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Different geometric shaped hydrogel theophylline tablets: statistical approach for estimating drug release

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Abstract

The objective of this study was to develop a mathematical equation for the calculation of drug release from different shaped matrix tablets. By this way, release rate related to the geometric shape could be predicted with the help of the developed mathematical equation. So, drug release could be estimated before the dissolution. Hydroxypropylmethylcellulose (HPMC) E_{50} as polymer and theophylline as active substance were used in the matrix tablets prepared for this purpose. Matrix tablets in three different geometrical shapes, namely in triangular, cylindrical and half-spherical forms were prepared by using two different drug–polymer ratio (1:0.5, 1:1) and diluent's in three different percentages (0, 20, 40%). Using rotating paddle and basket methods reported in USP XXIII carried out the release rate studies of these tablets. The Higuchi square-root time model best described the dissolution data. Differential scanning calorimetry (DSC) analysis was performed to identify any solid-state inactivation of the drug. The practical benefit of this work is to improve mathematical equation that can be used to predict accurately the required composition and in order to achieve the desired release profiles of different geometric shaped tablets. By using this equation new pharmaceutical products can be easily improved.

Keywords: Theophylline; HPMC; Geometric shaped matrix tablets; Analysis of covariance; Mathematical equation

1. Introduction

Drug release from dosage forms is known to be related to the used drug–polymer rate and polymer features. Among the various types of cellulose ether derivatives, HPMC polymers are popular in controlled release matrices due to their compatibility with numerous drugs [1–3]. HPMC offers the advantage that, although wet massing may be used to conventionally granulate the material [4,5], direct compression of the drug blended drug with HPMC is easily accomplished [6–8]. It would, however, be of benefit to have mathematical principles by which to formulate drugs with HPMC [7–11]. The adjustment of the polymer concentration and the viscosity grade and the addition of different types and levels of excipients in the HPMC matrix can modify the drug release rate [1,2,11]. In general, these formulations and processing factors such as pressure, density, particle size, pH, diluents affect the drug release profiles both kinetically and mechanistically [1,2,6,7,12,13].

How drug release has been affected by the geometric form of the dosage has always attracted the attention of the researcher and for this reason, some attempts were made to regulate the dissolution behaviour of drug matrices by controlling their geometry as spherical, cylindrical, holed cylindrical, planar, biconvex, square, clover leaf, hemisphere and cross shaped devices [1,12,14–20]. Drug release from surface-eroding devices with various geometries was firstly analyzed by Hopfenberg and a general mathematical equation was developed describing drug release from slabs, spheres and infinite cylinders [21]. Katzhendler et al. [9] described a situation where the erosion rates of the tablet are different in radial and axial directions. We calculated the shape factors of the triangular, cylindrical and half spherical tablets as 4, 2 and 1.5 respectively, using Katzhendler equation [22].

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In this study, changing the polymer–drug ratio, the percentage of diluent and the dissolution method in the cylindrical, triangular and half-spherical shaped tablets by using $3 \times 2 \times 3 \times 2$ experimental design it was observed statistically how the release profile of theophylline has changed. In order to show the effects of the geometric shape, drug–polymer ratio, percentages of diluent and dissolution method on the release rate of the active substance, analysis of covariance (ANCOVA) have been carried out with only one concomitant variable which was the square root of time. At the end of our study a new mathematical equation has been developed to describe drug release from HPMC based different geometric shaped pharmaceutical systems. In addition, the validity of this equation under various experimental conditions (e.g. vs. geometric shape, drug–polymer ratio, percentages of diluent and dissolution method) was investigated. So, drug release could be estimated before the dissolution.

2. Experimental

2.1. Materials

The following chemicals were obtained from commercial suppliers and used as received, theophylline (Dolder Ltd., Switzerland), hydroxypropylmethylcellulose (HPMC E_{50}) (Colorcon, UK), dibasic calcium phosphate (Merck, Germany), and magnesium stearate (Merck, Germany). All other reagents were of analytical grade.

2.2. Methods

2.2.1. Experimental design

2.2.1.1. Preparation of tablets. In the preparation of matrix tablets, experimental design was used for both different factors and levels. All tablets contain 300 mg theophylline, and magnesium stearate constitutes 0.1% of the final tablet weight as a lubricant. The effects of the following variations in tablet formulae on dissolution rates were examined.

a) Geometric shape of tablet: three different geometrical shapes (triangular, cylindrical and half spherical) have been used as tablet shapes.
b) Polymer ratio: in formulation prepared with HPMC E_{50} two different drug–polymer ratios (1:0.5, 1:1) have been used.
c) Percentages of diluent: each tablet has contained three different percentages of dibasic calcium phosphate as a diluent (0, 20, 40% on the polymer and drug mixture).
d) Dissolution testing: dissolution tests were performed in triplicate by using a USP dissolution apparatus I (basket at 100 rpm) and II (paddle at 50 rpm) in 900 ml of purified water. The amount of drug released was determined using a Shimadzu (UV–160A) spectrophotometer at 272 nm concomitantly with the matrix swelling observation. The average obtained from three tablets was used to determine the release profiles. The release profiles of the prepared tablets have been interpreted according to both the target profile of theophylline [22] and the criteria suggested by Parab et al. [23] for theophylline tablets.

In the experimental design ($3 \times 2 \times 3 \times 2$) performed by using different factors and levels, in order to show the effects of these factors (geometric shape, drug–polymer ratio, percentages of diluent and dissolution method) on the release rate of the active substance was carried out by ANCOVA with only one concomitant (covariate; $\sqrt{t}$) using SPSS 10.0.

2.2.1.2. Tableting. Three different tablet molds were prepared for the compression of the tablets. These molds were made of stainless steel and have been subjected to process of hardening. These tablets were pressed under the pressure of 5 tons force for 10 s under a hydraulic press (Perkin–Elmer) by direct compressing method.

These tablets were compressed by using triangular, cylindrical and half-spherical tablet shaped molds [22]. The dimensions of the tablets were measured prior to dissolution studies using a screw-gauge micrometer and used to calculate total surface area (A) of the tablets.

2.2.2. Release kinetics

For theoretical analysis; (1) zero-order kinetics, (2) first-order kinetics, (3) Hixson Crowell's cube-root equation, (4) Higuchi's square root of time equation were used and Higuchi rate constants (k) were calculated.

2.2.3. Differential scanning calorimetry (DSC)

In order to search possible interaction between theophylline and polymeric material of the tablets, differential scanning calorimetry (DSC) analysis was carried out on pure substances, their physical mixtures and final matrix systems before dissolution studies. So, DSC (92-France) analysis was carried out with 20 mg of sample. Hydrogel matrix formulations were scanned in aluminium pans from 25 to 300 °C at a rate of 5 °C per min^{-1} in air. The phase transition range was determined. The measurements were performed in triplicate.

Table 1
Confidence interval space values obtained as the result of releasing rate studies for geometric shaped tablets and the comparison of these values with the Parab's standard

Tablet shape and drug: polymer ratio	Dissolution apparatus	Time	Released (%)	SD	Confidence interval 95%	Standard [a]	Suitability
Triangular 1:1 40%	II	2	30	0.458	28.862–31.138*	25–40	+
		4	53.3	1.044	50.706–55.893*	40–60	
		8	85.9	0.794	83.928–87.872*	70–90	
	I	2	28.5	0.458	27.362–29.638*	25–40	
		4	51.5	0.458	50.362–52.638*	40–60	
		8	88.7	0.529	87.385–89.999*	70–90	
Cylindrical 1:1 40%	II	2	21.1	0.361	20.204–21.996	25–40	–
		4	38.9	0.7	37.161–40.639	40–60	
		8	66.4	0.436	65.317–67.483	70–90	
	I	2	23.2	0.656	21.571–24.829	25–40	
		4	41.0	0.2	40.503–41.497*	40–60	
		8	67.9	1.249	64.797–71.003	70–90	
Spherical cup 1:1 40%	II	2	24	0.656	22.371–25.626	25–40	–
		4	40.3	0.458	39.162–41.438	40–60	
		8	68.4	0.3	67.655–69.145	70–90	
	I	2	25.6	0.917	23.323–27.877	25–40	
		4	51.8	1.153	48.935–54.665	40–60	
		8	81.1	0.436	80.017–82.183*	70–90	

*$P > 0.05$.
[a] Standards of Parab et al. [23].

3. Results and discussion

The dissolution studies of hydrogel matrix tablets prepared in different geometrical shapes and formulations have been carried out according to both rotating paddle and rotating basket methods. Confidence interval calculated for percent releases obtained in all formulations and percent release values suggested by Parab et al. [23] for theophylline matrix tablets have been compared with each other (Table 1). When the percentages of the release rates obtained by two different dissolution methods have been compared with those suggested by Parab et al., only the triangular tablet containing a drug–polymer ratio of 1:1 and 40% diluent (0.841 ± 0.01) provided to be suitable. And besides, it has shown a release profile similar to the target profile of theophylline as shown in Fig. 1a and b.

The cumulative amount dissolved versus time data was evaluated by a computer program for the goodness of fit for these four kinetic equations. The dissolution of all tablets followed square root of time dependency (Table 2). Dissolution rates were determined by linear regression of the Higuchi square root of time data. The theophylline profiles were linear for the time period 4–22 $min^{1/2}$, but thereafter showed positive deviations. Positive deviations from Higuchi equation might be due to the air entrapped in the matrix and for hydrophilic matrices also due to the erosion of gel layer [24]. Moreover, Cobby et al. [25] showed that the differences in rates of release were also related to the shape factors.

The correlation coefficients and the Higuchi rate constants (k) of all formulations were summarized in Table 2. When k rate constants of different geometric shapes possessing the same formulation have been studied, it has been observed that k rate constants have been changing related to the geometrical shape. In addition, the order of the release rate of the active substance has been determined to be the highest in triangular, cylindrical and half-spherical tablets, respectively. Furthermore, rate constants (k) observed by using rotating basket method have been found to be higher than the ones observed by using rotating paddle method. It was observed that the release rate of the drug from the same formulation prepared with different geometric shape depends on the geometric shape of the tablets.

Formulation of matrix tablets may require the addition of excipients to alter the size of the tablet or to modify drug release rate [1,11]. It was decided to study the release pattern incorporating dibasic calcium phosphate into the hydrogel matrix because of release profiles approximate to target profiles. After this, release rate of hydrogel matrix tablets prepared with HPMC E_{50} contained 0, 20, 40% diluent with two different drug–polymer ratios and three different geometrical shapes were determined using rotating basket and paddle methods. When the HPMC and dibasic calcium phosphate contents increased, normally the area of the tablets increased but the release rate constants decreased. It is observed from Table 2 that Higuchi rate constants (k) decrease as the percentage of the diluent increases in tablets. It was declared that the negative effect on dissolution of increasing the ratio of dibasic calcium phosphate in a system containing an 'insoluble'

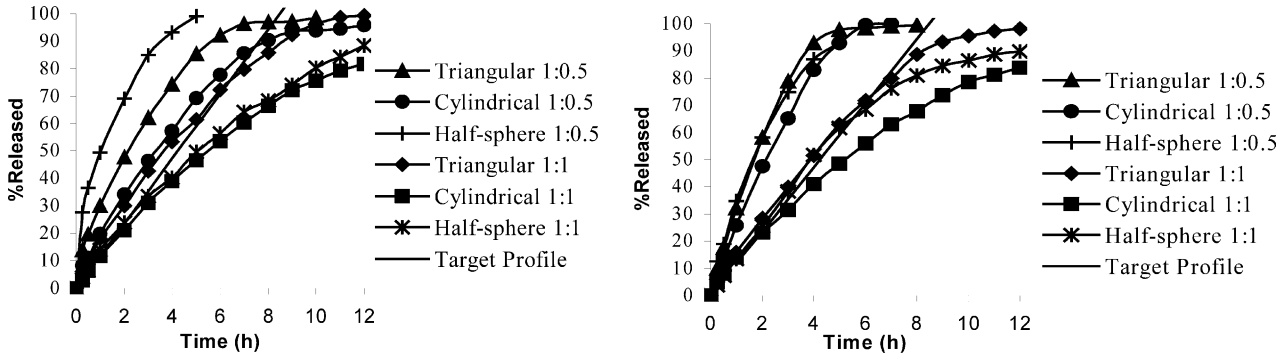

Fig. 1. Theophylline release from different geometrical shaped hydrogel matrix tablets at (a) USP apparatus II and (b) USP apparatus I.

drugs [26]. In our study the amount released decreased as the ratio of dibasic calcium phosphate increased, so our findings agree with literature.

Table 2 summarizes, the influences tablet shape on the $\sqrt{}$time release rates of theophylline hydrogel tablets compressed to the same weight and formula. It has been observed that, the release rate of the theophylline prepared in the different shapes but possessing the same formulations depends on the geometric shape of the tablets. In the Fig. 2, the erosion of hydrogel theophylline matrix tablets (1:1 drug–polymer ratio and 40% diluent) in the course of time has been shown according to USP Apparatus II. Time dependent erosion of the different geometrical shaped matrix tablets compressed to the same weight; same pressure and the same formula (1:1 drug–polymer ratio and 40% diluent) have been screened on the screw-gauge micrometer. Thus, it is understood that the drug release from different geometrical shaped tablets is related to erosion, because the surface areas of the tablets change and the dimensions of the tablets get smaller.

The results of ANCOVA were given in Table 3. As it was obtained from ANCOVA results, main effects of each factor and their interactions were also found significant ($P < 0.05$) except for geometric shape and percentages of diluent interactions (Table 3, (a) × (b) $P = 0.174$). Thus, geometrical shape (a), polymer ratio (b), percentages of diluent (c) and also dissolution methods (d) have been found important factors affecting the release rate of active substance.

Using the variables as versus geometric shape, drug–polymer ratio, percentages of diluent, dissolution method and the square root of time put a multiple regression equation forward. According to Eq. (1),

Table 2
Release rate constants ($min^{-1/2}$) and surface areas (cm^2) of triangular, cylindrical and half spherical tablets

Formulation	Dissolution methods				Surface area (A)
	Apparatus II		Apparatus I		
	k mean ± SD	r^2	k mean ± SD	r^2	
Triangular	6.350 ± 0.12	0.985	7.220 ± 0.66	0.968	3.61
	5.403 ± 0.94	0.968	6.723 ± 0.65	0.966	3.93
	5.352 ± 0.58	0.967	5.843 ± 0.87	0.982	4.07
	4.992 ± 0.34	0.984	5.605 ± 0.28	0.991	4.28
	4.862 ± 0.51	0.995	5.202 ± 0.16	0.979	4.48
	4.583 ± 0.38	0.993	4.697 ± 0.71	0.987	4.68
Cylindrical	6.622 ± 0.61	0.991	6.899 ± 0.58	0.979	3.63
	5.016 ± 0.58	0.982	6.720 ± 0.74	0.973	3.92
	5.055 ± 0.27	0.977	6.275 ± 0.88	0.987	4.00
	4.199 ± 0.13	0.974	5.349 ± 0.96	0.969	4.12
	4.076 ± 0.87	0.974	5.028 ± 0.11	0.968	4.32
	3.653 ± 0.46	0.975	3.694 ± 0.47	0.973	4.49
Spherical cup	6.095 ± 0.59	0.998	6.738 ± 0.21	0.969	4.05
	5.525 ± 0.63	0.969	6.365 ± 0.64	0.991	4.11
	5.135 ± 0.63	0.994	6.106 ± 0.52	0.994	4.18
	4.792 ± 0.54	0.969	4.889 ± 0.61	0.973	4.08
	4.769 ± 0.41	0.975	4.834 ± 0.16	0.969	4.25
	3.809 ± 0.12	0.976	4.793 ± 0.41	0.966	4.32

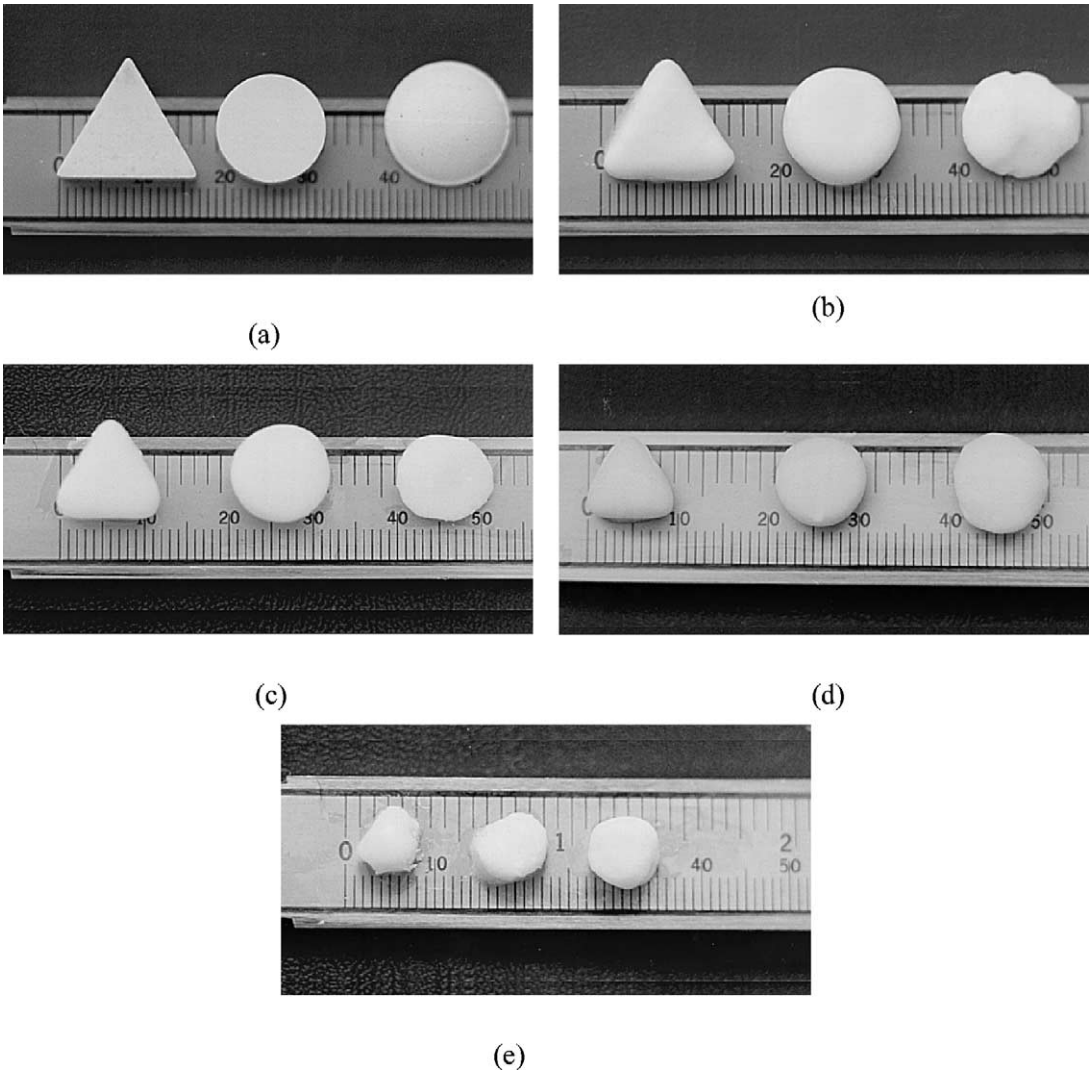

Fig. 2. The photograph of triangular, cylindrical and half-spherical hydrogel matrix tablets, before dissolution (a), taken 2 h (b), 4 h (c), 6 h (d) and 8 h (e) later from dissolution medium.

without using any graphics, by placing the variables into equation, the amount of the active substance in the dissolution medium could be calculated theoretically. Multiple regression data were given in Table 4.

The equation of the model was

$$\text{Release}\% = -54.167 + 4.436\sqrt{t} + 11.782A + 7.565B + 24.608C - 13.967D + 6.434E \quad (1)$$

where $r^2 = 0.960$; t = time (min); $A = 1$ for triangular shape, 0 for spherical cup and cylindrical shape; $B = 1$ for spherical cup shape, 0 for triangular and cylindrical shape; C = drug–polymer ratio (2 for 1:0.5 ratio; 1 for 1:1 ratio); D = diluent % (0.4 or 0.2 or 0); $E = 1$ for basket method and 0 for paddle method.

DSC thermograms indicated the qualitative composition of the drug formulations and verified the identity of each of the components by their thermal properties. DSC is also carried out to be able to understand the solid-state interaction in tablets [13]. So, interactions of polymers with theophylline investigated by DSC. In the DSC studies for the hydrogel matrix tablets, no thermal event corresponding to the melting of drug crystal was observed in Fig. 3 and Table 5. In the case of pure theophylline, a sharp endotherm peak was observed at 264 ± 3.3 °C, so there was no drug interaction or complex occurred during the manufacturing process (Fig. 3).

It is the scope of this article to review; the shape of the tablet has an effect on the release rate of active substance. For the active substance, the closest release profile to the target profile was existent in the triangular shaped tablet 1:1 drug–polymer ratio and 40% diluent. At the same time, it has been shown that predicting the drug release from polymer matrices of various shapes and various drug–polymer ratio will be capable by developed mathematical equation. On the other hand, the monitory of the dissolution results by equation will provide both a control on the process variabilities and

Table 3
The $3 \times 2 \times 3 \times 2$ ANCOVA findings of hydrogel matrix tablets prepared with HPMC E_{50} and diluent

Source	DF	SS	MS	*F*	*P*
Corrected Model	36	426207.046 [a]	11839.085	239.580	0.000
Intercept	1	10016.882	10016.882	202.705	0.000
$\sqrt{t}$ (Covariate)	1	409205.591	409205.591	8280.824	0.000
Geometric shape (a)	2	9783.450	4891.725	98.991	0.000
Polymer ratio (b)	1	64518.268	64518.268	1305.614	0.000
Diluents (%) (c)	2	1719.790	859.895	17.401	0.000
Dissolution method (d)	1	4287.464	4287.464	86.763	0.000
(a) × (b)	2	11768.780	5884.390	119.079	0.000
(a) × (c)	4	315.706	78.927	1.597	0.174
(b) × (c)	2	373.607	186.803	3.780	0.024
(a) × (b) × (c)	4	603.656	150.914	3.054	0.017
(a) × (d)	2	1225.624	612.812	12.401	0.000
(b) × (d)	1	549.247	549.247	11.115	0.001
(a) × (b) × (d)	2	297.137	148.568	3.006	0.051
(c) × (d)	2	491.322	245.661	4.971	0.007
(a) × (c) × (d)	4	510.420	127.605	2.582	0.037
(b) × (c) × (d)	2	433.193	216.592	4.383	0.013
(a) × (b) × (c) × (d)	4	1831.714	457.928	9.267	0.000
Error	390	19272.259	49.416		
Total	427	1944741.790			
Corrected total	426	445479.305			

$P < 0.05$.
[a] $r^2 = 0.960$.

Table 4
The data of multiple regression analysis [a]

Source	DF	SS	MS	*F*	*P*
Regression	6	408742.70	68123.777	778.841	0.000 [b]
Residual	420	36736.64	87.468		
Total	426	445479.30			

[a] Dependent variable: release (%).
[b] Predictors: (constant), $\sqrt{t}$, diluents (%), polymer ratio, triangular shape, spherical cup shape.

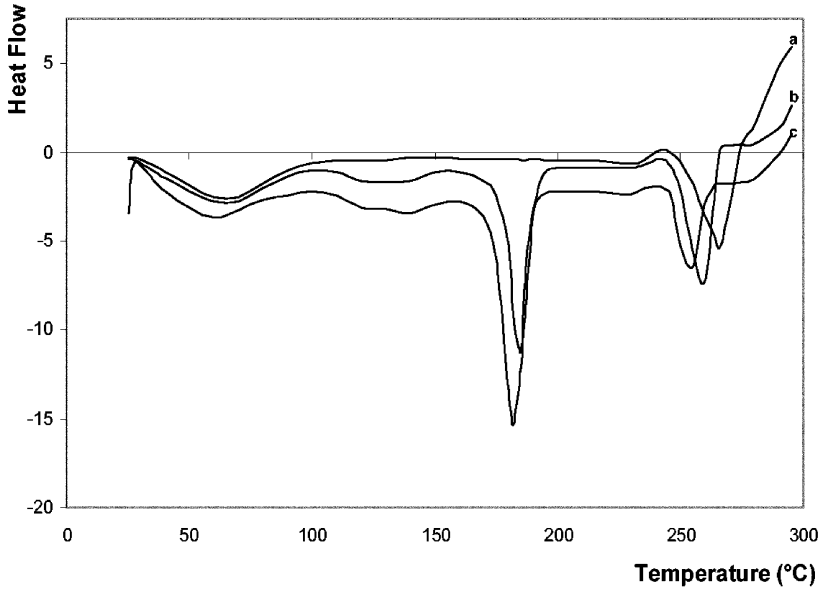

Fig. 3. DSC scans showing the melting endotherms of hydrogel matrix tablets (a, 0%; b, 20%; c, 40% dibasic calcium phosphate).

Table 5
Melting points (m.p.) of the HPMC E_{50} and dibasic calcium phosphate and theophylline obtained from differential thermal analysis of hydrogel matrix tablets

Formulation	HPMC		Dibasic calcium phosphate		Theophylline	
	m.p. (°C)	Endotherm (cal g^{-1})	m.p. (°C)	Endotherm (cal g^{-1})	m.p. (°C)	Endotherm (cal g^{-1})
1:1 0%	65.2	−9.804			268.3	−11.366
1:1 20%	62.2	−8.415	190.1	−12.722	264.0	−9.699
1:1 40%	64.3	−11.129	189.3	−20.747	261.7	−7.537

checking of the routine in vitro dissolution results using this equation provides an easiness and confidence to the investigators.

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