.00	80.122 ± 1.493	66.523 ± 9.359	80.889 ± 3.157	43.215 ± 0.988	54.877 ± 6.125	54.243 ± 1.054
8.00	83.470 ± 1.095	72.614 ± 9.359	84.426 ± 3.817	45.208 ± 1.378	59.258 ± 6.845	59.042 ± 0.817

Table 3

Analysis of Variance

Type	Sum of Squares	*GF*	Mean of Squares	*F*	*NC*
Average	1039864.99473	1	1039864.99473	9694.75	0.0000
M	7931.01516	1	7931.01516	73.94	0.0000
F	93147.88055	5	18629.57611	173.69	0.0000
M-F	5620.69741	5	1124.13948	10.48	0.0000
Error	4504.94654	42	107.26063	—	—
T	206835.40083	9	22981.71120	3852.87	0.0000
T-M	2332.84118	9	259.20458	43.46	0.0000
T-F	12203.18246	45	271.18183	45.46	0.0000
T-M-F	9481.69927	45	210.70443	35.32	0.0000
Error	2254.70700	378	5.96483	—	—

Note. M, method; F, formulation; T, time.

Table 4

Method A

Formulation	Equation	r^2
I (Higuchi, 1–5 hr)	$Q = -21.51 + 41.05t^{1/2}$	99.54
II (Higuchi, 0–8 hr)	$Q = -4.69 + 21.29t^{1/2}$	98.90
III (Higuchi, 0–2 hr)	$Q = -13.67 + 66.42t^{1/2}$	95.52
IV (Higuchi, 0–2 hr)	$Q = 16.61 + 38.39\ t^{1/2}$	86.51
V (Weibull)	$Q = 83[1 - e^{-(t/4.08)^{1.23}}]$	90.72
VI (Higuchi, 2–6 hr)	$Q = -47.77 + 49.21t^{1/2}$	98.24

Table 5

Method B

Formulation	Equation	r^2
I (Higuchi)	$Q = 2.39 + 15.58t^{1/2}$	98.53
II (Higuchi)	$Q = 5.42 + 23.40t^{1/2}$	97.45
III (Higuchi, 0–2 hr)	$Q = -15.52 + 59.44t^{1/2}$	90.29
IV (Higuchi, 0–2 hr)	$Q = -14.35 + 52.72\ t^{1/2}$	94.00
V (Weibull)	$Q = 67[1 - e^{-(t/5.16)^{0.86}}]$	92.58
VI	$Q^{1/2} = 2.11 + 1.96t^{1/2}$	99.23

observed that for formulation V (hydrophilic matrix), the Weibull equation explained the process with more accuracy.

When lipidic matrix tablets (formulation VI) release was analyzed using the USP apparatus, an unsatisfactory fitting of data to the three kinetic equations was obtained. Nevertheless, when the squared root of the released rate was represented on the square root of each experimental time, a coefficient of determination of 0.9909 was obtained [level of probability (*p.1.*) model = 0, *p.1.* lack of fitting > 0.05].

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