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The effect of processing variables on the compression properties of controlled release core-in-cup compressed tablets from a new adjustable punch

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Abstract

A novel adjustable punch that can be adjusted to produce compressed cup-shape tablets of different depth has been evaluated. The resultant cups have been compressed together with core tablets to produce compression coated tablets that have the ability to release active drug at a zero-order rate. The influence of three independent variables (percentage carnauba wax in the cup tablet, the compressed hardness of the cup tablet, and depth of the cup tablet) on the friability of the cup tablet and splitting of the cup tablet in aqueous dissolution fluid was studied using a 3^3 factorial design. The friability of the cup tablets were influenced by all the factors as well as the second-order interaction effects. The splitting of the cup tablets were only significantly influenced by the depth of the cup tablet and the hardness of the cup tablets. Core-in-cup tablets containing 5% w/w HPMC K4M in ibuprofen as the core, 4 mm final cup depth, 15% carnauba wax in ethylcellulose as the cup, and compressed to a cup hardness of approx. 100 N/m^2 and final core-in-cup hardness of approx. 160 N/m^2, released ibuprofen at zero-order rate of release for up to 18 h.

Keywords: Factorial design; Adjustable punch; Zero-order release; Core-in-cup system; Ibuprofen; Carnauba wax; Ethylcellulose; Friability; Tabletting

1. Introduction

Due to the shape of an average tablet (biconvex or disc), it is theoretically improbable for these tablets to release active drugs from it at a zero-order rate. This is because as the system erodes (which is the case with most polymers) the surface area exposed to the dissolution fluid constantly decreases or the diffusion path of the drug (with water-soluble drugs) increases in length. Whether the matrix releases drug via swelling control or erosion (or both), it is almost impossible to achieve a zero-order release (Langer, 1980). Most of these matrix-type tablets release drug according to the Higuchi (1962, 1963) square root

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of time kinetics (Lapidus and Lordi, 1968; Rhine et al., 1980; Hsieh et al., 1983; Ford et al., 1987).

A likely means of modifying the release kinetics from matrix systems is to alter the geometry of the matrix. Danckwerts (1994) has reported a method that describes the production of an active sustained-release disc-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 single stable eroding surface of constant surface area. 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 the grade of hydroxypropylmethylcellulose (HPMC) polymer used (or any other hydrophillic polymer or mixture of polymers that erodes constantly with time), the quantity of HPMC polymer used, and 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. The time of constant release varied from approx. 8 h for a 5% w/w HPMC K4M in caffeine core-in-cup tablets, to approx. 23 h for the 15% w/w HPMC K15M in ibuprofen core-in-cup tablets. Each set of punches used to produce the cup portion of the tablet, however, would have to be specific for each core-in-cup tablet, as it is the diameter and depth of the cup indentation that determine the amount of drug and polymer to be included in the tablets. In order to be able to produce cup tablets that have the ability to be adjusted for various core tablet thicknesses (which change in thickness according to the types of adjuvants used as well as the amounts of drug and adjuvants used) we have created a punch that can adjust the depth of the inert cup coating of the core-in-cup tablet. Fig. 1 graphically describes this new punch.

By adjusting the protrusion distance of the inner central bolt, the depth of the resultant cup tablets can be adjusted to accommodate cores of different hardness and mass. Fig. 2 graphically illustrates this resultant core-in-cup tablet in section.

The purpose of this study was to test the resultant effectiveness of the cup tablets of various depths as cups for core-in-cup tablets as well as test the most suitable formulation for release rates. Of course, as the depth of the cup tablet is increased, it becomes more and more fragile and there is a limit to its depth. A measure of the ability of a tablet to withstand impact, as would be required in the production of the core-in-cup tablets, is its friability. The main factors that impact on the friability of these ethylcellulose and carnauba wax cup tablets include, the depth of the cup, the amount of binder in the cup, and its hardness. Since HPMC swells when it comes into contact with an aqueous environment, it could swell to such an extent that it could cause

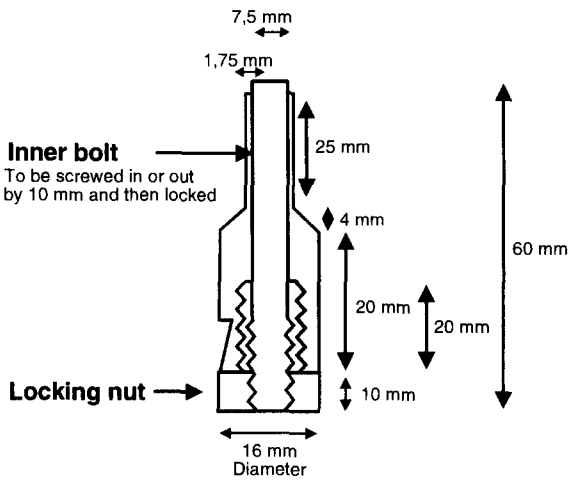

Fig. 1. Schematic diagram of new adjustable cup tablet punch for production of core-in-cup tablets.

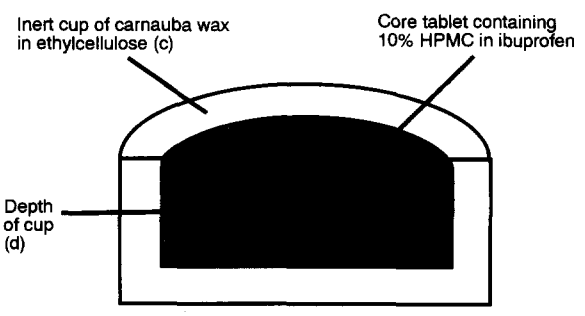

Fig. 2. Schematic diagram of the core-in-cup tablet shown in section.

the cup to be split. Accordingly, the different cup formulations were tested for their ability to resist splitting in aqueous dissolution medium or not. Therefore, it was decided to examine these three factors at three different levels to ascertain their effect on the friability and splitting open of the cup tablets. This study then results in a 3^3 factorial design. The dependencies were explained using analysis of variance and multiple regression analysis.

2. Materials and methods

2.1. Materials

HPMC K4M premium EP was supplied by Colorcon Ltd, UK. HPMC K4M has a viscosity of 3500–5600 cP as a 2% solution in water at 20° C. The HPMC had already been screened through a no. 40 standard US sieve.

Ibuprofen (Boots Co., S.A. Pty Ltd) was ground and the fraction passing through a no. 150 standard UK sieve was used.

Ethylcellulose (Riedel de Haën) and Carnauba wax (Sigma) were used as supplied. All other reagents used were standard laboratory grade.

2.2. Study design

The study followed a 3^3 factorial experimental design. The amount of carnauba wax in the cup (c), hardness of the cup (h) and cup indent depth (d) were used as independent variables. The normalized factor levels of the independent variables are presented in Table 1. In the 2^3 factorial points the cup tablets were made in duplicate batches and in the centre point in quadruplicate batches. Therefore, the total number of runs was 38. Friability of the cup tablet and splitting of the cup in the final core-in-cup tablet were the dependent variables. This design has also been used with success by Merkku et al. (1994) to determine the influence of granulation and compression process variables on the flow rate of granules and on tablet properties.

Table 1
Levels of independent variables

Variable	Factor level			Units
	−1	0	1	
Amount of carnauba wax in cup (c)	5	10	15	% w/w
Hardness of compressed cup (h)	50	75	100	N/m^2
Depth of the cup (d)	2	4	6	mm

2.3. Formulations

Cup tablets of various depths and amounts of carnauba wax in ethylcellulose were compressed in a Manesty F3 tabletting press. The hardness of the cup tablets were then measured on a Pharma Test PTB 311 hardness tester. The press was then adjusted to produce cup tablets of approximate hardness of 50, 75, and 100 N/m^2. Table 2 lists the crushing strength values of the cup tablets for the different runs tested in the study.

The ethylcellulose and the carnauba wax were thoroughly mixed and directly compressed into cup tablets by means of adjusting the protrusion of the inner bolt of the adjustable punch to the various depths tested so that it produced a cup-shaped tablet of 11 mm outer diameter, and an inner hollow core of 7.5 mm diameter. The bottom punch consisted of a flat round 11 mm diameter punch.

Production of core-in-cup tablets for release rate analysis, containing 5% w/w HPMC K4M in ibuprofen as the core, 4 mm final cup depth, containing 15% carnauba wax in ethylcellulose as the cup, and compressed to a cup hardness of approx. 100 N/m^2 and final core-in-cup hardness of approx. 160 N/m^2, were produced as described previously by Danckwerts (1994).

2.4. Measurement of friability

The friability of the cup tablets was measured on a Roche Friabilator (Hoffman la Roche, Basel). After weighing, 10 cup tablets from each run were rotated for 20 min and then re-weighed

to test for percentage loss of weight due to abrasion and fracture.

2.5. Measurement of cup splitting

The core-in-cup tablets were made by compressing the different cup tablets together with cores containing 15% w/w HPMC K4M in ibuprofen. Core tablets of approx. 100 N/m^2 of 2, 4 and 6 mm thickness to match the depth of the cup tablets were produced. Core-in-cup tablets were then compressed to 1, 3 and 4 mm for the 2, 4 and 6 mm cup tablets, respectively, to be tested for splitting. The core-in-cup tablets were placed in the dissolution apparatus as described below, and physically inspected for any splitting of the cup after 60 min. If any splitting of the cup tablets occurred it would occur before 60 min after being immersed in distilled water at 37° C and agitated at 70 rpm. The cup tablets

Table 2
Friability and splitting of cup tablets (c, % carnauba wax; h, hardness; d, depth of cup)

Run	c	h	d	Mean crushing strength (N/m^2) ± SD ($n = 3$)	Friability	Splitting
1_a	−1	−1	−1	53.17 ± 3.71	0.19	−1
1_b	−1	−1	−1	45.99 ± 3.79	0.51	−1
2	−1	−1	0	51.84 ± 1.67	1.06	1
3_a	−1	−1	1	63.07 ± 5.06	3.32	1
3_b	−1	−1	1	52.82 ± 4.92	2.80	1
4	−1	0	−1	72.97 ± 2.89	0.14	−1
5	−1	0	0	78.37 ± 3.72	0.48	1
6	−1	0	1	74.15 ± 6.55	1.32	1
7_a	−1	1	−1	98.16 ± 5.32	0.00	−1
7_b	−1	1	−1	106.39 ± 6.66	0.21	−1
8	−1	1	0	98.81 ± 7.43	0.18	1
9_a	−1	1	1	92.53 ± 3.73	0.67	1
9_b	−1	1	1	99.16 ± 6.06	0.41	1
10	0	−1	−1	56.91 ± 5.13	0.13	−1
11	0	−1	0	54.58 ± 5.85	0.40	1
12	0	−1	1	50.57 ± 7.03	1.13	1
13	0	0	−1	71.03 ± 7.36	0.07	−1
14_a	0	0	0	72.06 ± 3.43	0.44	1
14_b	0	0	0	78.15 ± 6.24	0.09	1
14_c	0	0	0	75.76 ± 8.47	0.26	1
14_d	0	0	0	70.19 ± 4.85	0.31	1
15	0	0	1	75.07 ± 2.88	0.64	1
16	0	1	−1	98.11 ± 6.71	0.03	−1
17	0	1	0	101.65 ± 7.83	0.06	−1
18	0	1	1	96.92 ± 8.00	0.28	−1
19_a	1	−1	−1	48.90 ± 5.89	0.04	−1
19_b	1	−1	−1	50.67 ± 7.27	0.04	−1
20	1	−1	0	56.76 ± 4.16	0.31	1
21_a	1	−1	1	48.75 ± 4.20	0.47	1
21_b	1	−1	1	55.74 ± 5.85	0.77	1
22	1	0	−1	74.99 ± 8.34	0.01	−1
23	1	0	0	69.30 ± 2.80	0.12	−1
24	1	0	1	78.49 ± 6.22	1.32	1
25_a	1	1	−1	96.24 ± 6.91	0.00	−1
25_b	1	1	−1	97.79 ± 9.37	0.00	−1
26	1	1	0	102.13 ± 5.56	0.00	−1
27_a	1	1	1	95.53 ± 7.96	0.01	1
27_b	1	1	1	103.55 ± 3.68	0.05	−1

were qualitatively adjudged to be split or not split.

2.6. Release studies

The BP 1988 paddle method dissolution apparatus was utilised in all the release studies. A volume of 1000 ml of deionized water, equilibrated at $37 \pm 0.5°$ C, was used as the release medium. All experiments were carried out at 70 rpm. The release rates of the tablets were monitored using a six-beaker Caleva model 7ST dissolution tester. At appropriate time intervals 2.0 ml samples were withdrawn for analysis, 2 ml methanol was added, mixed on a vortex mixer, and analyzed spectrophotometrically at a wavelength of 216 nm using a Beckman DU 650 spectrophotometer. Linearity was established for 50% v/v methanol in deionized water ibuprofen solutions in the range of 6.25–200 μg/ml. The release profiles of a minimum of three tablets from each of three different batches ($n = 9$) were analyzed.

2.7. Statistical analysis

Analysis of variance was performed on the data presented in Table 3 using STATGRAPHICS v. 5 (Statistical Graphics Corp., USA). The independent variables were percentage carnauba wax in the cup tablet, depth of the cup tablet, and hardness of the cup tablet, while the dependent variables were friability of the cup tablet and splitting of cup tablet in aqueous medium. 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 calculated. Simple regression models for the three indepen-

Table 3
Relevant statistical parameters

Source effect	Estimated effects ± SE (28 d.f.)	p value	Regression coefficients	Regression coefficients re-estimated
Friability				
Average	0.202 ± 0.096			
Constant			1.375	−0.271
c	−0.713 ± 0.101	< 0.0001	−0.198	−0.095
h	−0.713 ± 0.101	< 0.0001	−0.029	−0.008
d	0.823 ± 0.101	< 0.0001	0.689	0.989
ch	0.483 ± 0.115	< 0.0005	0.002	0.002
cd	−0.606 ± 0.115	< 0.0001	−0.030	−0.030
hd	−0.640 ± 0.115	< 0.0001	−0.006	−0.006
cc	0.257 ± 0.192	0.1908	0.005	
hh	0.174 ± 0.192	0.3824	0.000	
dd	0.300 ± 0.192	0.1284	0.037	
Splitting				
Average	0.600 ± 0.217			
Constant			−7.041	−2.885
c	−0.462 ± 0.229	0.0543	0.061	
h	−0.615 ± 0.229	0.0122	0.084	−0.012
d	1.692 ± 0.229	< 0.0001	2.023	1.731
ch	−0.400 ± 0.262	0.1380	−0.002	
cd	−0.200 ± 0.262	0.4596	−0.010	
hd	−0.400 ± 0.262	0.1380	−0.004	
cc	0.133 ± 0.434	0.7644	0.003	
hh	−0.533 ± 0.434	0.2297	−0.000	
dd	−1.200 ± 0.434	0.0100	−0.150	−0.163

dent variables were also developed from the results as follows:

$$Y_1(c,h,d) = a_0 + a_1c + a_2h + a_3d + a_4ch + a_5cd + a_6hd + a_7c^2 + a_8h^2 + a_9d^2a_{10}chd \quad (1)$$

where $a_0,...,a_{10}$ are the coefficients of the system. c, h and d denote the percentage carnauba wax in the cup tablet, hardness of the cup tablet and depth of the cup tablet, respectively.

Each term in the final regression equation for the friability or the splitting 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 re-estimated. All statistical analysis

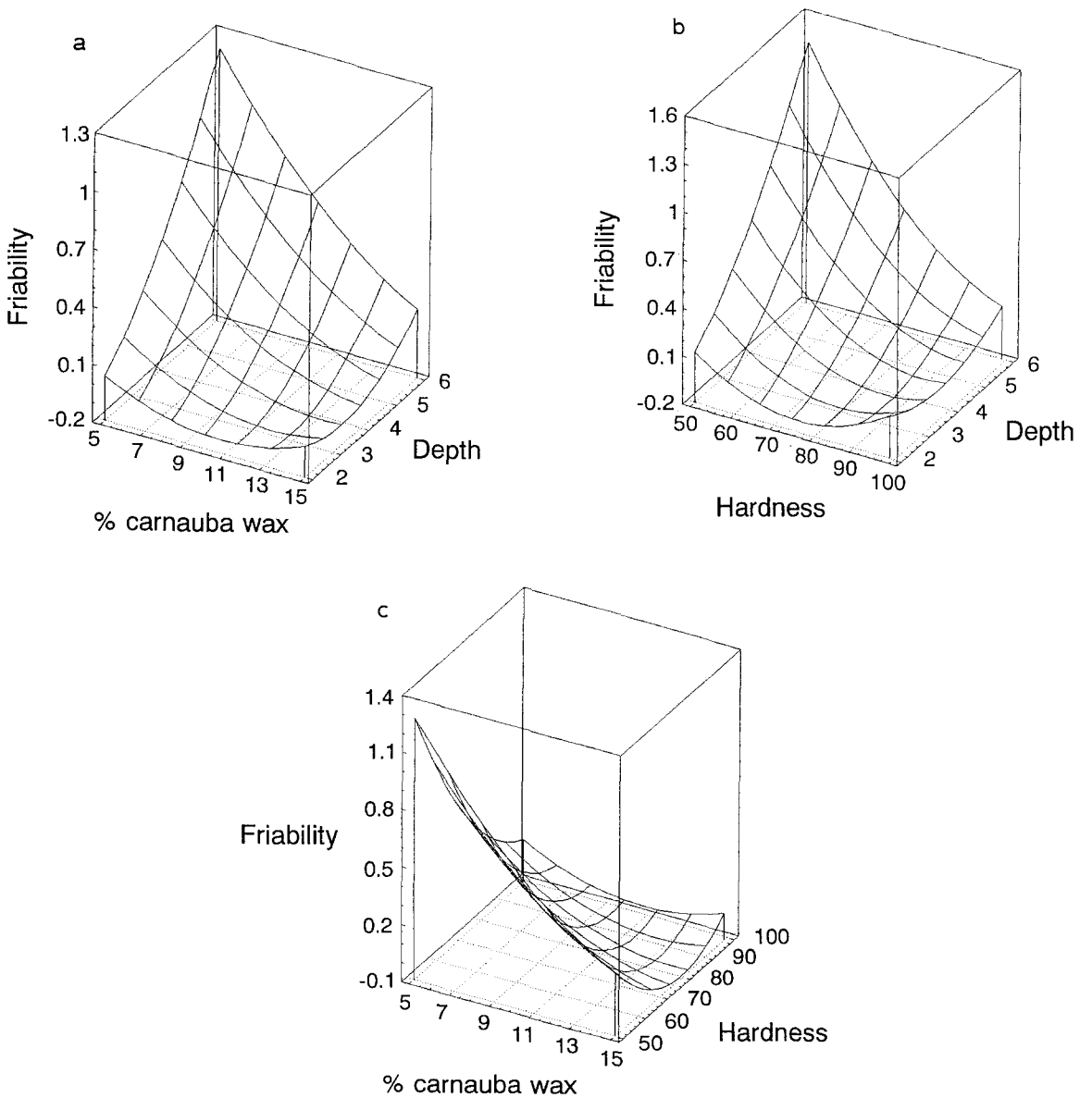

Fig. 3. (a–c) Response surface plots of the estimated effects of c, h and d on the friability of the tablet cups.

was performed using STATGRAPHICS v. 5 (Statistical Graphics Corp., USA).

3. Results and discussion

Table 3 lists the relevant statistical parameters calculated from the results of this study for the effect of the three independent variables on the friability and splitting of the cup tablets analyzed. All statistical analysis was carried out on all the experimental runs (total 38).

3.1. Friability

Fig. 3a–c are response surface plots of the estimated effects of the percentage carnauba wax, hardness and depth of cup tablet on the friability

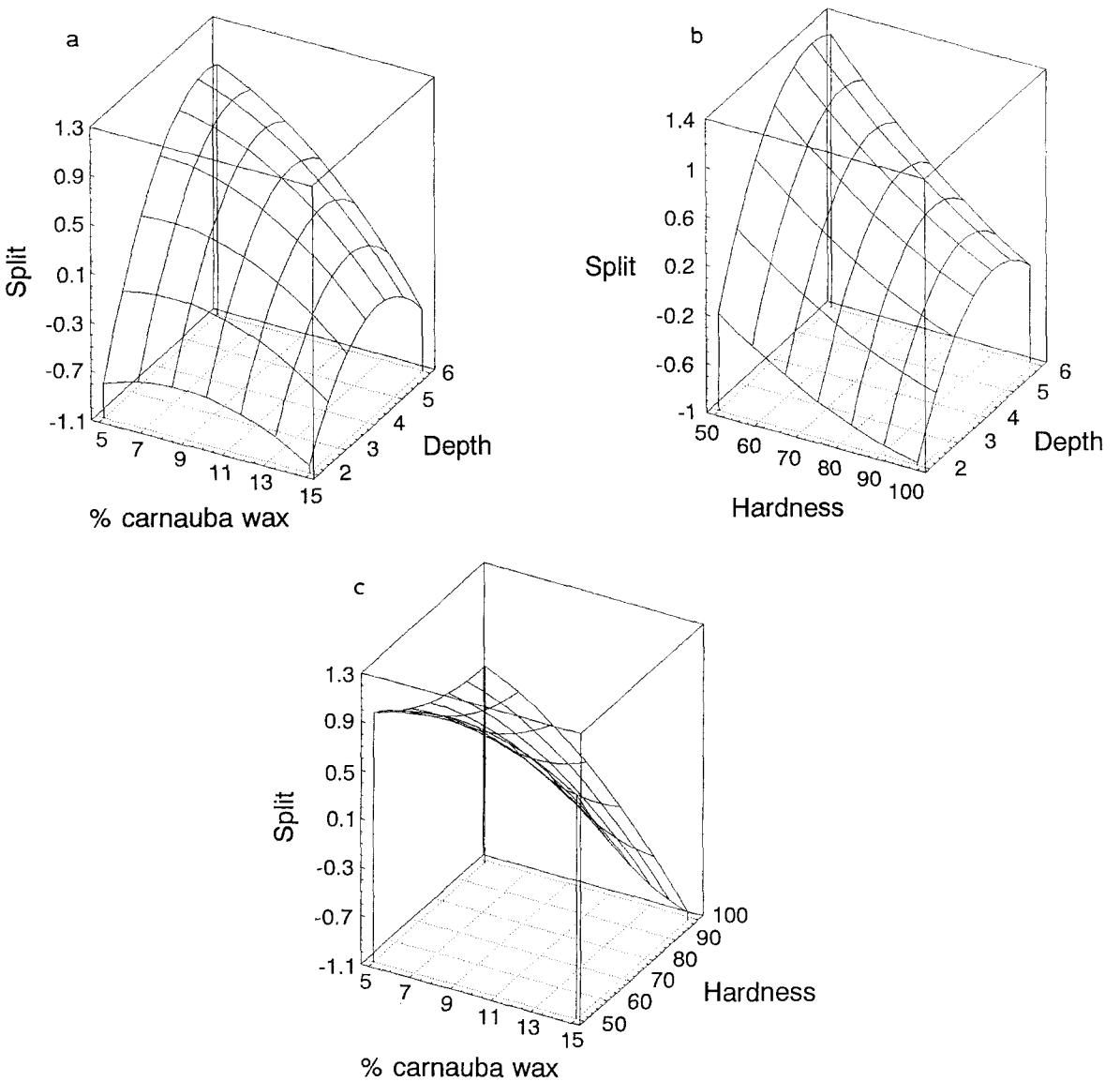

Fig. 4. (a–c) Response surface plots of the estimated effects of the c, h and d on the splitting of the cups in the core-in-cup tablets placed in an aqueous dissolution medium.

of the tablet cups. The plots have been drawn on the basis of the model by assigning a constant value to one of the variables. All three variables play a significant role in the resultant friability of the cup tablets. Depth of the cup tablet has the most significant influence on its friability (Fig. 3a and b). This is particularly more pronounced at lower levels of carnauba wax (Fig. 3a). As the percentage carnauba wax increases in the formulations the cup tablets have an increased ability to withstand the increase in friability as the depth of the cup increases. There is a similar ability of the cup tablet to withstand increased friability with an increase in depth, as the hardness of the tablet is increased (Fig. 3b). This similarity in effect on the friability is demonstrated from the estimated main effects of -0.713 for both c and h as well as the interaction effects of -0.606 and -0.640 for cd and hd, respectively.

As the percentage of carnauba wax in the cup tablets increases the friability of the cup tablets decreases (Fig. 3c). Since the carnauba wax acts as a binder for the ethylcellulose this effect is expected. This binding efficiency is at its maximum when the compression force is increased, and the difference in the friability at the higher compression force (equivalent to a hardness of ± 100 N/m^2) is less pronounced than that at the lower compression force (equivalent to a hardness of ± 50 N/m^2).

In developing a regression model for the effect of the independent variables on the friability dependent variable, the main effects as well as the second-order interaction effects were significant ($p < 0.05$). Therefore, the regression coefficients for these effects were included in the model. The rest of the coefficients were eliminated and the model was re-estimated by STATGRAPHICS.

$$Y_f(c,h,d) = -0.271 - 0.095c - 0.008h + 0.989d + 0.002ch - 0.030cd - 0.006hd \quad (2)$$

where Y_f (c,h,d) is the estimated friability of the cup tablets.

The squared multiple regression coefficient for this model was 0.90. This model shows that depth of the cup tablet has the major adverse effect on the friability of the cup tablet. As the depth increases the friability increases. The percentage carnauba wax then produces the next most significant effect on the friability. Carnauba wax and hardness of the cup tablet both decrease the friability of the cup tablet. Clearly, in order to produce a cup tablet with minimal friability the compression force (tablet hardness) and percentage carnauba wax must be maximised, and the depth of the cup should be minimised. However, it should be noted that the friability of the cup only really becomes a problem when the percentage loss after 20 min in the friabilator becomes larger than 4%. None of the formulations in this study exceeded this value.

3.2. Splitting

Fig. 4a–c are response surface plots of the estimated effects of the percentage carnauba wax, hardness and depth of cup tablet, on the splitting of the cups in the core-in-cup tablets placed in an aqueous dissolution medium. Those tablets that split in aqueous dissolution medium were assigned a value of -1.0 and those that remained intact (not split) were assigned a value of 1.0. Only the hardness and depth of the cup tablets play a significant part in the resultant splitting of the cup tablets. As with the friability, depth of the cup tablet has the most significant influence on its splitting in aqueous solution. (Fig. 4a and b). The response surfaces are reasonably stable over the ranges of hardness and percentage carnauba wax. There is a very slight decrease in the tendency to split as the percentage carnauba wax increases from 5 to 10%. However, as the percentage carnauba wax increases from 10 to 15% there is a slight tendency for the cup tablets to split at low hardness. This is made evident from the significant dd interaction. As the hardness of the cup tablet increases, there is a slight decrease in the tendency to split which is more pronounced at increased depths. The ability to split in aqueous medium, however, decreases in a linear fashion as the hardness of the cup is increased (Fig. 4c).

In developing a regression model for the effect of the independent variables on the splitting in

aqueous medium dependent variable, only depth and hardness main effects, as well as the second-order *dd* interaction effect, were significant ($p < 0.05$). Only these regression coefficients were therefore included in the model. The rest of the coefficients were eliminated and the model was re-estimated by STATGRAPHICS.

$$Y_s(h,d) = -2.885 - 0.012h + 1.731d - 0.163dd \quad (3)$$

where Y_s (h,d) is the estimated friability of the cup tablets.

The squared multiple regression coefficient for this model was 0.75. This model shows that the depth of the cup tablet has the principal adverse effect on the splitting of the tablet. As the depth increases the splitting in aqueous dissolution medium increases. The hardness of the cup tablet produces the next most significant effect on the friability. This effect, however, is much less significant as compared to the depth of the cup tablet. Nevertheless, it does decrease the ability of the cup tablet to split in aqueous medium. In general, splitting of the cup tablets at depths of 6 mm is a problem and will have to be investigated further. The problem of the splitting lies with the swelling of the HPMC polymer in aqueous solution.

3.3. Release rate

Fig. 5 plots the rate of release of ibuprofen from core-in-cup tablets containing 5% w/w HPMC K4M in ibuprofen as the core, 4 mm final cup depth, 15% carnauba wax in ethylcellulose as the cup, and compressed to a cup hardness of approx. 100 N/m^2 and final core-in-cup hardness of approx. 160 N/m^2.

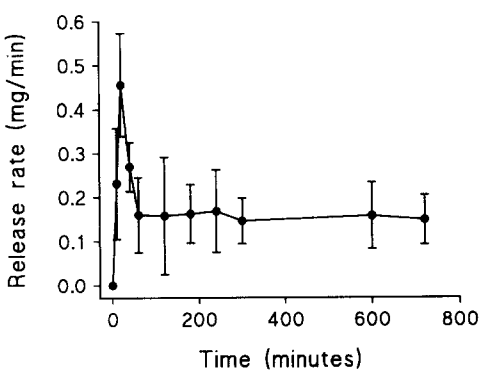

Fig. 5. Ibuprofen release rates from core-in-cup tablets.

The core-in-cup system releases the ibuprofen a near zero-order rate of 0.156 mg/min. This rate was calculated from the slope of the plot of cumulative concentration vs time from 60 to 720 min. The correlation coefficient for this plot was 0.99993. To check whether the rate of release was first order or according to the 'square root of time', plots of log of cumulative concentration vs time, and cumulative concentration vs square root of time, were plotted, respectively. The correlation coefficients for these were 0.98284 and 0.92070, respectively. Therefore, a zero-order rate of release best describes the release rate from the ibuprofen core-in-cup system. Extrapolating the zero-order rate of release of 0.156 mg/min. the core-in-cup system can release drug for up to 18 h. This is too long for an average oral system as gastrointestinal transit time is not much longer than 12 h on average. Polymers that erode at a quicker rate need to be (and will be) investigated to design a system that releases drugs from the core-in-cup system at a zero-order rate for a shorter time.

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