The butterfly effect: A physical phenomenon of hypromellose matrices during dissolution and the factors affecting its occurrence

C. Cahyadi[a], L.W. Chan[a], P. Colombo[b], P.W.S. Heng[a,*]

[a] GEA-NUS Pharmaceutical Processing Research Laboratory, Department of Pharmacy, National University of Singapore, 18 Science Drive 4, Singapore 117543, Singapore
[b] Dipartimento Farmaceutico, Università degli studi di Parma, 27/A Viale delle Scienze, Parma 43100, Italy

ARTICLE INFO

ABSTRACT

A phenomenon was observed for the behavior of hypromellose matrices during dissolution. The tablet laminated radially, with both edges curled outwards, forming a "butterfly" shape. The butterfly effect is thus coined to describe this behavior. Due to the flamboyant shape assumed by the hydrated matrix, the apparent surface area for drug release was significantly increased. This study attempted to elucidate mechanistically the cause of this butterfly effect. Two formative mechanisms were proposed based on the behavior of moving solvent fronts and the anisotropic expansion of materials in solution. It was hypothesized that the particle size of hypromellose, applied compaction force used and proportions of both insoluble and soluble excipients contributed to the butterfly effect. The influence of the expanded shape on the mechanism and rate of drug release was also investigated. Matrix formulation was an important factor. Greater drug release was observed when the butterfly-shaped hydrated matrix was formed. The drug release profiles generally fitted the Higuchi and Korsmeyer–Peppas equations, indicating a combination of both diffusion and erosional drug release mechanisms. A combination of both fine and coarse hypromellose size fractions and adequate compaction force (more than 3 kN) were necessary for the manifestation of the butterfly effect.

© 2010 Elsevier B.V. All rights reserved.

1. Introduction

Hypromellose, a hydrophilic cellulose ether, is a widely used pharmaceutical excipient of low toxicity, acceptable cost and wide availability (Dow, 2006). High viscosity hypromellose is commonly used as a drug release retardant in swellable matrices designed as oral controlled release drug delivery systems. Modulation of drug release from hypromellose matrices has been widely studied. Factors known to influence the release of drugs from hypromellose matrices include formulation variables such as polymer content (Heng et al., 2001), substitution type and viscosity of the polymer (Gao et al., 1996), polymer/drug ratio, particle size of drug/polymer (Mitchell et al., 1993), type and amount of fillers used in the formulation (Levina and Rajabi-Siahboomi, 2004) as well as processing variables such as compaction force (Velasco et al., 1999), tablet size and tablet geometry. Upon contact with water or biological fluids, polymer chain relaxation occurs with volume expansion and swelling, followed by hydration and gelation of the polymer. Drug release is dependent on both the diffusion of the dissolved drug in the resultant gel during swelling and the erosion of the gel layer (Bettini et al., 2001).

In a preliminary study, a phenomenon was observed whereby some hypromellose compressed matrices, prepared at certain manufacturing conditions, split into two layers of hydrated matrix when placed in the dissolution medium. This unique behavior of hypromellose tablet matrices has not been reported in the literature. This observed shape assumed by the wetted matrix tablet greatly enhanced the apparent surface area of the tablet, which in turn affected drug release (Bettini et al., 1994; Colombo et al., 1992). This peculiarity in shape observed was defined as the "butterfly effect". Hence, the aim of this study was to understand the propensity for the manifestation of this effect. In particular, the influence of material and manufacturing conditions were of interest. It was hypothesized that the particle size of hypromellose, the compaction force used to prepare the tablets and the proportions of both insoluble and soluble excipients affected the formation of the butterfly-shaped matrix. The influence of the butterfly-shaped hydrated matrix on the mechanism and rate of drug release was also investigated.

2. Materials and methods

2.1. Granulation of flurbiprofen

Micronized flurbiprofen (mean volume diameter of 14.34 μm) (Recordati S.p.A., Italy) was wet granulated together with manni-

Table 1
Composition of tablets studied.

	Materials	Formula A		Formula B		Formula C	
		Wt/tablet (mg)	%	Wt/tablet (mg)	%	Wt/tablet (mg)	%
Granules	Flurbiprofen	37.50		37.50	33.13	37.50	
	Mannitol	24.01	33.13	24.01		24.01	33.13
	PVP K30	3.37		3.37		3.37	
Extra-granular excipients	Mannitol	90.82	46.37	67.02	34.22	43.24	22.07
	MCC PH102	0.00	0.00	23.80	12.15	47.59	24.30
	Hypromellose K4M	39.17	20.00	39.17	20.00	39.17	20.00
	Magnesium stearate	0.98	0.50	0.98	0.50	0.98	0.50
	Total	195.85	100.00	195.85	100.00	195.86	100.00

tol (Lisapharma, Italy). Table 1 shows the composition of materials used in granulation. Binding liquid was composed of 20% (w/v) polyvinylpyrrolidone (PVP; Kollidon K30, BASF, Germany) in 1:1 water and ethanol. The total granulation load was approximately 50 g. Flurbiprofen and mannitol were first mixed in a geometric manner. Binding liquid was subsequently added dropwise with constant trituration. The mixture was then passed through an oscillating granulator (AR400, Erweka, Germany) fitted with an 800 μm mesh. The granules collected were subsequently tray-dried in an oven at 60 °C for 6 h.

2.2. Sieving of hypromellose

Particle size distribution of hypromellose (Methocel K4M, Colorcon, USA) was determined using a nest of sieves (Endecotts, UK), vibrated with the aid of a sieve shaker (Fritsch, Germany). The amplitude of vibration was set at 1 mm and the sieve shaker was operated for a total duration of 10 min. Four size fractions (<63, 63–90, 90–125, 125–180 μm) and unsieved hypromellose were used to prepare the tablets used in this study.

2.3. Preparation of tablet cores

Table 1 shows the composition of tablets used in this study. The materials required for the tablet formulation were individually weighed and mixed in a blender (Turbula T2A, Willy A Bachofen, Switzerland) for a duration of 15 min. Magnesium stearate was then added and blending continued for a further 10 min. A specific amount of the resultant powder blend was compressed using a single-punch tablet press (LA 80 a-6, Korsch, Germany) fitted with 11 mm round and flat-faced punches. Four different size fractions, as well as unsieved hypromellose powder were used in the formulations. The different powder blends were compressed at various compaction forces, measured using a transducer (Kistler Instruments, Switzerland). The analog data was amplified (Type 5700, Kistler, Switzerland), digitized (Powerlab 1400, AD Instruments, Australia) and analyzed using a computer system.

2.4. Tablet characterization

The weight (PM 460, Mettler-Toledo, Germany) and thickness (500-311 digital micrometer, Mitutoyo, Japan) of tablets prepared were measured. A minimum of six tablets were measured for each formulation (Table 2).

2.5. Dissolution test for tablets

Dissolution testing of tablets was performed using a dissolution tester (DT6R, Erweka, Germany). The USP Apparatus 2 method was employed with the paddle rotating at 50 rpm. Dissolution was carried out in 900 mL of phosphate buffer (pH 7.2) maintained at 37 °C (T1500, Erweka, Germany) (USP/NF, 2007). A mesh was placed at the bottom of the dissolution vessel to minimize tablet sticking, which would impair three-dimensional swelling of the tablet and drug release. The dissolution test was carried out for a total duration of 4 h. Samples of 5 mL were collected from the dissolution vessel at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, and 4 h and replaced with an equal volume of fresh medium. Dissolution tests were performed in triplicate and the results averaged.

2.6. Quantification of flurbiprofen content

Samples collected from the dissolution tests were analyzed for their flurbiprofen content using a UV spectrophotometer (Lambda 25, Perkin Elmer, USA) at a detection wavelength of 247 nm (USP/NF, 2007).

The amount of flurbiprofen released from each tablet during dissolution was expressed as a percentage of the average amount of flurbiprofen present. A 196 mg tablet should theoretically contain 37.5 mg of flurbiprofen. Tablets prepared from each formulation were assayed for its average drug content. The tablets were pulverized and a known amount of the powder was dispersed in phosphate buffer (pH 7.2). The suspension was sonicated (Branson 2200, Opto-Lab, Italy) for 15 min to extract the flurbiprofen. The suspension was then filtered and the filtrate further diluted appropriately for assay of flurbiprofen.

2.7. Analysis of flurbiprofen release data

The mechanism of flurbiprofen release from the tablet matrix was studied by fitting the dissolution data obtained to the following equations using KaleidaGraph version 4.0 (Synergy Software, USA).

Korsmeyer–Peppas equation (Power law)

$$\frac{M_t}{M_\infty} = Kt^n$$

where M_t/M_∞ is the fraction of drug released at time t, K is a constant and n is the exponent indicative of release mechanism.

Higuchi square-root equation

$$M_t = K_H t^{1/2}$$

where M_t is the amount of drug released at time t and K_H is the Higuchi rate constant.

The rate indicating parameter K obtained from the Korsmeyer–Peppas equation for the different tablet formulations were compared only when the formulations exhibited similar release mechanism as indicated by comparable n-values. The Higuchi rate constant (K_H) was used to compare drug release rates where appropriate. Dissolution parameters T50% and T75%, each representing the time taken in minutes to achieve 50% and 75% drug release, respectively, were also used to compare the drug release characteristics of formulations that exhibit different mechanisms of drug release. In general, T50% and T75% were only used when the fit to the Higuchi model was poor. Good fit to the

Table 2
Average weight and thickness of tablets studied.

Compaction force (kN)	Sieved hypromellose size fractions (μm) (Formula C)								Unsieved hypromellose					
	<63		63–90		90–125		125–180		Formula A		Formula B		Formula C	
	Weight (mg)	Thickness (mm)	Weight (mg)	Thickness (mm)	Weight (mg)	Thickness (mm)	Weight (mg)	Thickness (mm)	Weight (mg)	Thickness (mm)	Weight (mg)	Thickness (mm)	Weight (mg)	Thickness (mm)
3	–	–	–	–	–	–	–	–	–	–	–	–	197.4 (2.9)	1.84 (0.02)
5	196.5 (2.1)	1.78 (0.05)	198.0 (1.4)	1.79 (0.03)	197.5 (2.2)	1.74 (0.03)	197.5 (2.2)	1.75 (0.04)	196.2 (2.8)	1.68 (0.04)	197.5 (1.9)	1.73 (0.01)	196.5 (1.3)	1.70 (0.02)
10	197.0 (4.5)	1.61 (0.01)	198.5 (1.3)	1.66 (0.04)	198.3 (1.9)	1.63 (0.02)	200.0 (2.4)	1.62 (0.01)	196.8 (2.5)	1.61 (0.02)	197.3 (3.9)	1.58 (0.02)	198.0 (1.8)	1.63 (0.03)
20	198.2 (1.5)	1.54 (0.02)	197.0 (0.8)	1.53 (0.02)	199.5 (1.6)	1.56 (0.04)	198.7 (1.5)	1.57 (0.03)	196.8 (2.6)	1.55 (0.03)	197.8 (2.6)	1.51 (0.02)	196.5 (1.9)	1.51 (0.02)
30	196.7 (2.5)	1.50 (0.03)	197.3 (2.4)	1.52 (0.01)	197.3 (2.1)	1.52 (0.02)	197.0 (2.7)	1.53 (0.04)	197.5 (1.7)	1.53 (0.03)	197.5 (1.9)	1.50 (0.03)	199.8 (2.2)	1.54 (0.05)
40	–	–	–	–	–	–	–	–	–	–	–	–	197.1 (1.7)	1.54 (0.02)

Note: Value in brackets indicates the average standard deviation.

kinetic models was considered when the R^2 value was greater than 0.90. The use of T50% or T75% was avoided as far as possible because they are single-point measurements and lack rigor though they are model-independent and easy to apply (Costa and Lobo, 2001).

2.8. Study design

Particle size of hypromellose powder and compaction force for tableting were the variables investigated in this study. The size fractions of hypromellose powder used were <63, 63–90, 90–125 and 125–180 μm. A separate tablet formulation was also prepared using unsieved hypromellose. The compaction forces used were 5, 10, 20 and 30 kN. Additional tablets were prepared at 3 and 40 kN for formulations containing unsieved hypromellose. The final part of this study was to briefly investigate the effects of changing the ratio of soluble (mannitol) and insoluble (microcrystalline cellulose (MCC)) extra-granular excipients (Formulae A and B) on the formation of the butterfly effect (Table 1).

2.9. Statistical analysis

Analysis of variance (ANOVA) was carried out to compare the drug release rates of more than two groups at significance level of 0.05 using Minitab Release 14 (Minitab Inc., USA), followed by post hoc comparison using Tukey's test when p was found to be less than 0.05.

3. Results

3.1. The butterfly effect

The progression of geometric events leading to the formation of this peculiar butterfly-shaped matrix during dissolution is illustrated in Fig. 1. For tablet formulations which exhibited the butterfly-shaped matrix, the phenomenon generally presented itself within the first hour of dissolution. The exact duration of the butterfly effect was not recorded as the time sequence for the manifestation and disappearance of the effect was subjective, prone to variation and difficult to determine with precision. Therefore, the qualitative determination of the butterfly effect was considered to be more pragmatic. Fig. 1A shows that the hydration of hypromellose occurred immediately when the matrix tablet was introduced into the dissolution medium, resulting in tablet swelling in both the axial and radial directions. Then, in most cases, the radial edge of the tablet split, followed by the curling of the tablet edge outwards, leading to the formation of a butterfly-shaped tablet matrix (Fig. 1B). The butterfly shape evolved as two forms. In the first instance, the two halves of the tablet remained attached at one end (Fig. 1C). Alternatively, the two halves detached completely (Fig. 1D). As dissolution progressed, the butterfly shape gradually appeared as a thin sheet composed of two halves attached to each other at the edge. Following erosion of the matrix, only a small residue was left behind at the end of each dissolution cycle.

3.2. Influence of hypromellose particle size

Fig. 2 shows the drug release profiles of tablets produced from different hypromellose size fractions according to Formula C at a compaction force of 20 kN. Particle size of hypromellose was found to exert a significant effect ($p < 0.05$) on the rate of drug release from the tablets. Based on the T50% and T75% values shown in Table 3, release rate decreased as polymer particle size decreased. The tablets containing hypromellose of size fraction greater than
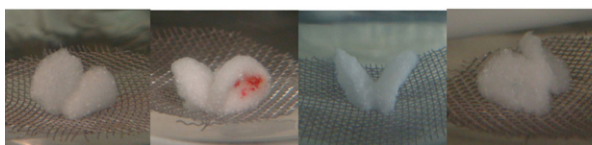
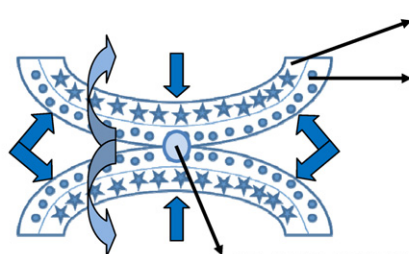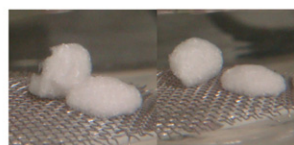A: SWELLING OF THE TABLET MATRIX UPON CONTACT WITH THE DISSOLUTION MEDIA
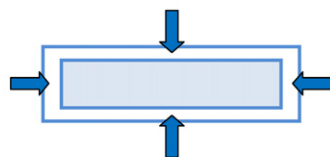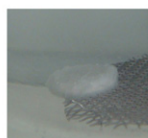
B: SPLITTING OF RADIAL SURFACE OF TABLET
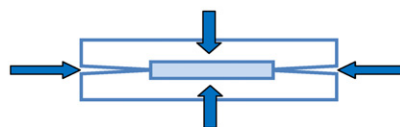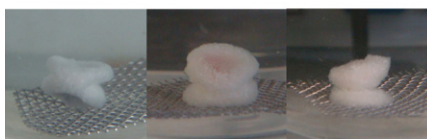
C: CURLING OF THE TWO SIDES OF THE TABLET OUTWARDS AND FORMATION OF THE BUTTERFLY-SHAPED HYDRATED MATRIX

D: SEPARATION OF THE BUTTERFLY-SHAPED TABLET INTO TWO INDIVIDUAL MATRICES

Outer layer of tablet is exposed to dissolution medium for a longer duration. Hypromellose is hydrated and the layer is therefore gel-like and more 'bendable'.

Inner layer of tablet is exposed to dissolution medium when splitting occurs at the radial surface of the tablet. Hydration of inner layer begins, leading to large differential swelling pressure. The inner layer expands to a greater extent and forces the tablet edges to curl outwards, forming the butterfly shape.

The swelling fronts meet and the glassy polymer core disappears. Stress relaxation and rearrangement occurs, leading to large swelling pressure, thus splitting the tablet into the butterfly shape.

Fig. 1. Progression of events during tablet dissolution and illustration of the mechanism of action for manifestation of the butterfly effect (⬛ dissolution medium, ▭ glassy core). (A) Swelling of the tablet matrix upon contact with the dissolution media. (B) Splitting of radial surface of tablet. (C) Curling of the two sides of the tablet outwards and formation of the butterfly-shaped hydrated matrix. (D) Separation of the butterfly-shaped tablet into two individual matrices.

90 μm disintegrated rapidly, resulting in fast drug release. No butterfly effect was observed as these tablets disintegrated rapidly. The butterfly effect was also not observed for tablets produced from the finer size fraction of hypromellose (<90 μm), regardless of the compaction force applied. Only a slight splitting at the radial surface of tablets was observed in this case.

3.3. Influence of compaction force

Fig. 3 shows the drug release profiles of tablets produced using unsieved hypromellose powder (Formulae A, B and C) at different compaction forces. The butterfly effect was observed in both Formulae A and B. However, for Formula C, no butterfly effect was observed in tablets produced at very low compaction force of 3 kN. However, there was rapid swelling of the tablets, leading to high drug release even though no butterfly effect was observed. At higher compaction forces, all the tablets displayed the butterfly effect. It should be noted that no significant differences were observed ($p > 0.05$) among the dissolution profiles for tablets prepared at all the compaction forces. This non-sensitivity to compaction force was consistent among formulations containing unsieved hypromellose. The use of high compaction forces could have reduced drug release rates. However, the manifestation of the butterfly effect counteracted this by increasing the release surface area (Colombo et al., 1992). The butterfly effect was more predominant than the effect of compaction force on drug release as all the tablets showed comparable drug release profiles regardless of the compaction force applied.
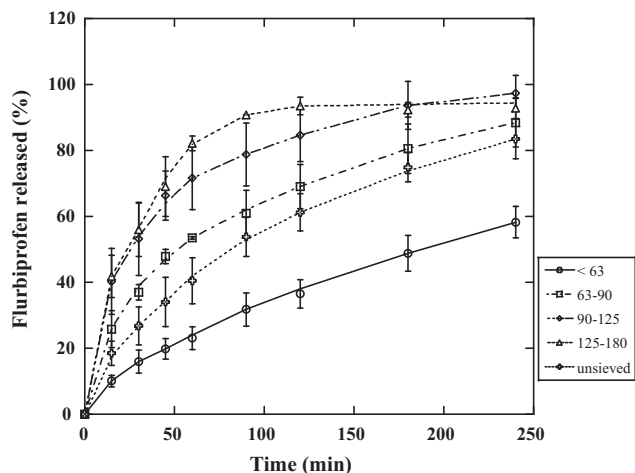
Fig. 2. Drug release profiles of tablets produced from different hypromellose particle size fractions according to Formula C at compaction force of 20 kN.

Table 3
Kinetic parameters and squared-regression coefficients of flurbiprofen release from tablets produced from different formulations at compaction forces of (I) 5, (II) 10, (III) 20 and (IV) 30 kN.

Formula	Hypromellose size fraction (μm)	Korsmeyer–Peppas equation		Higuchi square root equation		Time for 50 or 75% drug release	
		n	R^2	K_H (% min$^{-1/2}$)	R^2	T50% (min)	T75% (min)
I							
C	<63	0.59	0.99	5.01	0.99	95	213
C	63–90	0.31	0.89	8.14	0.78	21	63
C	90–125	0.13	0.82	9.12	0.30	10	25
C	125–180	0.03	0.68	8.21	0.12	9	8
C	Unsieved	0.43	0.99	7.04	0.97	60	143
B	Unsieved	0.41	0.93	7.93	0.98	32	68
A	Unsieved	0.46	0.99	6.11	0.99	42	92
II							
C	<63	0.64	1.00	4.35	0.98	128	247
C	63–90	0.40	0.99	7.12	0.95	37	100
C	90–125	0.28	0.99	8.04	0.81	16	60
C	125–180	0.12	0.75	7.93	0.25	10	32
C	Unsieved	0.46	0.98	7.24	0.97	60	153
B	Unsieved	0.47	0.96	8.50	0.97	43	78
A	Unsieved	0.47	1.00	6.01	1.00	42	84
III							
C	<63	0.63	1.00	3.46	0.97	187	a
C	63–90	0.44	0.99	6.18	0.98	50	134
C	90–125	0.32	0.96	7.55	0.84	27	65
C	125–180	0.30	0.81	7.86	0.71	26	52
C	Unsieved	0.56	0.95	7.24	0.97	82	180
B	Unsieved	0.61	0.98	7.20	0.99	51	91
A	Unsieved	0.56	0.99	5.44	0.99	48	94
IV							
C	<63	0.66	1.00	3.58	0.97	169	a
C	63–90	0.66	0.94	6.65	0.96	65	152
C	90–125	0.43	0.99	6.66	0.97	50	122
C	125–180	0.24	0.87	7.59	0.64	24	53
C	Unsieved	0.64	0.98	6.47	0.98	69	150
B	Unsieved	0.68	0.98	7.47	0.98	51	96
A	Unsieved	0.58	0.98	5.94	0.99	58	115

Note: (a) Value not determined.

Fig. 4 shows the drug release profiles of tablets produced according to Formula C using different size fractions of hypromellose and different compaction forces. Regardless of the size fraction, tablets produced at 5 kN disintegrated rapidly, giving rise to significantly higher drug release than those produced at higher compaction forces. There was no significant difference among the release profiles of most of the tablets produced at the higher compaction forces. Exception was observed for tablets produced using the fine hypromellose size fraction (<63 μm), where 20 and 30 kN also resulted in significantly slower release than 10 kN. No butterfly effect was observed for the tablets prepared using sieved hypromellose size fraction (<90 μm), regardless of the compaction forces employed. Only some slight splitting at the radial surface of tablets was observed. The extent of this splitting generally increased when the compaction force applied was higher. On the other hand, for tablets prepared using the coarser hypromellose size fraction (>90 μm), the tablet disintegrated rapidly without manifestation of the butterfly effect.

The tablets produced using sieved and unsieved hypromellose, respectively, showed dissimilar drug release rates and tablet behavior when compaction force was varied (Table 3). The presence of unsieved hypromellose powder was critical to the formation of the butterfly effect. Changes in compaction force did not affect drug release rates greatly. Conversely, tablets containing sieved hypromellose size fractions did not manifest the butterfly effect and drug release rates were observed to decrease with increase in the compaction forces applied. It was also noted that the tablets produced using the fine hypromellose size fraction (<63 μm) gen-

erally resulted in slower drug release regardless of the compaction force, further emphasizing the significant influence of particle size on drug release.

3.4. Influence of extra-granular excipients

A comparison of the drug release profiles of the tablets produced using different formulations but the same compaction force is shown in Fig. 5. As mentioned in Section 3.2, the drug release rates within each formulation using unsieved hypromellose were not significantly affected by compaction force. At all compaction forces, the rate of drug release fell in the following order: Formula B (12.15% (w/w) MCC) > Formula A (0% (w/w) MCC) > Formula C (24.3% (w/w) MCC). Although the butterfly effect was manifested in all three formulations, Formula B showed the most extensive butterfly effect which corresponded to the fastest drug release.

Table 3 shows the kinetic parameters and R^2 of flurbiprofen release from the tablets produced using different hypromellose size fractions and compaction forces. In the Korsmeyer–Peppas power law equation, n is the diffusional exponent indicative of the drug release mechanism. An n-value of approximately 0.45 indicates diffusion control, and an n-value of more than 0.89 indicates erosion or relaxational control (Super Case-II transport). n-values between 0.45 and 0.89 can be regarded as an indicator for the superposition of both phenomena (anomalous transport), while n-value of 0.89 indicates Case-II transport and zero-order release (Siepmann and Peppas, 2001). From Table 3, it can be seen that the n-values varied over a large range. The drug release mechanism of the tablet was affected by the size frac-
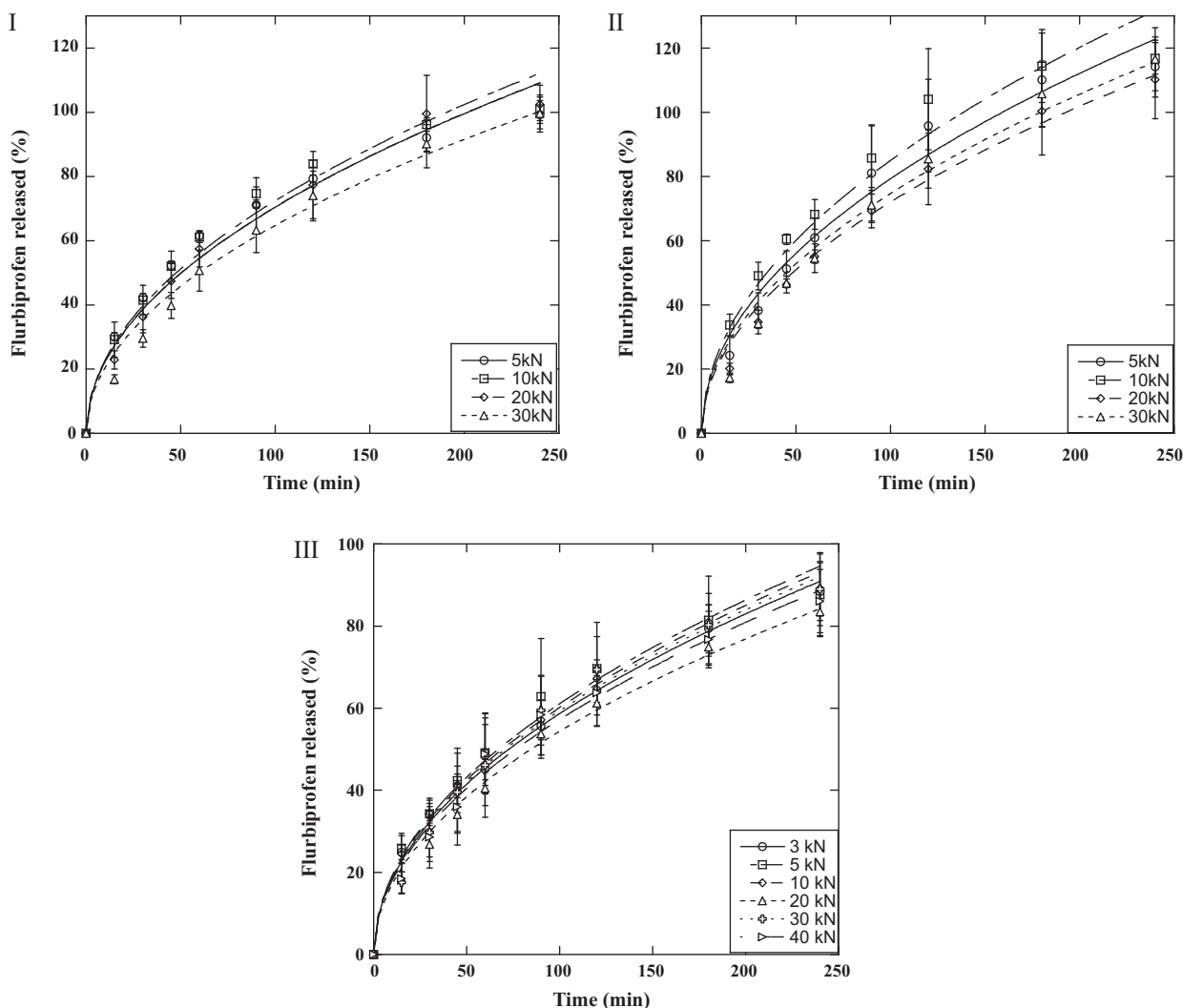
Fig. 3. Drug release profiles of tablets produced from unsieved hypromellose: (I) Formula A, (II) Formula B and (III) Formula C, at different compaction forces.

tion of hypromellose used. The coarser hypromellose size fractions (>90 μm) resulted in rapid disintegration of the tablet which caused poor correlations in the modeling of the dissolution data. The fine hypromellose size fraction (<63 μm) resulted in drug release by anomalous transport at all compaction forces employed. For tablets containing the 63–90 μm hypromellose size fraction (borderline between disintegrating and matrix forming system), n-values ranged between 0.31 and 0.66 which generally suggests diffusion control. On the other hand, the tablets containing unsieved hypromellose had n-values which ranged between 0.41 and 0.68, indicating that both surface erosion and diffusion within the matrix were controlling the rate of drug release.

4. Discussion

4.1. Effect of hypromellose particle size

Particle size of hypromellose is known to affect the drug release control of hypromellose matrices (Heng et al., 2001; Camposaldrete and Villafuerterobles, 1997). For the same polymer content, reduction in particle size is accompanied by numerical increase in the polymer particle quantity, which collectively enables greater polymer chain entanglement and prevents tablet lamination during dissolution. Thus, it was postulated that when larger hypromellose particles were employed, the opposite effect would occur, causing

radial tablet lamination and a greater tendency for the formation of the butterfly effect. It was reported that coarser fractions of hypromellose hydrate too slowly to allow sustained drug release from the hypromellose matrix (Alderman, 1984). Moreover, water can penetrate into the centre of such matrices at a faster rate, ultimately resulting in the burst release of the drug (Mitchell et al., 1993). In contrast, the finer fractions of hypromellose powder possess greater surface areas, enhancing polymer–water contact and resulting in the formation of a gel barrier that prevents premature matrix disintegration and drug release.

The butterfly effect was only clearly observed when unsieved hypromellose was used in the tablet formulations. Size analysis showed that the mass median sieve diameter of the hypromellose unsieved powder was 28 μm and almost 70% of its weight was made up of particles less than 63 μm. In this study, the small proportion of coarse particles present in the hypromellose powder played a critical role in the formation of the split that formed the butterfly-shaped matrix. On the other hand, the fine hypromellose particles prevented rapid disintegration and aided matrix formation. The tablets produced from unsieved hypromellose provided a balance between coarse and fine particles essential for the manifestation of the butterfly effect and gave an intermediate rate of drug release between formulations containing fine (<63 μm) and coarse hypromellose size fractions (>90 μm).
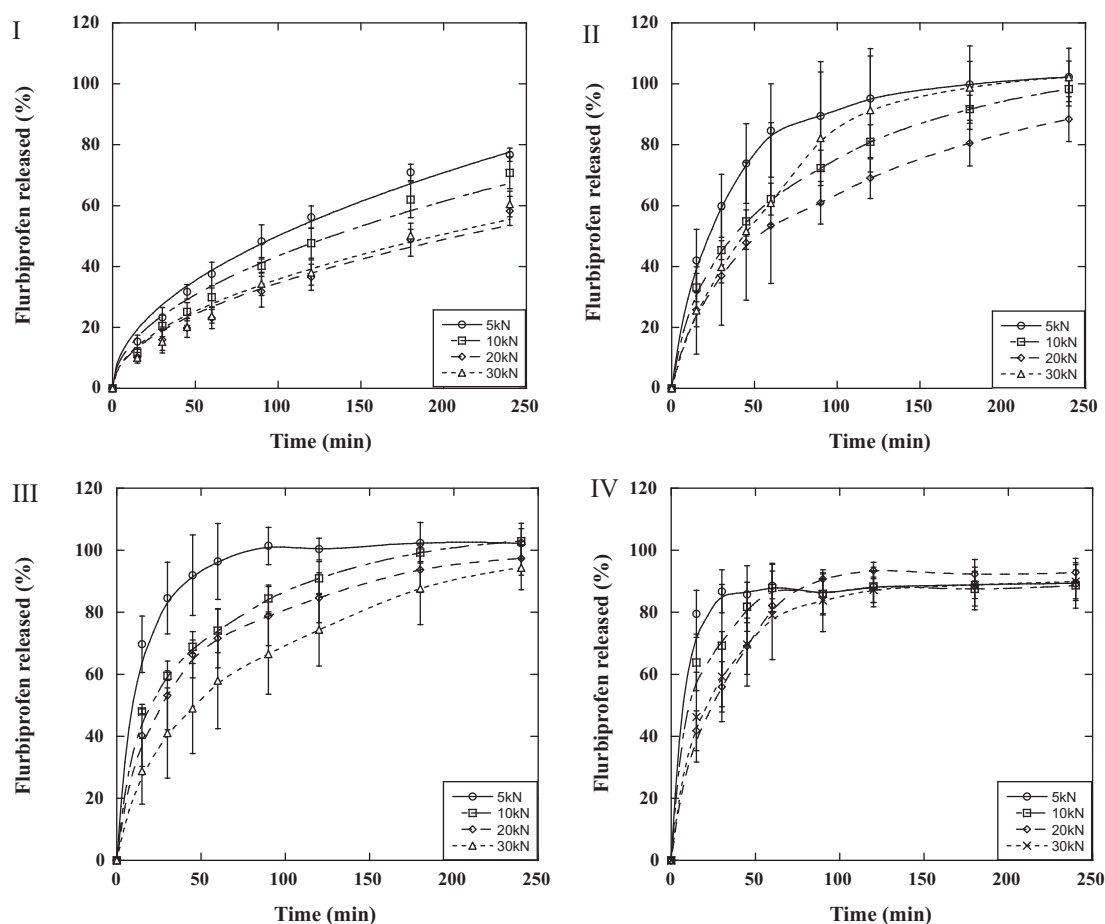
Fig. 4. Drug release profiles of tablets produced according to Formula C, using (I) <63, (II) 63–90, (III) 90–125 and (IV) 125–180 µm hypromellose size fractions at different compaction forces.

4.2. Effect of compaction force

It was postulated that the development of the butterfly effect was due to stress relief of the hypromellose particles under pressure. Swelling pressure exist during dissolution as a result of matrix hydration. To relieve this swelling pressure in water, the particles impart pressure on the surrounding particles, hence creating splits on the tablet and the development of the butterfly effect. The strong recovery and swelling force was likely to be dependent on the compaction force employed during tableting. Increased compaction force would impart greater stress and stored energy on the resultant tablet, resulting in greater axial recovery of the tablet (Nokhodchi et al., 1996). The effect of compaction force on the formation of the butterfly effect was therefore investigated. Other researchers had reported that compaction force was a significant factor affecting hypromellose tablet hardness, but its effect on drug release was minimal (Ford et al., 1985; Bettini et al., 1994). Modifications to the initial porosity of the hypromellose matrix by varying the compaction force affected only the initial period of release as the porosity of the hydrated matrix was independent of initial porosity. However, Levina and Rajabi-Siahboomi (2004) reported that the applied compaction force could influence drug release rate depending on the type of filler used.

A certain level of stress was found to be necessary to trigger the split that served as the starting point of the butterfly effect. However, the main trigger which elicited the separation of the swellable matrix tablet into two halves was not clear. It was observed that

the separation was likely to occur to thin matrix tablets that were prepared using high compaction forces. High compaction force has been reported to increase the incidence of lamination in tablet manufacturing (Patel et al., 2006). This translated to the same behavior when the tablet was placed in solution. While compaction force played a significant role in the butterfly effect, its influence on drug release was less prominent. When lower compaction force was employed, the initial porosity of the tablet was higher, allowing the dissolution medium to penetrate the tablet more rapidly. This led to more rapid drug release. When larger compaction forces were employed, the low initial porosity allowed particles to be in greater contact with one another. The hydration of the tablet matrix would thus lead to the development of a strong swelling pressure.

4.3. Effect of extra-granular excipients

It was thought that the proportion of soluble and insoluble excipients present in the formulation might also affect the formation of the butterfly-shaped matrix and influence drug release. Soluble excipients will dissolve and diffuse out of the matrix while insoluble excipients will be held in place until the matrix or surrounding material erodes or dissolves away. MCC is an insoluble excipient, but it is able to absorb water and may aid as a disintegrant at concentrations of 5–15% (Galichet, 2006). As such, MCC was hypothesized to aid in the tablet splitting that would lead to the butterfly effect. The effect of MCC was investigated using two additional formulations, one in which MCC was completely replaced
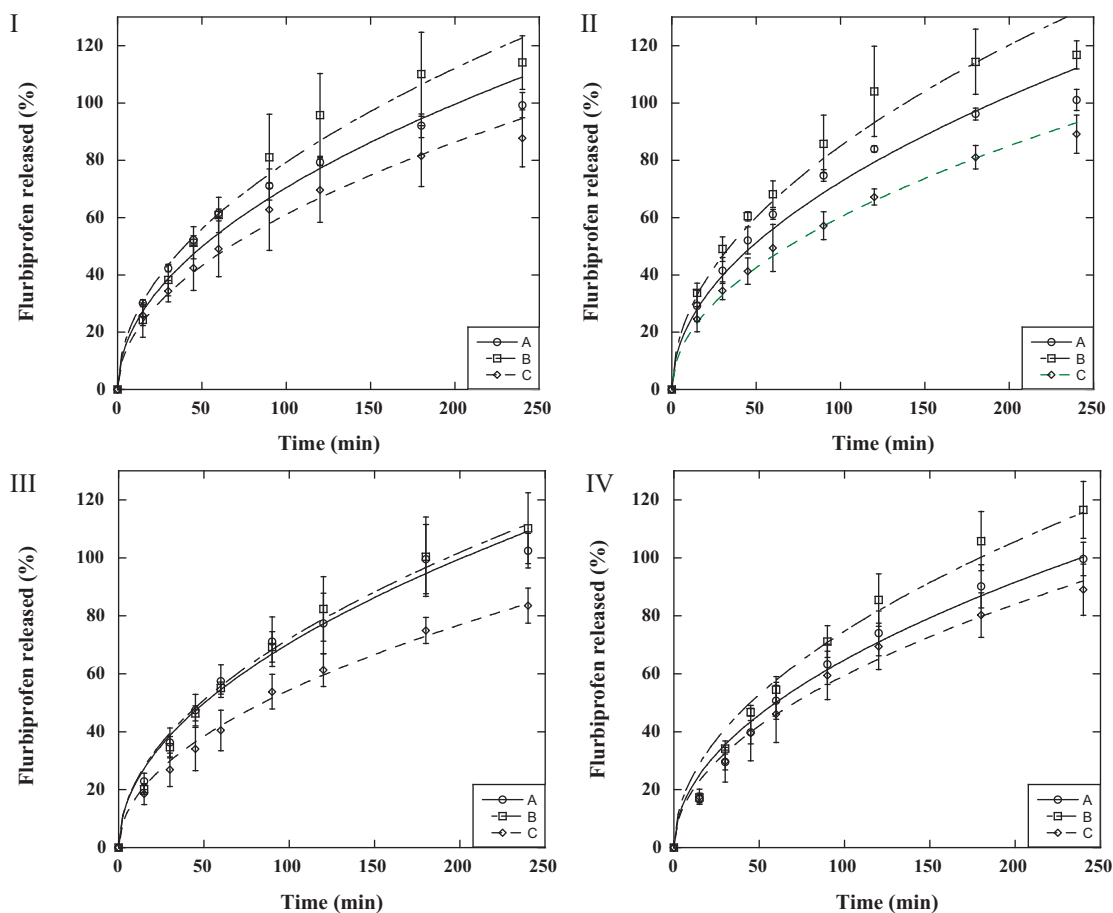
Fig. 5. Drug release profiles of tablets (Formulae A, B and C) prepared at compaction forces of (I) 5, (II) 10, (III) 20 and (IV) 30 kN.

by the soluble excipient mannitol (46.37% (w/w)), while the other formulation contained a partial mix of extra-granular mannitol (34.33% (w/w)) and MCC (12.15% (w/w)). The tablets were produced using unsieved hypromellose and all the tablets had comparable thickness.

The addition of soluble filler was expected to increase porosity which would facilitate diffusion and increase rate of erosion, thereby increasing drug release and decreasing the strength of the matrix. On the other hand, insoluble material in the formulation was expected to serve as a physical barrier and hinder polymer–polymer interaction and gelation. Hence, the tablet containing the most mannitol (Formula A) should theoretically display the fastest drug release. Interestingly, this was not found to be the case. During dissolution of Formula A tablets, the butterfly effect was observed despite the absence of MCC. Collectively, the above observations suggest that the butterfly-shaped matrix was contributed mainly by the effects of hypromellose, while MCC only helped to promote the butterfly effect through the additional disintegrant effect it provided. On closer examination, the butterfly-shaped hydrated matrix observed in Formula A tablets was not as well formed. The butterfly shape was deformed when the large amount of mannitol dissolved and weakened the matrix. It was interesting to note that Formula B showed the most extensive butterfly shape formation and not Formula C which contained the most MCC. In short, the hypromellose:MCC:mannitol ratio is an important factor affecting the formation of the butterfly-shaped matrix. However, this study was limited and future studies should focus on evaluating how further changes in formulation can influence the presentation of the butterfly effect.

4.4. Drug release kinetics

In this study, drug release was modeled using Korsmeyer–Peppas power law and Higuchi square-root equation. The Korsmeyer–Peppas power law is recommended for the determination of drug release mechanism from non-inert, swellable matrices. However, rate of drug release was also determined by curve-fitting dissolution data to the Higuchi equation for comparative purposes. Drug release from tablets produced using unsieved hypromellose was best described by the Higuchi square-root and Korsmeyer–Peppas equations. Following the presentation of the butterfly effect, the matrix split into two thinner matrices which still behaved as a thin cylindrical compact. Hence, good correlations were obtained with the usual Higuchi, and power law equations. In addition, the anomalous behavior of butterfly-shaped tablets also resulted in good correlations with these equations.

4.5. Mechanisms for the formation of the butterfly effect

Hypromellose is composed of non-ionic cellulose ether and its hydration and gel formation is not affected by changes in pH. The other excipients present in the formula, mainly mannitol and MCC, are also not known to be affected by changes in pH. When tablets were placed in either phosphate buffer (pH 7.2) or acid medium (pH 1.2) (data not shown), the tablet matrix split and the butterfly effect was observed. Therefore, the butterfly effect was not deemed to be pH-dependent, but more likely to be a physical phenomenon.

Fig. 1 shows the pictorial representation of the mechanisms involved in the formation of the butterfly effect. Two mechanisms were proposed:

1. Swellable matrix tablets are moving boundary delivery systems whereby drug release is governed by the hydration, swelling and dissolution of the swellable polymer/drug mixture. These phenomena give rise to the formation of boundaries, called fronts, separating different physical conditions inside the swelling matrix that are responsible for the release kinetics exhibited. The swelling front separates the glassy from the rubbery polymer state and is a region of high stress (Korsmeyer and Peppas, 1984). These high stress regions develop as the outer portions of the polymer begin to swell. The stressed zone moves inward as swelling progresses until stress relaxation occurs when the centre of the matrix becomes plasticized by the dissolution medium (Korsmeyer et al., 1986). The dynamic swelling behavior of the polymer controls the mechanism and rate of drug release. It is well-known that in a disc matrix tablet, the swelling fronts moving from the two bases of the disc meet at the centre of the matrix. At this point, no more glassy polymer is present in the matrix and the disappearance of the glassy core produces a sudden increase in the volume (thickness and diameter) of the matrix. This phenomenon is generally observed before the swelling equilibrium and is preferred to be slow to allow adequate drug release control. Otherwise, matrix disintegration can occur.

It was suggested that the butterfly-shaped hydrated matrix was formed when the symmetric swelling fronts meet. When the centre of the disc became plasticized by the incoming penetrant medium, stress relaxation and rearrangements occur. The glassy core tends to restrict the rubbery phase to one-dimensional swelling. However, the disappearance of the glassy core removed this swelling constraint, leading to a drastic decrease in swelling modulus (Lustig and Peppas, 1987) and the formation of the butterfly-shaped hydrated matrix. Although the experimental data obtained did not appear to directly suggest this formative mechanism, this phenomenon is well-known to exist in hypromellose matrices, and is likely to contribute to the manifestation of the butterfly effect. The thickness of the tablet also played a role in the formation of the butterfly-shaped hydrated matrix. A thicker tablet of the same formulation, prepared by compressing a correspondingly greater amount of materials, did not result in the butterfly effect (data not shown). No splitting on the radial surface was observed. This could possibly be attributed to the greater amounts of hypromellose present in the matrix, allowing the matrix to retain its shape better. In addition, a thick tablet was more likely to be able to accommodate the swelling stress following the disappearance of the glassy core when the swelling fronts of the tablet meet.

2. Hypromellose tablet matrices swell predominantly in the axial rather than the radial direction on exposure to aqueous fluids (Colombo et al., 1990). In addition, there is inherent mechanical anisotropy within tablets as the materials are confined radially by a rigid die while being compressed axially by a moving punch (Moe and Rippie, 1997). Radial and axial stress and strain exist in the compact due to the highly directional nature of the compaction process. The anisotropy in compact structure resulted in non-uniform porosity within compacts as well as differences in axial and radial tensile strength of tablets (Malamataris et al., 1996; Mullarney and Hancock, 2006). In another study on sodium alginate compacts, it was postulated that the axial porosity gradient could have resulted in the non-uniform hydration and swelling of alginate particles along the axis of the matrix, resulting in local heterogeneity in distribution of stress and strain which gave rise to cracks within the rigid alginic acid bar-

rier (Ching et al., 2008). Cracks were also formed on the radial surface, extending towards the dry core as dissolution proceeded and gradually increased the surface area exposed to the dissolution medium. However, there was no report of the butterfly effect.

In this study, the formation of the butterfly-shaped hydrated matrix was generally preceded by a radial split of the tablet. The more rapid release of stress in the axial direction would cause the tablet to split in the radial side if the swollen matrix cannot accommodate the sudden stress relaxation. This split almost always occurred along the equator (half thickness) of the tablet. As the cracks extended to the core, the edges of the tablet were found to curl outwards. As the dissolution medium penetrated into the core through the split, it would cause the area of immediate contact (inner layers) to swell, exerting a swelling pressure. The inner layer expanded to a greater extent compared to the outer top and bottom tablet surfaces, thus causing the bisected tablet halves to curl outwards. This outward swelling pressure could also be partly attributed to the presence of a hydration gradient along the radial split, from periphery to centre. As the radial split progressed towards the centre of the tablet, the more peripheral regions got wetted first and started to swell while the interior regions were wetted later. Differential swelling caused a curvature at the inner layer to develop due to differences in the surface swelling rates as the earlier wetted regions swelled more strongly. This manifested as outward curling and the formation of the butterfly-shaped matrix. The rate of water ingress was related to the rate and extent of the radial split formation which was in turn, dependent on formulation and processing factors. This was likely to be the reason as to why the butterfly effect was not exhibited under certain circumstances, even though slight radial splitting was observed. The butterfly effect was more likely to manifest if the radial split was extensive enough to allow the hydration gradient to develop. Meanwhile, the outer layers of the tablet, which were hydrated much earlier, would probably form a gel-like and viscous layer which was more 'bendable' and would therefore move outwards with greater ease. Hence, if the split sections were not sufficiently thick and strong, their edges would curl outwards under the influence of swelling pressure.

Investigations have shown that the butterfly effect was largely attributed to the interplay between hypromellose particle size, compaction force and formulation. All the aforementioned parameters played a role in creating anisotropy and inhomogeneity in the compact structure. Therefore, the penetration of the dissolution medium into the tablet caused it to swell non-uniformly (Moe and Rippie, 1997).

5. Conclusion

In a swellable hypromellose matrix, the large swelling pressure associated with the disappearance of the glassy core when the two symmetrical moving swelling fronts meet could result in the lamination of the tablet and the formation of the butterfly-shaped hydrated matrix. The anisotropic nature of the compact structure also resulted in non-uniform swelling, which leads to cracks on the radial side and the penetration of the dissolution medium through the split. Under the influence of swelling pressure and the differential extent of hydration of the split region, the edges of the matrix would curl outwards leading to the formation of the butterfly-shaped matrix.

The presence of unsieved hypromellose powder was critical for the manifestation of the butterfly effect. A balance of hypromellose size fractions was necessary as the fine size fraction was required to hydrate the matrix rapidly to form the gel structure

while the coarser fraction aided the splitting of the tablet into the butterfly shape. For matrices to exhibit the butterfly effect, a compaction force greater than 3 kN was needed. While compaction force played a significant role in the butterfly effect, its influence on drug release was less prominent. The use of high compaction forces could have reduced drug release rates. However, the manifestation of the butterfly effect for tablets prepared at higher compaction forces counteracted this by increasing the release surface area. Greater recovery and swelling force of polymer in solution which facilitated the manifestation of the butterfly effect was attributed to the higher compaction forces employed, which resulted in greater residual stresses within the tablet. The ratio of hypromellose:MCC:mannitol was also important in influencing the extent of the butterfly effect. In Formula B which contained both mannitol and MCC, an extensive butterfly effect was observed during dissolution. The increase in surface area presented to the dissolution medium led to an increase in the rate of drug release. The drug release mechanism of the butterfly-shaped tablets was generally a combination of diffusion and erosion control. The drug release profiles from the butterfly-shaped tablets also fitted the Korsmeyer–Peppas and Higuchi square-root equations relatively well even though these equations were established for regular-shaped matrix tablets.

The manifestation of the butterfly effect was limited to very thin tablets compressed to adequate hardness. It is therefore important to keep the butterfly effect in mind when formulating thin tablets, especially those which may contain suitable proportions of insoluble or soluble excipients. Thin tablets may be applied as part of multi-layered tablets in drug delivery. It is essential to evaluate the tablet matrix behavior to ensure that the variation in shape will not affect the desired release properties of the tablet. With the splitting of the tablet into the butterfly shape during dissolution, there will be more rapid penetration of the media into the centre of the tablet and greater drug release is expected together with the increase in tablet surface area. The butterfly effect may be useful as a platform technology when increased surface area for drug release is desired. However, further studies are required to understand the phenomenon better in order to possibly utilize the phenomenon in drug delivery.

Acknowledgements

References

Alderman, D., 1984. A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. Int. J. Pharm. Technol. Prod. Mfr., 1–9.

Bettini, R., Catellani, P.L., Santi, P., Massimo, G., Peppas, N.A., Colombo, P., 2001. Translocation of drug particles in HPMC matrix gel layer: effect of drug solubility and influence on release rate. J. Control. Release 70, 383–391.

Bettini, R., Colombo, P., Massimo, G., Catellani, P.L., Vitali, T., 1994. Swelling and drug-release in hydrogel matrices – polymer viscosity and matrix porosity effects. Eur. J. Pharm. Sci. 2, 213–219.

Camposaldrete, M.E., Villafuerterobles, L., 1997. Influence of the viscosity grade and the particle size of HPMC on metronidazole release from matrix tablets. Eur. J. Pharm. Biopharm. 43, 173–178.

Ching, A.L., Liew, C.V., Chan, L.W., Heng, P.W.S., 2008. Modifying matrix micro-environmental pH to achieve sustained drug release from highly laminating alginate matrices. Eur. J. Pharm. Sci. 33, 361–370.

Colombo, P., Catellani, P.L., Peppas, N.A., Maggi, L., Conte, U., 1992. Swelling characteristics of hydrophilic matrices for controlled release new dimensionless number to describe the swelling and release behavior. Int. J. Pharm. 88, 99–109.

Colombo, P., Conte, U., Gazzaniga, A., Maggi, L., Sangalli, M.E., Peppas, N.A., Lamanna, A., 1990. Drug release modulation by physical restrictions of matrix swelling. Int. J. Pharm. 63, 43–48.

Costa, P., Lobo, J.M.S., 2001. Modeling and comparison of dissolution profiles. Eur. J. Pharm. Sci. 13, 123–133.

Dow, 2006. Using Dow Excipients for Controlled Release of Drugs in Hydrophilic Matrix Systems. Dow Chemical Company, USA.

Ford, J.L., Rubinstein, M.H., Hogan, J.E., 1985. Formulation of sustained-release promethazine hydrochloride tablets using hydroxypropylmethylcellulose matrices. Int. J. Pharm. 24, 327–338.

Galichet, L.Y., 2006. In: Rowe, R.C., Sheskey, P.J., Owen, S.C. (Eds.), Handbook of pharmaceutical excipients. , 5 ed. Pharmaceutical Press and American Pharmacists Association, London and Washington.

Gao, P., Skoug, J.W., Nixon, P.R., Ju, T.R., Stemm, N.L., Sung, K.C., 1996. Swelling of hydroxypropyl methylcellulose matrix tablets. 2. Mechanistic study of the influence of formulation variables on matrix performance and drug release. J. Pharm. Sci. 85, 732–740.

Heng, P.W.S., Chan, L.W., Easterbrook, M.G., Li, X.M., 2001. Investigation of the influence of mean HPMC particle size and number of polymer particles on the release of aspirin from swellable hydrophilic matrix tablets. J. Control. Release 76, 39–49.

Korsmeyer, R.W., Peppas, N.A., 1984. Solute and penetrant diffusion in swellable polymers. 3. Drug release from glassy poly(HEMA-co-NVP) copolymers. J. Control. Release 1, 89–98.

Korsmeyer, R.W., Vonmeerwall, E., Peppas, N.A., 1986. Solute and penetrant diffusion in swellable polymers. 2. Verification of theoretical models. J. Polym. Sci. Part B: Polym. Phys. 24, 409–434.

Levina, M., Rajabi-Siahboomi, A.R., 2004. The influence of excipients on drug release from hydroxypropyl methylcellulose matrices. J. Pharm. Sci. 93, 2746–2754.

Lustig, S.R., Peppas, N.A., 1987. Solute and penetrant diffusion in swellable polymers. 7. A free volume-based model with mechanical relaxation. J. Appl. Polym. Sci. 33, 533–549.

Malamataris, S., Hatjichristos, T., Rees, J.E., 1996. Apparent compressive elastic modulus and strength isotropy of compacts formed from binary powder mixes. Int. J. Pharm. 141, 101–108.

Mitchell, K., Ford, J.L., Armstrong, D.J., Elliott, P.N.C., Hogan, J.E., Rostron, C., 1993. The influence of the particle size of hydroxypropylmethylcellulose K15M on its hydration and performance in matrix tablets. Int. J. Pharm. 100, 175–179.

Moe, D.V., Rippie, E.G., 1997. Nondestructive viscoelastic analysis of anisotrophy in compressed tablets. J. Pharm. Sci. 86, 26–32.

Mullarney, M.P., Hancock, B.C., 2006. Mechanical property anisotropy of pharmaceutical excipient compacts. Int. J. Pharm. 314, 9–14.

Nokhodchi, A., Ford, J.L., Rowe, P.H., Rubinstein, M.H., 1996. The effects of compression rate and force on the compaction properties of different viscosity grades of hydroxypropylmethylcellulose 2208. Int. J. Pharm. 129, 21–31.

Patel, S., Kaushal, A.M., Bansal, A.K., 2006. Compression physics in the formulation development of tablets. Crit. Rev. Therap. Drug Carrier Syst. 23, 1–65.

Siepmann, J., Peppas, N.A., 2001. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv. Drug Deliv. Rev. 48, 139–157.

USP/NF, 2007. United States Pharmacopeia Rev. 31/National Formulary Ed. 26 2008. The United States Pharmacopeial Convention. Port City Press, Baltimore.

Velasco, M.V., Ford, J.L., Rowe, P., Rajabi-Siahboomi, A.R., 1999. Influence of drug: hydroxypropylmethylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets. J. Control. Release 57, 75–85.