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CHARACTERIZATION OF THE *IN VITRO* DISSOLUTION OF SOME COMMERCIAL SUSTAINED RELEASE THEOPHYLLINE DOSAGE FORMS

VEIGA, F., SIMÕES, S., MOREIRA, J.N., SOUSA, A.

Pharmaceutical Technology Laboratory
Faculty of Pharmacy
University of Coimbra
3000 Coimbra-Portugal

ABSTRACT

A dissolution study of five commercial sustained release theophylline dosage forms, concerning their pH dependency, is described. The experiment was carried out in a flow through dissolution apparatus, at constant pH and at pH gradient, being the pH values of 1,2, 6,5 and 7,5. In both cases, they were treated in terms of the dissolution profile and the dissolution rate, complemented with the dissolution efficiency at pH gradient in order to make a correlation with the *in vivo* experiments that will be done in the future. The absorbance was measured at a wavelength of 264 nm. According to the results obtained, was selected the best pharmaceutical form, concerning the pH dependency and taking as a basis, just, the *in vitro* experiments.

INTRODUCTION

Theophylline is one of the most important drugs used in the treatment of acute or chronic obstruction of respiratory diseases [1]. This drug is very well known by its short half-life of elimination (4-9 hours) and its rather small therapeutic range (10-20 $mg.l^{-1}$) [2]. Thus, the administration of sustained release preparations, once or twice a day, has been recommended for better control of the therapeutic levels, improving patient compliance, resulting small fluctuations of theophylline plasma concentrations [1] and decreasing the secondary effects by a slow and total release over a certain period of time [3].

Several studies on the biopharmaceutical properties of some commercial sustained release theophylline products have been published, especially concerning the influence of some parameters on the *in vitro* release profile [3], [4]-[7], absorption [8], [9], bioavailability [10] and also the *in vitro/in vivo* correlation [10], [11], [2].

The aim of this work is to study the pH influence on the theophylline release profile from four commercially sustained release theophylline products available on the portuguese market. This study will be complemented by the *in vivo* experiments, that will be object of another paper.

MATERIALS AND METHODS

Test Samples

All these dosage forms, whose characteristics are described in Table 1, were purchased commercially in a random choosed pharmacy.

Dissolution Studies

Buffer Solutions

Dissolution experiments were performed using buffer solutions with the following pH values: 1,2 ± 0,1; 6,5 ± 0,1; 7,5 ± 0,1. The

TABLE 1

Main Features of the Sustained Release Dosage Forms Used.

Products	Pharmaceutical form	Dose* (mg)	Posology (hours)	Batch
(A)	Pellets	125	12	OCXXB02
(B)	Tablets	180	12	9023120
(C)	Tablets	128	12	89H21
(D)	Tablets	400	24	1001C12
(E)**	Tablets	80	8	T50223

* Anhydrous theophyline.

** Immediate Release Dosage Form.

first was prepared by dissolving 68,05g of potassium dihydrogen phosphate (KH_2PO_4) and 28,6 ml of glacial acetic acid (CH_3COOH) in 10l of distiled water and subsequently adjusting the pH value to 1,2 with 37% hydrochloric acid. The others were prepared in a similar way, being the pH value adjusted with a 4N sodium hydroxide solution. In either case, it was used an automatic pH apparatus. All the reagents used were of analytical grade.

Procedure

It was used a flow through dissolution apparatus consisting of a thermostated (SOTAX CH-4008 Basel,Type UT) water bath (SOTAX, Type CE 6) at 37°C, fitted with five dissolution units assembled next to each other on top of the bath. After the dissolution medium has been submited to a rotation speed of 100±0,1 r.p.m., it was pumped by a pistons pump (SOTAX, Type CY 6) with five channels through a closed system. This included a U.V. spectrophotometer (Shimadzu, UV-160),

with a cell positioner and a temperature cell control (Shimadzu CPS-240 A), set at 37°C.

The experiment was carried out at constant pH and at pH gradient. In the former three tests were performed, respectively at pH values of 1,2, 6,5 and 7,5. In the later, by addition of known amounts of sodium hydroxide 4N, the pH was raised from 1,2 to 6,5 and then to 7,5 at two hours intervals, after which, it remained constant until the end of the experiment. Absorbance was measured every thirty minutes at a wavelength of 264 nm. At this value the absorbance is pH independent [12], which was checked experimentally.

The experiments were carried on during 12 hours, excepting the one concerning product D, which took 24 hours, and product E, which took 8 hours.

RESULTS AND DISCUSSION

The results obtained were divided in two parts, according to the procedure, at constant pH or at pH gradient. In both cases, they were treated in terms of the dissolution profile and of the dissolution rate in order to better evaluate the pH dependency and the *in vitro* release.

The analysis of the results showed that only product A proved to be pH dependent, especially during the first four hours. In fact, the differences namely in the high dissolution rate were only significant at pH 7,5, as can be observed both from the *in vitro* release profile (Figure 1) and from the dissolution rate variation (Figure 2). This can be justified by the nature of the coating substance (metacrylates), which is insoluble in acid and alkaline fluids. However, it presents an increase permeability in alkaline medium which implies the increased dissolution rate at pH 7,5 as refered by other authors [6].

Although product B presents some differences on the dissolution rate, especially in the first two hours (Figure 4), it wasn't considered a pH dependency, in agreement with the observations of other authors [13] who have also worked with sustained released products based on the use of hidroxyethilcelulose. This aspect can be easily observed from the analysis of the *in vitro* release profiles (Figure

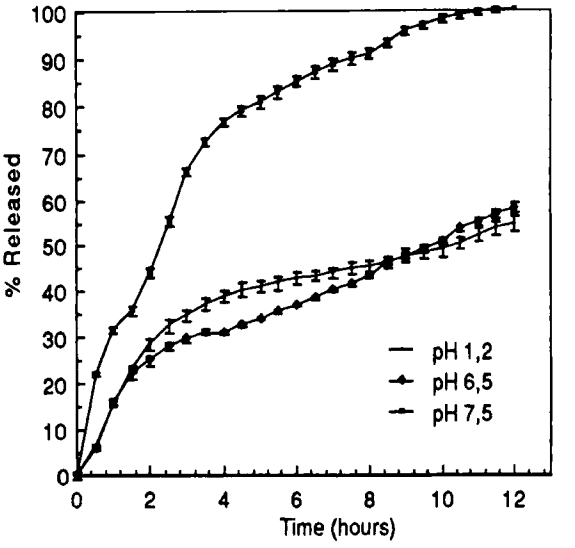

Figure 1
In Vitro Release Profile of Product A.

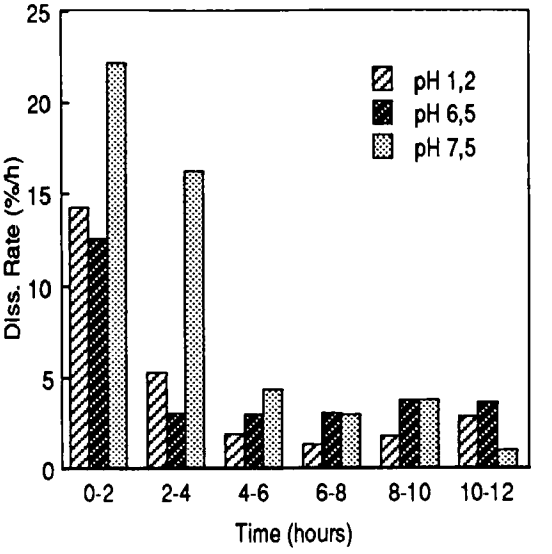

Figure 2
Dissolution Rate Variation in Time of Product A.

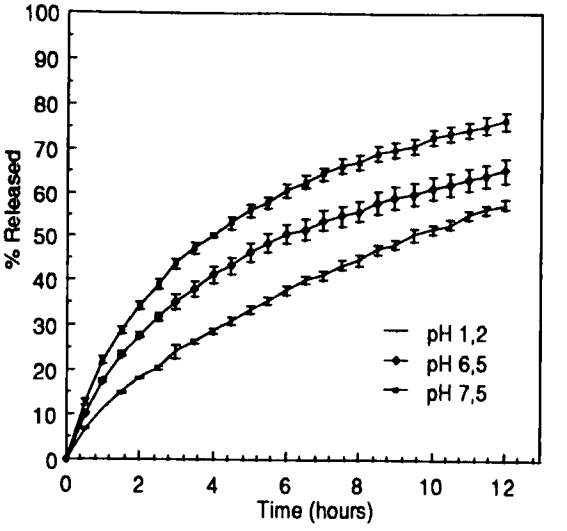

Figure 3
In Vitro Release Profile of Product B.

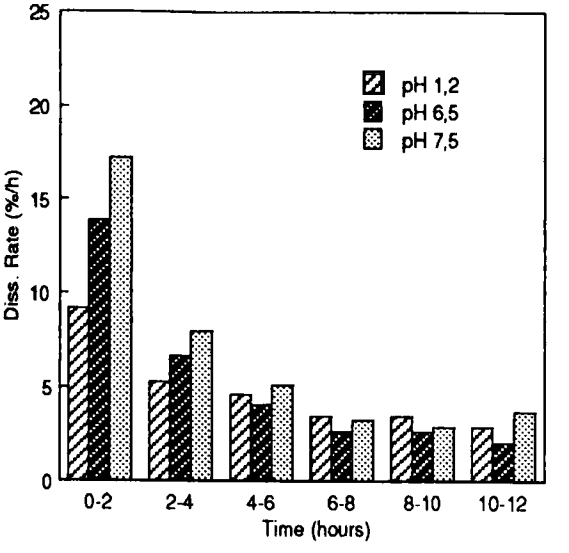

Figure 4
Dissolution Rate Variation in Time of Product B.

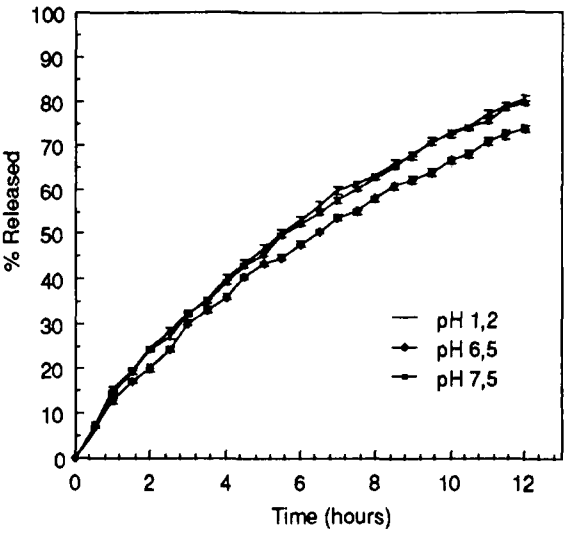

Figure 5
In Vitro Release Profile of Product C.

3), as the curves present a similar profile. The differences can be justified by an increase of the theophylline solubility due to the presence of ethylenediamine (in the form of aminophylline complex), which might determined an increase of the micro pH value inside the matrix.

In what concerns to products C (Figures 5 and 6) and D (Figures 7 and 8), it wasn't observed any pH dependency, since curves were obtained with similar profiles. This idea is reinforced by the constancy of the dissolution rates every hours. For the last one, the result was in agreement with the one obtained for product B, as both contained hidroxyethilcelulose in their formulations.

The figures 9 and 10 allowed a comparison of the theophyline released between the several products, when submited to a pH gradient. This experiment is complemented by another dissolution parameter, the dissolution efficiency (Table 3).

From the results presented in Table 2, it could be deduced that although product A had shown less released quantities at pH 1,2 than at pH 7,5, it didn't affect the final amount released, since there was a dissolution rate increase when the pH reached a alkaline value.

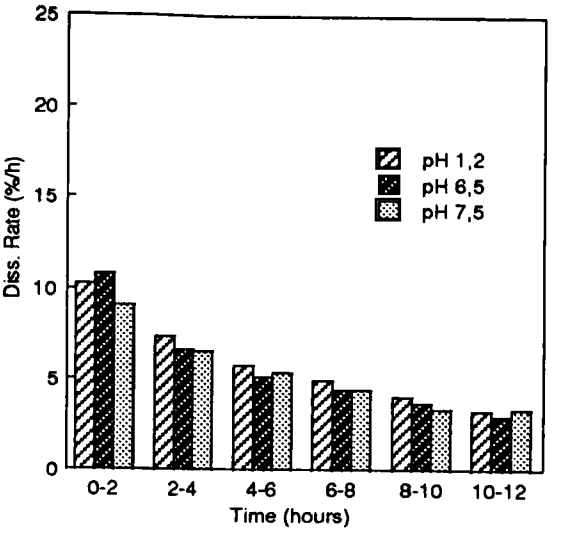

Figure 6
Dissolution Rate Variation in Time of Product C.

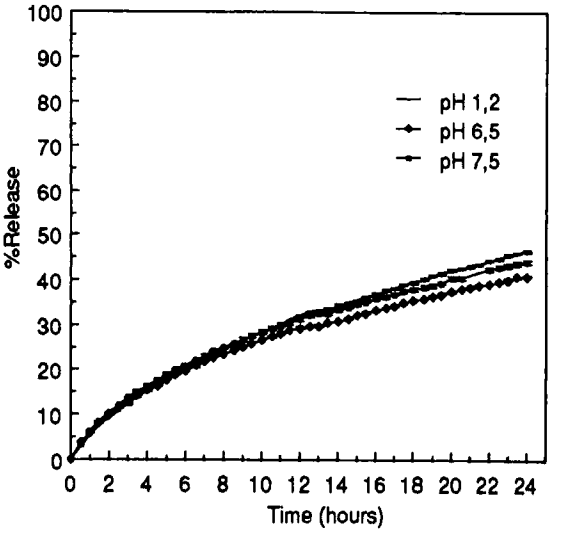

Figure 7
In Vitro Release Profile of Product D.

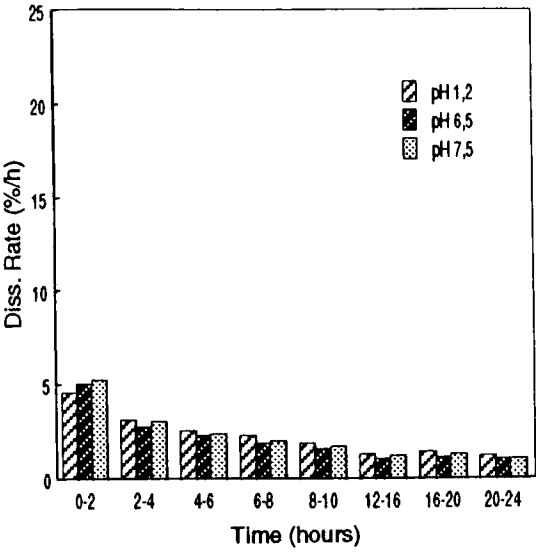

Figure 8
Dissolution Rate Variation in Time of Product D.

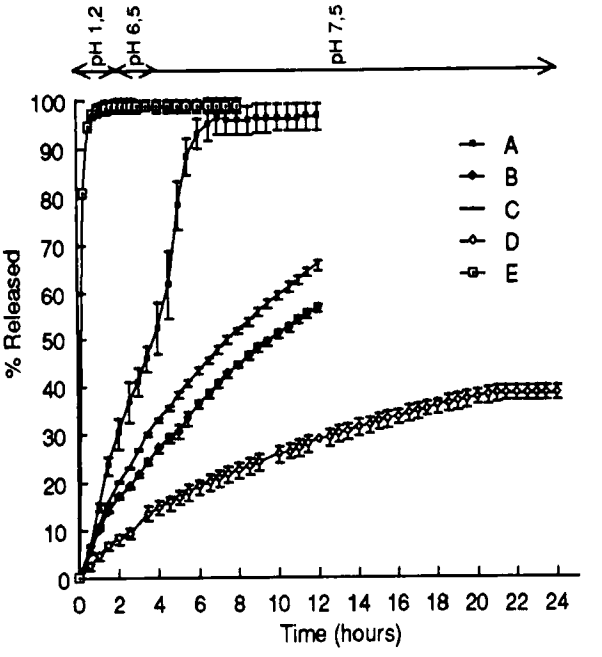

Figure 9
In Vitro Release Profile of the Five Formulations Obtained With pH Gradient.

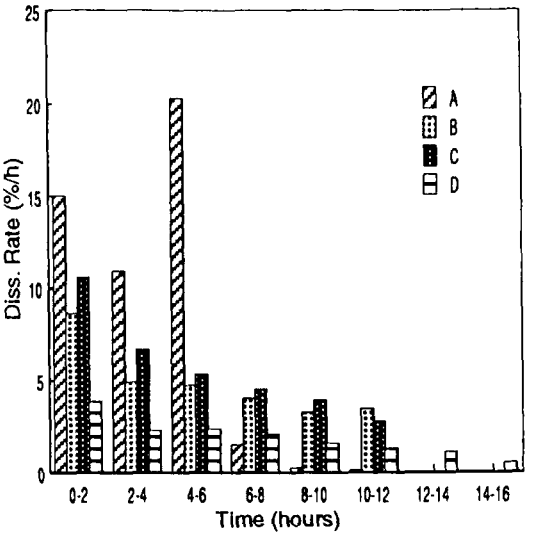

Figure 10
Dissolution Rate Variation in Time With pH Gradient,Concerning the Four Formulations.

TABLE 2
Absolute and Relative Quantities of Drug Released

	pH			
PRODUCTS	**1,2**	**6,5**	**7,5**	**Variable**
A	70 mg (56% ± 1,509)	70 mg (56% ± 0,900)	125 mg (100% ± 0,574)	120,6 mg (97% ± 2,595)
B	102,6 mg (57% ± 1,005)	117 mg (65% ± 2,596)	124 mg (76% ± 1,767)	101 mg (56,5% ± 0,852)
C	85,7 mg (67% ± 0,674)	85,7 mg (67% ± 0,955)	85,7 mg (67% ± 0,449)	88 mg (68,5% ± 0,928)
D	124 mg (31% ± 0,164) 176,4 mg (44% ± 0,209)	124 mg (31% ± 0,130) 176,4 mg (44% ± 0,134)	124 mg (31% ± 0,300) 176,4 mg (44% ± 0,399)	109,2 mg (27,3% ± 1,607)[1] 152 mg (38% ± 1,444)[2]

1- After 12 hours.

2- After 24 hours.

TABLE 3
Dissolution Efficiency

Products	Dissolution Efficiency (% , t=12 h)
A	70,0 ± 2,6
B	39,0 ± 1,7
C	41,9 ± 2,0
D	16,0 ± 1,4

(±) - confidence interval - 95 %
t - 0,05
N - 4

Furthermore, this product presented an higher initial dissolution rate than the other pharmaceutical forms (Figure 10), which was probably due to the great dissolution surface offered by the pellets and, consequently, to the liberation of a great amount of drug [6].

Despite product B was assumed as being non pH dependent it was observed that the low dissolution rate at pH 1,2 determined the total release quantities. This can be confirmed by comparing the relative quantities of drug released at constant 7,5 pH and at variable pH.

Concerning products C and D the results were in agreement with the ones obtained at constant pH, which were expected since they were considered non pH dependents.

In Figure 9 it is shown the release profile of a theophylline immediate release dosage form (product E), characterized by a rapid and total release within, more or less, 2 hours, which demonstrates the non pH dependency of this drug.

From Table 3 it can be observed that product A is the one that presents the best *in vitro* dissolution efficiency, for t=12 hours, followed by products C, B and D.

CONCLUSIONS

Attending to the concept of dissolution efficiency [14] and taking as a basis the *in vitro* data obtained, product A probably presents the best proportionality between the *in vivo* drug absorption and the concentration of drug in solution and the time this solution is in contact with a suitable absorptive region of the gastrointestinal tract. However, the observed pH dependency might compromise its performances.

The results obtained reveal that products C and D are those that present the most uniform behaviour in terms of sustained release. The observed non pH dependency, decreases the influence of some variability factors on the drug release as, for example, the standing time in the gastrointestinal tract.

Although the high contents of theophylline and the particular posology presented in product D can be justified by its absorption in colon [15], it might cause therapeutic accidents (for example, overdosage) if the tablet matrix is affected by an incorrect employment (as for example, tablet mastication). An irregular absorption at this level can also cause some problems.

If a good correlation is to be obtained between the *in vitro/in vivo* experiments, it might be suggested that, concerning the pH dependency, product C is technologically the best pharmaceutical form, despite the choice should attend each individual posology.

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