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Effect of Temperature on Characteristics of Hydroxypropylcellulose Tablets Prepared by Wet Granulation Methods

O. D. Opota,[1] J. Joachim,[2] H. Maillols,[3] R. Acquier,[3] and H. Delonca[3]

[1]*Departement de Galenique, Faculté de Pharmacie, Université de Kinshasa B.P. 127 Kinshasa XI, Zaïre*
[2]*Laboratoire de Galenique Industrielle, Faculté de Pharmacie, Université d'Aix Marseille II, 13385 Marseille Cedex 5, France*
[3]*Laboratoire de Technique Industrielle, Faculté de Pharmacie,Université de Montpellier I, 34060 Montpellier, France*

ABSTRACT

In this work, we will study the effect of temperature (35–45°C) on the disintegration and dissolution rate of theophylline from the tablets containing hydroxypropylcellulose as a binder (binder in solution). The results showed that in all cases the increase of the temperature led to the acceleration of the disintegration and the dissolution rate of theophylline tablets except in basic formula. The disintegration and dissolution times decrease gradually, then abruptly fall in time at the demixing temperature and take the same time as the basic formula. It was also observed that the demixing temperature varies with the concentration of the polymer in the tablet formulation and shows no change in rheological formulation.

INTRODUCTION

The results of the previous research to evaluate the apparent viscosity of three types of the hydroxypropylcellulose solutions (LF, GF and HF) with variation of the temperature have shown that there was demixing temperature characteristic for each polymer. During this study it was observed that the variation of these temperatures with the modification of the concentrations of the polymers were negligible (1).

The aim of this work is the comparison between the results of hydroxypropylcellulose compressed manufactured and the previous results of the rheological study of hydroxypropylcellulose aqueous solutions (1).

MATERIALS AND METHODS

This study uses a basic simplified formula containing theophylline monohydrated (100 mg), corn starch (12 mg), talc (6.8 mg), magnesium stearate (1.2 mg), and

calcium sulfate (q.s. for 400 mg). The concentrations of each polymer solution incorporated into basic formulation were 3%, 5%, 7%, 9%, 11% for LF, 2%, 3%, 5% for GF, and 1%, 1.4%, 2% for HF. The solutions of polymers have been prepared according to the same method discussed previously for the rheological analysis (2,3).

The powders were mixed without lubricant and granulated in a mixer-granulator (Lodigë M5RG). The wet granulation for each formula was obtained by using 60 ml of various binders. The granules obtained were dried in an oven at 45°C for 30 minutes in fluidized bed apparatus (Glatt TR5). After drying, the granules were calibrated on a Frewitt MG204 (sieve 1 mm/0.65) and lubricated in a Turbula mixer for 15 minutes and compressed using a single-punch tablet machine (Frogerais OA).

A disintegration test was carried out on six tablets with distillated water at 35–48°C using Erweka ZT3 according to the pharmacopoeia method (4).

The dissolution test was carried out with 1000 ml of dissolution medium (pH 1.2) at 35–48°C using USP XXII apparatus with the rotating basket method at 100 rpm(5). The quantity of theophylline was determined at 272 nm.

RESULTS AND DISCUSSION

Tablet Control

The results of the control of the tablets are indicated in Table 1.

The friability test values showed that the introduction of polymer in the basic formula improves tablet cohesion. However, it was observed that the percentage of concentrations and the type of polymer appear to have little effect on the friability. This may be due to identical hardness of the tablets for all the formulas at lower polymer concentration.

Drug Release

The disintegration and the dissolution tests were used as bases for evaluating the effect of temperature on the type and concentration of polymer.

Disintegration Test

Macroscopic appearances of the manipulations have been shown for two disintegration types depending on the concentration of polymer incorporated in the tablet. One type is granular particles observed at low concentrations and the other is erosive particles observed at high concentrations. The erosive type is obtained beyond the concentrations 1.05% for LF and 0.75% for GF. Table 2 shows the disintegration times obtained.

The disintegration times obtained were different according to the formula used, showing the influence of the polymer as a binder in spite of the very low concentration used.

The results of the formula containing the polymers indicate that disintegration times increase with increasing polymer concentration and vary according to the type of polymer. The highest times correspond to high molecular weight polymers.

The study of the influence of temperature showed very little variation in disintegration time at high temperature for the base formulation, while incorporation of polymer in formulation led to gradual decrease of disintegration times as the temperature increased.

This decrease of disintegration times becomes more important behind 40°C and abrupt falling in these times at the demixing temperature. At this temperature, the times become identical to those observed with the formulation basic.

The effects of two factors, concentration of polymers with temperature and nature of polymers with temperature, on the disintegration times were studied from 35°C to 40°C. The results of those investigations were ana-

Table 1

Physical Properties

Type	0	LF					GF			HF		
Polymer (mg)	0	1.8	3.0	4.2	5.4	6.6	1.2	1.8	3.0	0.6	0.84	2
Average weight (mg)	400	401	401	393	406	397	397	400	402	399	398	405
Hardness (kg)	5.4	5.7	5.5	5.5	5.5	5.7	5.6	5.6	5.8	5.8	5.3	4.9
Friability(%)	2.3	1.6	1.7	1.6	1.5	1.0	1.9	1.6	1.5	2.1	1.6	1.8

Table 2

Disintegration Time and Parameters of WEIBULL

Type	T°C	0	LF					GF			HF		
Percentage		0	0.45	0.75	1.05	1.35	1.65	0.3	0.45	0.75	0.15	0.25	0.3
Disintegration time (min)	35	1.5	8.6	11.9	20.1	24.4	27.7	6.6	10.7	21.8	5.4	8.6	10
	37	1.4	6.8	10.1	15.2	18.3	22.5	5.6	8.5	17.1	4.2	6.3	8.5
	40	1.4	5.4	7.2	16.6	14.5	16.2	4.3	6.5	14.2	2.2	2.2	4.0
	45	1.6	2.5	1.2	2.8	1.8	4.8	1.5	1.5	2.2	1.0	1.0	1.8
b	35	↑	1.7	1.6	1.5	1.3	1.1	1.8	1.4	1.2	2.2	2.2	2.0
	37	1.6	2.0	1.8	1.8	1.4	1.2	1.7	1.4	1.4	2.6	2.0	2.0
	40		1.2	2.0	2.0	1.9	1.8	1.8	1.9	1.7	2.6	2.0	2.0
	45	↓					1.8			1.8			2.0
Td(min)	35	↑	18	20	39	64	87	14	33	78	12	17	20
	37	13	12	16	28	43	63	11	27	55	9	13	14
	40		8	11	16	25	35	9	12	23	7	8	7
	45	↓					8			10			7

lyzed statistically by ANOVA to verify the effects of temperature on those factors. The comparison of F values (snedecor factor) obtained in this ANOVA with the tabulated F values at 5% probability level indicated that the influences of the concentration and temperature on the disintegration time were due to the presence of polymer in the formula. The existence of a concentration-temperature interaction observed during this analysis indicated that the influence of temperature on the disintegration time depends on the concentration used.

From Table 2, it was observed that the disintegration times depend on the type of the polymer when it is used at equal concentrations. These times increased when the mean molecular weight of the polymer incresed.

Dissolution Test

The mechanism of kinetics release of theophylline was expressed from the *b* and *Td* parameters of the WEIBULL equation, which was developed and applied for the first time by Langenbucher, for dissolution kinetics (6,7):

$$q = 1 - \exp(-T/Td)b,$$

where q is the cumulative fraction of the amount of theophylline dissolved at time *T*.

$T = t - to$ where *t* is the experimental time sampling, *to* is the lag time (here *to* is neglected), and *b* is the slope parameter. *Td* is the time parameter for release of 63.2% of total drug. The logarithmic form of the previous equation is written as

$$\ln(-\ln[1 - q]) = b \ln t - b \ln Td$$

By using this expression, parameters *b* and *Td* are determined by the least squares method. The different values of *b* and *Td* calculated are grouped in Table 2.

These results showed that for all concentrations studied the *b* values greater than 1 indicate rapid drug release. The influence of the concentration becomes clear at 1.05% for LF and 0.45% for GF. Those are the critical concentrations at which slowing drug release was started.

Observation values of *Td* led to the following conclusions:

- There is no significant difference for the dissolution mechanism of basic formulation at all temperatures.
- For similar polymer concentrations, *Td* values increase as the mean molecular weight increases.
- Incorporation of polymers led to dissolution kinetic modifications at various temperatures and concentrations.

In all cases analyzed, the dissolution times decrease gradually with increasing temperatures, then abruptly fall at the demixing temperature and take the same time

as the formula without polymer. It seems that the polymer at critical temperature develops no more viscosity due to its insolubility, and does not play its role as a binder. However, the characteristics for high concentrations of polymers were different from those discovered in rheological studies. This phenomenon is probably due to concentration effect, which acts on viscosity and displaces the demixing temperature in the case of tablets. Then the concentration factor should be considered when using HPC in tablet formulation.

CONCLUSION

The comparison of the different formulations with the basic formula without polymer showed that the binder activity of the Klucel increases as the concentration or the molecular weight increases, and each polymer behaves differently at various temperatures.

At the demixing temperature, there was abrupt falling of disintegration and dissolution times of the formula containing a polymer with identical characteristics to those of the formula without the polymer. This phenomenon may be explained by the fact that at the demixing temperature the polymer is unable to solubilize and it does not play its role as a binder. This study has shown that the loss of cohesion at the critical temperature depends on the polymer concentration. This phenomenon of the displacement of the critical temperature according to the concentration has not been observed during the rheological study. Thus, the formulator who wants to use HPC as a binder only must make sure that the demixing temperature is around 35–41°C because an increase in this temperature causes inhibition of the binding effect of the polymer.

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