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The Effect of Processing Variables on the Release of Ibuprofen and Caffeine from Controlled-Release Nonswellable Core-in-Cup Compressed Tablets

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ABSTRACT

An aqueous soluble polymer such as hydroxypropyl methylcellulose (HPMC), which is widely used in oral sustained-release drug delivery systems, swells when it comes into contact with an aqueous environment. In core-in-cup systems the swelling of the HPMC splits open the cup portion of the tablet. This study investigated the use of acacia, tragacanth, polyethylene glycol 6000 (PEG 6000), and hydroxyethylcellulose (HEC) as possible alternatives to the use of HPMC to control the release of caffeine (soluble) and ibuprofen (insoluble) from core-in-cup compressed tablets. It also investigated the possibility of producing a core-in-cup system that had the ability to release caffeine and ibuprofen for a maximum time of constant release of 8–12 hr. A preliminary study revealed that acacia was most effective for the release of caffeine from the core-in-cup compressed tablets, and that PEG 6000 was most effective for the release of ibuprofen from the core-in-cup compressed tablets. On further investigation it was found that by means of adjusting the hardness of compression and the concentration of polymers used, it was possible to formulate a core-in-cup system that could release drug at a constant rate from the core-in-cup compressed tablets for 8 to 12 hr.

INTRODUCTION

Most matrix-type tablets release drug according to the Higuchi (1,2) square root of time kinetics (3–6). One way to modify the release kinetics from matrix systems is to alter the geometry of the matrix. Danckwerts (7) has reported a method that describes the production of an active sustained-release disk-shaped matrix core, which is compression coated on one side as well as the circumference to form a cup around the core. This core-in-cup tablet releases drug from a constantly eroding surface or constant diffusional area and path. These tablets have the ability to release soluble and insoluble drugs at a zero-order rate from an inactive cup. It was found that it is possible—through the manipulation of (i) the grade of HPMC used or any other hydrophilic polymer or mixture of polymers that erodes constantly with time, (ii) the quantity of HPMC polymer used, and (iii) the exposed surface area of the core of the HPMC polymer matrix—to produce a core-in-cup compressed tablet that can release a constant amount of drug over a predetermined period of time. Unfortunately, as the depth of the cup portion of the core-in-cup compressed tablet increased to 6 mm or more, some of the cups began to split in aqueous dissolution medium. This is because the efficiency of the binder in the cup portion of the tablet was not enough to overcome the swelling of the HPMC polymer when it comes into contact with aqueous medium. As the viscosity grade and concentration of the polymer used increases, so does the swelling of the polymer increase (8), especially in the vertical direction (9).

The purpose of this study, therefore, was to test the effectiveness of nonswellable polymers in producing the core of a core-in-cup tablet that does not swell to any appreciable extent when it comes into contact with aqueous dissolution fluid. The advantage of such a polymer would be that it would not split the cups open, and it would release the drug from a constantly eroding surface or constant diffusional area and path. It must, however, be capable of releasing drugs over a period of at least 8 hr at a constant rate.

Accordingly, it was decided to first test the rate of release of a soluble drug (caffeine) and an insoluble drug (ibuprofen) from polyethylene glycol 6000 (PEG 6000), acacia gum, tragacanth, and hydroxyethylcellulose (HEC) from core-in-cup tablets. Secondly, it was decided to examine the effects of the processing variables concentration of polymer (c) and hardness of tablet core (h) on the maximum time of constant release (t_{max}) of caffeine and ibuprofen from the most suitable polymers. The rate of release of caffeine was tested in 0.1 M HCl aqueous dissolution fluid. The rate of release of ibuprofen was tested in 0.2 M phosphate buffer at a pH of 7.2. This study then results in a 3^2 factorial design. The dependencies were explained using analysis of variance and multiple regression analysis.

MATERIALS

Acacia, PEG 6000, and tragacanth gum were supplied by Saarchem (Pty) Ltd., South Africa. The acacia, PEG 6000, and tragacanth gum had viscosities of 53 cps, 43 cps, and 1250 cps, respectively, as 4% aqueous solutions at 23°C. HEC was supplied by Riedel de-Haën, South Africa, and had a viscosity of 2100 cps as a 4% aqueous solution at 23°C. Ibuprofen (Boots Co, S.A. Pty Ltd.) and caffeine (Sigma Chemical Company, USA) were ground and the fractions passing through a No. 150 standard U.K. sieve were used. Ethylcellulose (Riedel de-Haën, South Africa) and carnauba wax (Sigma Chemical Company, USA) were used as supplied. All other reagents used were standard laboratory grade.

METHODS

Study Design

The study followed a sequential 2^1 preliminary study followed by 3^2 factorial experimental design. In the preliminary experimental phase, the caffeine and ibuprofen were formulated in each polymer at two different concentrations in order to assess which polymer gave a constant release time closest to a maximum of 8–12 hr. Once the most suitable polymer was found, a 3^2 factorial design study was conducted for each of ibuprofen and caffeine. The amount of polymer in the core (c) and hardness of the core (h) were used as independent variables. The normalized factor levels of the independent variables are presented in Table 1. All the outside factorial points of the core tablets were made in duplicate batches, and in quadruplicate batches in the center point. Therefore, the total number of runs was 20 for each drug. The maximum time of constant release (including the initial higher release rate) of drug from the core-in-cup in the relevant dissolution fluid was the dependant variable.

Formulations

For the preliminary study on the suitability of the polymers to caffeine or ibuprofen, flat disk-shaped core

Table 1

Levels of Independent Variables

Variable	Factor Level			Units
	-1	0	1	
Concentration of polymer in core (c)	5	10	15	% (w/w)
Hardness of compressed core (h)	40	50	60	N/m^2

tablets of 7 mm diameter and 5 mm depth were compressed on a Manesty F3 single-punch tableting press. The hardness of the core tablets was first measured on a Pharma Test PTB 311 hardness tester. The press was then adjusted to produce core tablets of approximate hardness of 50 N/m^2. Table 2 lists the composition of the different cores that were compressed and used for the preliminary study.

The cores were then compressed together with the 10% (w/w) carnauba wax in ethylcellulose cups to a depth of 4 mm as described previously (10). Figure 1 graphically describes such a core-in-cup tablet.

Once it was established that acacia was most suitable for the release of caffeine, and PEG 6000 was most suitable for the release of ibuprofen, from the core-in-cup tablets, cores of the compositions listed in Table 3

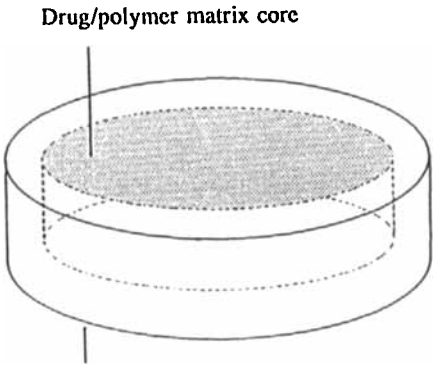

Figure 1. Schematic diagram of the core-in-cup compressed tablet.

Table 2

Maximum Time of Constant Release (t_{max}) for Caffein and Ibuprofen from Different Polymers

Drug	Polymer (%)				$t_{max} \pm SD$ (hr) ($n = 3$)
	Acacia,	PEG-6000	Tragacanth	HEC	
Caffeine	5				7.50 ± 0.73
Caffeine	10				11.50 ± 0.82
Caffeine		5			3.67 ± 0.27
Caffeine		10			6.83 ± 0.08
Caffeine			5		1.33 ± 0.52
Caffeine			10		1.83 ± 0.89
Caffeine				5	3.17 ± 0.87
Caffeine				10	6.50 ± 0.38
Ibuprofen	5				20.17 ± 0.73
Ibuprofen	10				24.33 ± 0.70
Ibuprofen		5			12.50 ± 0.82
Ibuprofen		10			8.33 ± 0.38
Ibuprofen			5		3.83 ± 0.17
Ibuprofen			10		4.33 ± 0.36
Ibuprofen				5	4.17 ± 0.38
Ibuprofen				10	5.00 ± 0.42

were produced and compressed to a hardness of 40, 50, or 60 N/m^2.

Release Studies

The BP 1988 paddle method was utilized in all the release studies. A volume of 1000 ml of 0.1 M HCl in deionized water, equilibrated at 37°C ± 0.5°C, was used as the release medium for the caffeine tablets. For the ibuprofen tablets, 1000 ml of 0.2 M phosphate buffer BP at a pH of 7.2 and equilibrated at 37°C ± 0.5°C, was used. All experiments were carried out at 70 rpm. The release rates of the tablets were monitored using a Caleva model 7ST dissolution tester connected to a Beckman DU 650 spectrophotometer via a flow-through cell. Dissolution medium was pumped through Elkay solvent flex PVC tubing (ID of 0.1 in.) with bridge tubing at a rate of 3.9 ml/min by means of a Desaga STA peristaltic pump. The bridge tubing was connected to acid flexible manifold tubing which was connected to the flow cell, and also from the flow cell back into the dissolution flask. In order to constantly monitor the release of the drugs, the spectrophotometer was programmed to read the concentration of the drug in the flow cell at 10-min intervals. Ibuprofen was measured spectrophotometrically at a wavelength of 216 nm, while caffeine was measured at a wavelength of 242 nm. Linearity was established for 0.1 M HCl aqueous solutions of caffeine, and 0.2 M phosphate buffer aqueous solutions of ibuprofen, in the range of 6.25–200 μg/ml.

Statistical Analysis

Analysis of variance was performed on the data presented in Table 3 using STATGRAPHICS vers. 5 (Statistical Graphics Corporation, USA). The independent variables were % polymer in the core (*c*) tablet and hardness of the core tablet (*h*), while the dependent variable was maximum time of constant release (t_{max}) from the core-in-cup tablets. Response-surface plots were constructed for the above variables, in order to determine the optimal combination of the variables. Main effects and significant interactions were also cal-

Table 3

Maximum Time of Constant Release (t_{max}) for Caffeine and Ibuprofen (c, % polymer; h, hardness)

Run	*h*	*c*	Mean crushing Strength ± *SD* (N/m^2) (*n* = 3)		t_{max} (hr)	
			Caffeine	Ibuprofen	Caffeine	Ibuprofen
1_a	-1	-1	38.16 ± 2.94	43.19 ± 3.33	4.17	12.83
1_b	-1	-1	45.99 ± 8.46	35.51 ± 7.82	4.00	11.17
2_a	-1	0	36.84 ± 4.43	41.06 ± 8.64	5.67	9.67
2_b	-1	0	43.07 ± 2.40	44.32 ± 5.55	7.33	6.83
3_a	-1	1	42.72 ± 4.94	42.80 ± 5.11	10.67	6.83
3_b	-1	1	42.94 ± 4.75	40.14 ± 7.20	11.83	6.00
4_a	0	-1	52.24 ± 5.66	50.48 ± 3.98	6.33	11.00
4_b	0	-1	54.55 ± 8.02	51.32 ± 6.46	5.83	12.67
5_a	0	0	48.16 ± 4.14	48.00 ± 9.76	10.17	9.83
5_b	0	0	51.60 ± 7.85	53.21 ± 5.68	10.50	10.67
5_c	0	0	48.81 ± 2.07	50.18 ± 9.29	11.33	10.33
5_d	0	0	52.53 ± 5.96	53.67 ± 5.47	9.50	9.83
6_a	0	1	49.76 ± 4.19	50.41 ± 5.80	13.33	6.67
6_b	0	1	52.91 ± 7.88	51.13 ± 8.02	12.17	6.83
7_a	1	-1	64.55 ± 9.95	64.40 ± 6.91	7.83	15.33
7_b	1	-1	58.27 ± 8.33	60.13 ± 8.47	8.83	14.33
8_a	1	0	66.56 ± 4.03	66.07 ± 4.09	11.83	8.00
8_b	1	0	62.86 ± 6.41	62.44 ± 4.16	12.50	8.83
9_a	1	1	68.62 ± 6.19	64.09 ± 3.27	14.83	7.33
9_b	1	1	65.69 ± 7.43	60.26 ± 5.41	13.67	7.50

culated. Simple regression models for the two independent variables were also developed from the results as follows:

$$Y_1(c,h) = a_0 + a_1c + a_2h + a_3ch + a_4c^2 + a_5h^2 \quad (1)$$

where $a_0, \ldots, a_5$ are the coefficients of the system. c and h denote the % polymer in the core tablet and hardness of the core tablet, respectively.

Each term in the final regression equation for the maximum time of constant release was only included if the t-test p value was less than 0.05. The regression coefficients for those effects that were considered insignificant were eliminated and the model was reestimated. All statistical analysis was performed using STATGRAPHICS vers. 5 (Statistical Graphics Corporation, USA).

RESULTS AND DISCUSSION

Table 3 lists the t_{max} values of the release of caffeine and ibuprofen from the formulations. Table 4 lists the relevant statistical parameters calculated from the results of this study for the effect of the two independent variables on the maximum time of constant release (t_{max}) of the core-in-cup tablets analyzed. All statistical analysis was carried out on all the experimental runs (total 20).

Caffeine Release from Acacia

Figure 2 is the response surface plot of the estimated effects of the % acacia and hardness of the core tablet on the t_{max} of caffeine from the core-in-cup tablets. Both the concentration of acacia and the hardness of the core tablet play a significant role in the resultant t_{max} of the core-in-cup tablets. Concentration of acacia in the core tablet has the most significant influence on its t_{max} (Fig. 2). Since the acacia acts as a binder for the caffein, this effect is expected. This binding efficiency is at its maximum when the compression force is increased, and the difference in the t_{max} at the higher compression force (equivalent to a hardness of $\pm$ 60 N/m^2) is similar to that at the lower compression force (equivalent to a hardness of $\pm$40 N/m^2). The similarity in effect on the t_{max} is evidence from the estimated main effects of 6.583 for c and 4.358 for h. There were no significant ($p < 0.05$) interaction effects from the % acacia and hardness of the tablets on the rate of release of caffeine.

In developing a regression model for the effect of the independent variables on the t_{max} dependent variable, only the main effects were significant ($p < 0.05$).

Table 4

Relevant Statistical Parameters

Source	Estimated Effects ± Standard Error (13 *df*)	*p* Value	Regression Coefficient	Regression Coefficient Reestimated
Caffeine release from acacia				
Average	10.040 ± 0.381			
Constant			-20.470	-7.837
c	6.583 ± 0.512	<0.0001	1.211	0.658
h	4.358 ± 0.512	<0.0001	0.629	0.218
ch	-0.609 ± 0.627	0.3588	-0.006	
cc	-0.619 ± 0.825	0.4742	-0.012	
hh	-0.700 ± 0.825	0.4206	-0.003	
Ibuprofen release from PEG 6000				
Average	9.2863 ± 0.514			
Constant			4.775	15.626
c	-6.028 ± 0.690	0.0000	-0.735	-0.603
h	1.332 ± 0.690	0.0758	0.381	
ch	-0.915 ± 0.845	0.2987	-0.009	
cc	1.473 ± 1.113	0.2083	0.029	
hh	-0.447 ± 1.113	0.6989	-0.002	

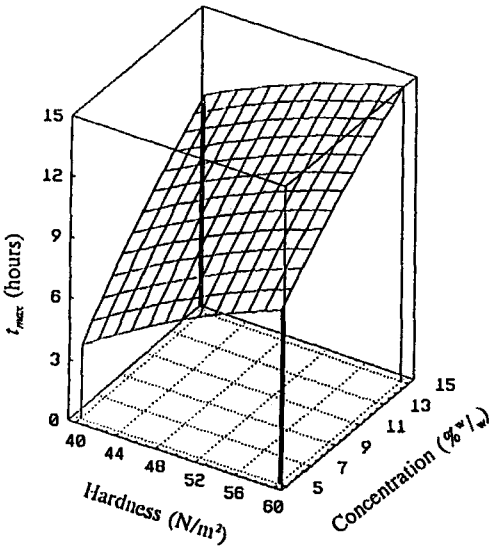

Figure 2. Response-surface plots of the estimated effects of c and h on the t_{max} of caffeine from the core-in-cup tablets.

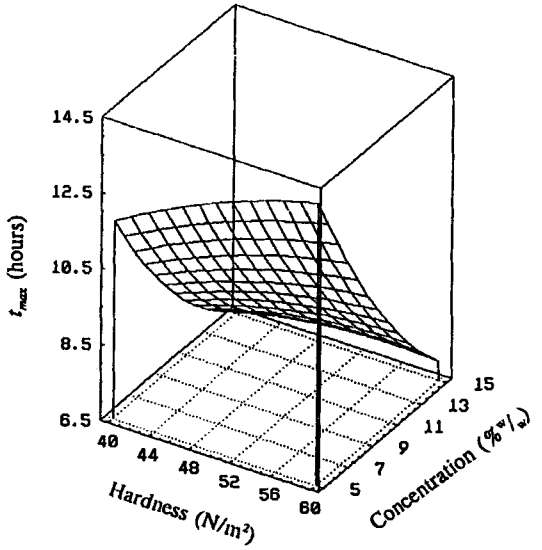

Figure 3. Response-surface plots of the estimated effects of c and h on the t_{max} of ibuprofen from the core-in-cup tablets.

Therefore, the regression coefficients for these effects were included in the model. The rest of the coefficients were eliminated and the model was reestimated by STATGRAPHICS.

$$Y_{tc}\ (c,h) = -7.837 + 0.658c + 0.218h \qquad (2)$$

where $Y_{tc}\ (c,h)$ is the estimated t_{max} of caffeine from the core-in-cup tablets.

The squared multiple regression coefficient for this model was 0.9487. This model shows that % concentration of acacia in the core tablet has the major effect on the t_{max}. As the concentration increases, the t_{max} increases. The hardness of compression also produces an increase in the t_{max}. Clearly, in order to produce a core-in-cup tablet that needs to release drug for a t_{max} of approximately 8–12 hr, the concentration of acacia and hardness of compression can be adjusted to produce the required t_{max}.

Ibuprofen Release from PEG 6000

Figure 3 is a response surface plot of the estimated effects of the % PEG 6000 and hardness of the core tablet cup on the t_{max} of ibuprofen from the core-in-cup tablets tested. Only the concentration of PEG 6000 in the core tablet plays a significant role in the resultant t_{max} of the core-in-cup tablets (Fig. 2). Since the PEG 6000 is water soluble, it causes the ibuprofen to be released at a quicker rate than if the ibuprofen were compressed on its own. As the concentration of PEG 6000 increases from 5 to 15% (w/w), the quicker is the release from the core-in-cup tablets and the shorter is the t_{max}. The t_{max} values decreased from 15.33 hr to 6.83 hr, depending on the hardness of compression of the core tablet. Hardness of compression, on the other hand, had very little significant effect on the release of ibuprofen from the tablets. As the hardness increased from 40 N/m^2 to 60 N/m^2, the t_{max} only increased, on average, over all % concentration levels of PEG 6000, from 8.888 hr to 10.220 hr.

The effect of hardness of compression on the t_{max} of ibuprofen from PEG 6000 was even less pronounced at the 15% (w/w) PEG 6000 level. The t_{max} only increased on average from 6.415 hr to 7.415 hr. There were no significant ($p < 0.05$) interaction effects from the % PEG 6000 and hardness of the core tablets on the rate of release of ibuprofen.

In developing a regression model for the effect of the independent variables on the t_{max} dependent variable, only the concentration of PEG 6000 was significant ($p < 0.05$). Therefore, the regression coefficient for this effect only was included in the model. The rest of the coefficients were eliminated and the model was reestimated by STATGRAPHICS.

$$Y_{ti}\ (c,h) = 15.626 - 0.603c \qquad (3)$$

where Y_{ti} (c,h) is the estimated t_{max} of ibuprofen from the core-in-cup tablets.

The squared multiple regression coefficient for this model was 0.8659. This model shows that % concentration of PEG 6000 in the core tablet is the only factor that has a significant effect on the t_{max}. As the concentration increases, the t_{max} decreases. The hardness of compression produces an increase in the t_{max}, but not a significantly one. In order to produce a core-in-cup tablet that needs to release ibuprofen for a t_{max} of approximately 8–12 hr, the concentration of PEG 6000 can be adjusted to produce the required t_{max} from Eq. (3).

From the above results it can be seen that it is possible to produce a core-in-cup tablet that can release aqueous soluble (caffeine) and insoluble (ibuprofen) drugs at a zero-order rate, depending on the type of erodible polymer used. For insoluble drugs, it is best to use an aqueous soluble polymer such as PEG 6000; and for a soluble drug, it is best to use an erodible polymer like acacia. Neither PEG 6000 nor acacia swelled to any noticeable extent in the aqueous dissolution fluid used and, therefore, there was no splitting (which could lead to dose dumping) of the cup portion of the core-in-cup tablet as can be the case with polymers that swell in aqueous fluids.

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