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Kinetics of theophylline release from suppositories in vitro: influence of physicochemical parameters

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Summary

In order to choose an excipient for the preparation of suppositories, some physicochemical tests were carried out with 5 vehicles with or without the active material and stored at 4 °C and 30 °C. In an attempt to improve the evaluation of availability for the forms examined a release kinetics study was undertaken with various apparatus. Using a membrane apparatus, two excipients were selected. After analysis of their physicochemical characteristics, one of them appeared more interesting. These results were also justified by the composition of the selected formula.

Introduction

The aim of this work was to determine the best formulations for theophylline suppositories, by an in vitro study. There are many methods for the formulation of suppositories, but the most common have been described and classified in a first work (Zuber and Pellion, 1987). Five excipients which differed by their melting points, lower than or equal to 37 °C, and their hydroxyl index were used. The physicochemical characteristics of the suppositories were determined by several tests, which were required by different Pharmacopoeias (weight variation, disintegration and liquefaction times, melting point) or which allowed us to make a quality control on the fabrication (dosage, hardness), or to predict the availability (spreading surface). These assays were performed on suppositories with or without theophylline, stored at 4 °C to keep the base in metastasis and on material kept at 30 °C, for 8 days, to evaluate the influence of the ageing on the physicochemical characteristics (Moes, 1975). The relationships between these results were studied using the independence test (Philippe, 1967) to examine whether it would be possible to reduce the number of assays. The release kinetics was examined using groups of 6 suppositories stored at 4 °C (in the metastasized form) using two methods: the USP XXI rotating basket or the parallel bar basket (Palmieri, 1981) and the Guyot-Hermann cell (Guyot-Hermann et

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al., 1975). The Mann–Whitney test was used to compare the percentage release (Philippe, 1967) given by each method.

Materials and Methods

Materials

Five formulations of suppositories were prepared using cocoa butter ((CB-Cocoa, Barry Soc.) and 4 semisynthetic glycerides (suppocires AIML, AP, AM, AS_2X, Gattefosse Est.) (Table 1). The particle size of the theophylline, listed in the European and French Pharmacopoeias, was 125–250 μm.

Preparation of suppositories

These were prepared by melting the suppository base and adding theophylline to the liquid, which was then kept at room temperature to solidify, to avoid polymorphism and cracking. Suppositories without theophylline were prepared under the same conditions to be used as a reference control.

Solubility of theophylline in the excipients

In a series of glass vials, increasing quantities of theophylline were added to 10 g of each excipient of suppositories. The vials were placed at 60 °C and agitated regularly for 7 days. The sample, which did not contain any active component in suspension after this period of time, corresponded to the maximum solubility in the vehicle studied.

Physicochemicals tests

Weight variation and disintegration time were verified according to the French and European Pharmacopoeias assays (10^{th} and 2^{nd} editions). For the latter, an automatic apparatus was used (Erweka-ST_6, Euraf, Paris).

Melting point was measured by the U-tube method.

Liquefaction time was determined by Krowczynski's manual and automatic methods (Suppotester ST3, Sotax, OSI, Paris).

Homogeneity was verified with the entire suppository and with half suppositories, cut either transversally or longitudinally. The theophylline, extracted by petroleum ether, was measured by ultraviolet spectrophotometry at 272 nm (Perkin Elmer 550, OSI, Paris). The excipient did not interfere with the dosage.

Hardness was measured by the resistance to crushing (Erweka SBT, Euraf, Paris).

Surface spreading was calculated according to the watch glass method (Villemey, 1975).

Kinetics of theophylline release

The dissolution assay was carried out at 36.5 ± 0.5 °C with purified water as the dissolution medium. With the rotating basket methods, one liter was used. The Guyot-Hermann cell, equipped with a cellophane membrane (porosity 0.023 μm, Nojax, Paris), was immersed in 350 ml of the receiving phase. The suppository was placed on this membrane with 2 ml of water. The samples were taken at 5, 10, 15, 30, 45, 60, 90 and 120 min.

Results

Physicochemical tests

The solubility of theophylline in the excipient was very low and it was always in suspension.

The results of the dosage showed that the theophylline concentration was homogeneous (Table 2).

The results of the weight variation test showed that they were in accordance with the French and European Pharmacopoeias.

TABLE 1

Physicochemical characteristics of the different excipients

	AIML	AP	AM	AS_2X	CB
Melting point (°C)	33–35	33–35	35–36.5	35–36.5	33–34
Hydroxyl index	6	30–50	6	15–25	0

TABLE 2

Levels of theophylline in several excipients

	AIML	AP	AM	AS_2X	CB
Half suppository					
$\bar{X}$ (1)	23.11	27.52	25.41	28.10	29.70
$\bar{X}$ (2)	24.42	20.71	23.12	20.32	19.38
Whole suppository					
$\bar{X}$	48.02	49.18	47.70	50.47	50.65
σ	1.60	1.13	1.05	1.16	1.77
VC	3.34	2.30	2.20	3.09	3.50

$\bar{X}$, mean (mg); σ, standard deviation (mg); VC, variation coefficient (%); 1 and 2, transversal and longitudinal cuts.

Only AM and AS_2X showed significant increases in melting point on incorporation of theophylline. All the melting points increased after ageing; this might be related to the excipient transformation into a stable crystalline form (Table 3).

Theophylline increased the disintegration time, mainly for AP and AS_2X excipients. The melting point and the hydroxyl index influenced the disintegration time. Indeed, for suppositories with similar melting points, the disintegration time decreased when hydroxyl value increased. For a similar hydroxyl index, it decreased with the melting point. An increase of the disintegration time was noted after ageing for almost all the formulations, probably due to an increase of the melting point (Table 3).

An increase of the liquefaction time was observed, particularly with the cocoa butter, after incorporation of the active material. This observation was more pronounced by the manual method than by the automatic method. All the formulations showed a larger liquefaction time after ageing (Table 3).

The hardness of AP and AS_2X decreased when theophylline was added. However, the hardness value remained above 30 N. A significant decrease was observed for all excipients stored at 30 °C, except for cocoa butter. This phenomenon which made manipulation difficult, might be explained

TABLE 3

Results of various tests

Tests		AIML		AP		AM		AS_2X		CB	
		C	S	C	S	C	S	C	S	C	S
Hardness (N)	4 °C	54	54	54	40	54	54	48	44	54	54
	30 °C	28	25	26	24	40	26	27	24	54	54
Melting point	4 °C	34.25	34.46	35.10	35.17	35.20	35.83	35.35	35.83	33.20	33.20
(°C)	30 °C	36.10	36.17	36.90	36.87	37.07	37.53	37.20	37.50	34.85	34.83
Disintegration	4 °C	5	6.0	3.33	5.75	10	10.5	6.17	8.75	6.85	8.50
time (min)	30 °C	10	9.08	6.41	9.33	10	16.0	8.67	13.85	8.67	8.50
Liquefaction											
time (manual	4 °C	6.27	6.31	6.25	7.00	8.15	11.09	6.45	8.23	3.63	7.42
method) (min)	30 °C	6.90	6.64	7.97	8.21	12.92	12.67	7.42	9.38	8.97	9.18
Liquefaction											
time (automatic	4 °C	5.72	5.79	5.18	5.58	7.04	7.5	5.43	6.62	3.75	6.92
method) (min)	30 °C	6.26	5.68	5.84	6.09	10.40	9.34	6.41	7.84	7.76	7.84
Spreading surface	4 °C	1112	977	730	671	378	340	368	357	1180	950
(mm^2)	30 °C	190	434	527	340	202	200	217	57	543	612

C, control; S, suppository with theophylline; samples were stored at 4 °C and 30 °C.

TABLE 4

Percentages of theophylline released as a function of time in the Guyot-Hermann method (mean of 6 trials)

Time (min)	AIML	AP	AM	AS_2X	CB
5	2.30	3.39	1.97	1.80	1.60
10	5.97	7.80	5.40	4.70	4.14
15	13.60	14.70	10.22	8.50	7.35
30	27.50	30.70	25.90	18.30	19.55
45	41.0	46.0	41.90	32.30	30.86
60	57.60	59.0	56.0	39.20	40.75
90	74.0	78.40	77.0	52.90	56.59
120	83.0	91.0	87.10	63.30	70.0

by a rearrangement of the crystalline structure (Table 3).

Theophylline decreased the spreading surface, due to an increase in viscosity.

A decrease in the spreading surface was observed for all formulations after ageing (Table 3).

Release kinetics

Semi-synthetic glycerides. For all the studied formulations, the rate of release was greater with the methods not using a membrane. Indeed, theophylline, which is soluble in water, was completely released after 15 min, whereas with the Guyot-Hermann cell the release continued for 120 min. This was mainly due to the presence of the membrane, but also to the formation of a more or less lipophilic barrier which resulted from the fusion of the excipient and through which the active material diffused very slowly.

Cocoa butter. Using the USP XXI rotating basket technique, the release of the substance was not complete after 45 min, because the theophylline remained in the basket. This phenomenon was not observed for the parallel bar basket. As for the semi-synthetic glycerides, the rate of release was slow for the device using cellophane. Only the results obtained with the membrane method are shown in Table 4 and Fig. 1, since for the two other methods, the rate of release was too fast to permit a differentiation between the excipients. Fig. 1 shows two groups of excipients: AP, AM, AIML, which released a large amount of theophylline, and cocoa butter and AS_2X which released less.

Correlation study between the physicochemical characteristics of suppositories (for $df = 15$ and $P < 0.05$, $r = 0.482$)

Melting point and disintegration time. The statistical study showed only a very weak relationship ($r = 0.5237$).

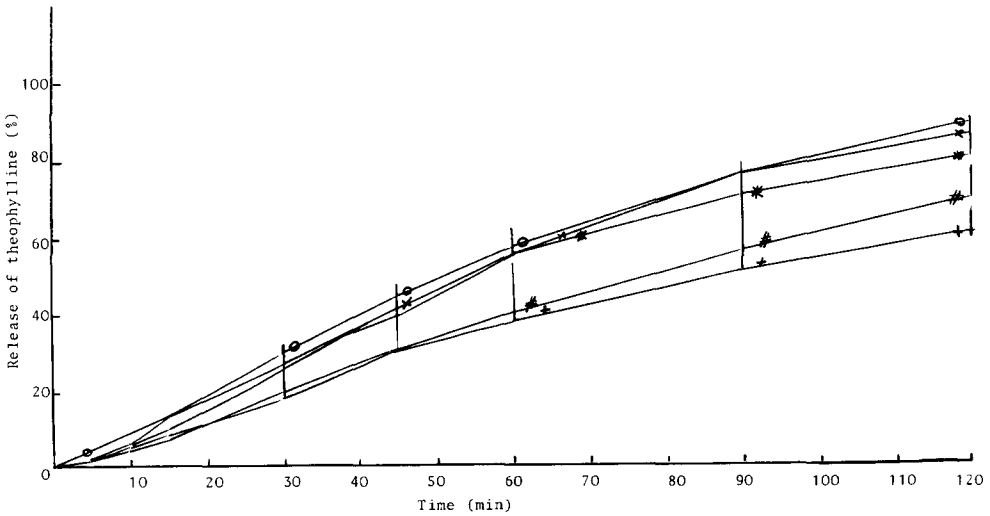

Fig. 1. Release study by the Guyot-Hermann method. ○, Excipient AP; ×, excipient AM; +, excipient AS_2X; *, excipient AIML; #, excipient cocoa butter.

Liquefaction time and hardness. The correlation study showed a very weak relationship, only for suppositories stored at 30 °C ($r = 0.6117$).

Spreading surface and other characteristics of suppositories. Two correlations were observed for suppositories stored at 4 °C and 30 °C, but in a less significant way for those stored at 30 °C: a first correlation between the spreading surface and the melting point ($r = 0.7522$ and $r = 0.5341$) and the second one between the spreading surface and the liquefaction time ($r = 0.7040$ and $r = 0.5652$).

Manual and automatic Krowczynski's methods. Since the values obtained with the two methods were not the same, a statistical analysis, which was carried out to evaluate whether the two series of results could be correlated, showed a very significant correlation for the two qualities of suppositories ($r = 0.9188$ and $r = 0.9547$). These results were interesting since they showed that the use of the automatic apparatus should give many advantages: an important reduction of the time for controls, and better results, since 3 assays can be carried out simultaneously without intervention of the experimenter.

Statistical results of release kinetics. For the methods without membrane, no significant difference was obtained between the excipients. For the method with membrane, the results are shown in Table 5.

TABLE 5

Statistical test of the release trials using the membrane method (Mann–Whitney test)

Comparison between	Significance for P
AP/AM	n.s.
AP/AIML	**
AP/CB	**
AP/AS_2X	**
AM/AIML	n.s.
AM/CB	**
AM/AS_2X	**
AIML/CB	*
AIML/AS_2X	**
CB/AS_2X	n.s.

n.s., not significant; *, significant, $P < 0.05$; **, significant, $P < 0.01$.

According to the values obtained, the following observations could be made: (1) the differences between the two groups of excipients were significant; (2) when comparisons were made within one group, the rates of release were not significantly different, except for the suppositories prepared with AP and AIML.

Discussion

Release kinetics with the Guyot-Hermann method allowed the selection of two vehicles (AP, AM), which had given the greatest amount of theophylline liberation. After analysis of their physicochemical characteristics, it appeared that AP was more interesting than AM: after maturation, the latter presented a higher melting point (37 °53′) than the former (36 °87′) which caused an increase of disintegration and liquefaction times, and a small spreading surface (200–400 mm^2). There was a small difference between the physicochemical results obtained with AIML and AP. However, the latter must not be considered, since the statistical analysis showed a significant difference for release kinetics.

The hydroxyl index seemed to have a variable influence. Indeed, AM and AIML excipients had hydroxyl indices lower than AS_2X and their availability was better. But the AP vehicle, which gave the best results, had the greatest value. The excipient composition could explain this result: AS_2X is made hydrophilic by polysorbate while AP contains hydrophilic derivatives.

This in vitro study seemed to be in accord with the in vivo study carried out by Rodriguez (1982) who showed that the absorption of monohydrated theophylline was satisfactory with the AP excipient.

This work has shown that to formulate suppositories, it is important to determine the physicochemical parameters of samples stored at different temperatures: the increase of the melting point, after ageing, had a repercussion on different parameters. The decrease in hardness with the semisynthetic glycerides was an important problem, which must be resolved by an additive. The correlation study has shown that it is possible to

reduce the number of assays. However, the evaluation of the availability must be completed by a kinetic release study with a method compatible with the characteristics of the active material, in particular its solubility in the dissolution phase.

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