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## Sustained release of acetaminophen from a heterogeneous mixture of two hydrophilic non-ionic cellulose ether polymers

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### Abstract

This study examined the release of acetaminophen (APAP) from hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC) matrices. The effect of pseudoephedrine (PE) as a co-active, HPMC:HPC ratio, polymer loading, pH of the dissolution media, and compression force on APAP release were studied. Granules formulated with APAP or both APAP and PE, and various blends of HPMC and HPC were compressed into tablets at different compression forces. APAP release from the matrix tablets was not considerably influenced by changes in HPMC:HPC ratio or compression force. The rate of drug release was significantly affected by pH of the dissolution media, total polymer loading, and the presence of PE. Drug release from the formulations containing both APAP and PE was slower than those containing only APAP. Drug release from tablets formulated with APAP only showed an initial burst at pH 1.16 or 7.45. Formulations containing both APAP and PE showed slower drug release at pH 1.16 than at pH 7.4. The drug release data showed a good fit to the Power Law Model. The mechanism of drug release is consistent with a complex behavior. The results of the tablet erosion studies indicated that the amount of APAP released was linearly related to the percentage of tablet weight loss. The kinetics of tablet water uptake was consistent with a diffusion and stress relaxation mechanism.

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**Keywords:** Acetaminophen; Sustained release; Heterogeneous hydrophilic matrix; Pseudoephedrine

### 1. Introduction

The use of hydrophilic matrices has become extremely popular in controlling the release of drugs from solid dosage forms (Huber et al., 1966; Wan et al., 1993; Alderman, 1984; Wilder et al., 1991; Al-Hmoud et al., 1991). A sustained release matrix

tablet consists of a compressed compact containing a mixture of one or more active ingredient(s) with one or more gel forming agent(s), which retards the release of the drug(s) (Rao et al., 1988; Cardinal, 1984). For many reasons, oral drug delivery continues to be the preferred route of pharmaceutical administration of drug substances (Deshpande et al., 1996; Bae et al., 1991). During the last two decades, polymers which swell in aqueous medium, have been used for the preparation of oral sustained release dosage forms (Dhopeshwarkar and Zatz, 1993; Vazquez et al.,

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1992; Lee and Peppas, 1987; Rubio and Ghali, 1994; Mitchell et al., 1993a). These polymers have been broadly grouped into two categories, hydrogels and the hydrophilic polymers. Hydrogels are swellable polymers that are water insoluble, whereas the hydrophilic polymers are swellable and water soluble. The increasing need for suitable polymers to achieve a desired drug release has facilitated screening of a large variety of both synthetic and natural polymers for their ability to retard the release of specific drug substances. Since the cost of synthesizing a new polymeric substance and testing for its safety is enormous, a new focus has been directed towards investigating the use of polymer blends of pharmaceutically approved polymeric materials as matrix excipients to retard drug release.

Oral sustained release dosage forms are commonly prepared by incorporating the drug into a hydrophilic polymeric matrix. The hydrophilic matrix consists of a mixture of one or more active ingredient(s) with one or more gel forming agent(s). The mixture is usually compressed into tablets (Rao et al., 1988; Hogan, 1989). Various types of polymers used as hydrophilic matrices have been extensively reviewed (Alderman, 1984; Rao and Devi, 1988; Hariharan et al., 1997). Although many different polymers have been used in swellable controlled release systems (Rao and Devi, 1988; Skoug et al., 1993), water-soluble polymers, such as cellulose ethers, are probably the most frequently encountered in pharmaceutical literature as matrices for drug delivery system (Rao et al., 1988). The most commonly used cellulose ethers include the following: hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), sodium carboxymethylcellulose (NaCMC), and methylcellulose (MC). Their popularity stem from their non-toxic nature, ease of compression, ability to accommodate a large percent of drug and negligible influence of the processing variables on drug release rates (Alderman, 1984; Skoug et al., 1993).

The rapid formation of a viscous gel layer upon hydration has been regarded as an essential first step in achieving controlled drug release from HPMC matrices (Alderman, 1984). Ford et al. (1987) have reported that drugs, such as tetracycline hydrochloride, may interact with the hydration process of HPMC following contact with water. Propranolol and other water-soluble drugs have also been indicated

to contribute to the extent of swelling in MC- and HPMC-based gels (Mitchell et al., 1993b).

For matrix devices, drug is often released by diffusion process such that a receding drug boundary will exist within the device (Roseman and Higuchi, 1970). This boundary moves inward with time creating a zone of depletion. As the thickness of the zone increases with time, the distance each drug molecule must diffuse also increases. Since flux is inversely proportional to the zone thickness, the release rate will decrease with time. For devices, such as spheres, the area at the receding drug boundary will also decrease with time leading to a more pronounced decline in the release rate (Cardinal, 1984). Therefore, an initial large burst is predicted followed by a slowly declining release rate.

In order to achieve a constant release rate, a number of matrix devices have been formulated using diverse polymeric excipients. The rate of drug release is influenced by several factors, which include structural and geometric factors. The incorporation of a rate-limiting barrier at the surface of the matrix device has been speculated to produce constant drug release over a given period of time. In such a device, the drug-containing core is blended with a variety of rapidly hydrating polymeric excipients to facilitate fast gel formation and therefore regulate drug release from the tablet core. Thus, the rate of swelling of the matrix in contact with the release medium is controlled.

Acetaminophen (APAP) is a commonly used analgesic and antipyretic drug, which has often been used in combination with a decongestant, for example, pseudoephedrine (PE). Burst drug release is one of the primary limitations of sustained release commercial products containing APAP. Preliminary experiments have identified polymeric matrix combinations that are capable of rapidly hydrating to form a gel layer with variable consistency around the tablet core to regulate drug release.

In this study, HPMC and HPC were used as polymeric carriers for APAP to investigate drug release behavior. The effect of a co-active (PE), polymer ratio, polymer loading, compression force, and pH of dissolution media on APAP release was studied. The kinetics of tablet swelling was also investigated and correlated to drug release. In our previous paper, we investigated the effect of PE on the compaction behavior of APAP matrix (Ebube et al., 1997a).

## 2. Materials and methods

### 2.1. Materials

APAP (Rhone-Poulenc, New Jersey, USA) and pseudoephedrine sulfate (PE; Knoll Pharmaceutical Co., New Jersey, USA) were used as model drugs for this investigation. The following materials were also used in this study: HPMC (Methocel® E4M, DOW Chemical Co., Michigan, USA), HPC (Klucel® LF, Aqualon, Wilmington, DE, USA), magnesium stearate, NF (Mallinckrodt, Inc., Missouri, USA), and Cabosil® M5 (Cabot Corporation, Illinois, USA). All materials were used as received without further purification.

### 2.2. Methods

#### 2.2.1. Preparation and characterization of granules

The method for preparing and characterizing the granules has been described earlier (Ebube et al., 1997a). The granules were formulated such that each tablet contained 750 mg of APAP and 60 mg of PE. Batches of the granule formulations ranging from 787 to 940 g containing 0.25% (w/w) Cabosil® and various ratios of HPMC and HPC were prepared. The ratios of HPMC to HPC used were 2:1, 4:1.5, 5:1.3, while the total polymer content varied from 3.5 to 19.2% (w/w). The composition of the powder blends is shown in Table 1.

The properties of the granules for each formulation were evaluated by determining the particle size dis-

tribution, moisture content, bulk density, tap density, and Carr's index. The results of this study have been previously presented (Ebube et al., 1997a).

#### 2.2.2. Compaction to tablets

A quantity of the base granulation for each formulation, enough to make 2000 tablets, was weighed and placed in an 8-quart plastic container. Magnesium stearate (1%, w/w, as lubricant) was premixed with an equal portion of the granulation and passed through a #20 mesh sieve by hand. The mixture was blended with the remainder of the granulation for 3 min using a PK blender (Patterson-Kelly Co., USA) and compressed into matrix tablets on a Manesty B3B instrumented tablet press using a 9/16 in. flat-faced punches and dies at a compression speed of 203 tablets/min. Tablets were compressed at varying compression forces ranging from 2000 to 6000 lb. The tablet compression profile data have been presented in our previous report (Ebube et al., 1997a). However, only those tablets that were compressed at 2000 and 3000 lb were tested for in vitro drug release, since beyond a compression force of 3000 lb, the compressed tablets showed a tendency to cap. This may be attributed to the poor compressibility of APAP.

#### 2.2.3. Tablet properties

The properties of the compressed matrix tablets, such as the crushing strength, friability, disintegration time, weight variation, and thickness, were determined and the results have been previously presented (Ebube et al., 1997a).

#### 2.2.4. In vitro dissolution studies

In vitro drug release studies were carried out at  $37 \pm 0.5^\circ\text{C}$  using the USP apparatus II (automated dissolution testing system, Model VK-7000, VanKel Industries, Edison, NJ, USA) fitted with paddles rotated at 50 rpm. A tablet was placed in a beaker containing 900 ml of deionized water (pH 5.9) and the percentage of drug released from the tablet in a 24-h period was determined. Samples of 8 or 10 ml were withdrawn (without replacement) from the dissolution vessel at 1, 2, 4, 8, 12, 18, and 24 h using an autosampler (Model VK-8000, VanKel Industries).

Two batches of formulations containing APAP (B) and APAP + PE (H) were selected and tested for drug

Table 1  
Composition of matrix formulations

Matrix formulation	Polymer ratio <sup>a</sup>	Model drug	Total polymer (%)
A	2:1	APAP	6.3
B	4:1.5	APAP	6.3
C	5:1.3	APAP	6.3
D	4:1.5	APAP	3.5
B	4:1.5	APAP	6.3
E	4:1.5	APAP	9.6
F	4:1.5	APAP	19.2
G	2:1	APAP + PE	6.3
H	4:1.5	APAP + PE	6.3
I	5:1.3	APAP + PE	6.3

<sup>a</sup> HPMC:HPC.

dissolution in 900 ml of 0.08N HCl (pH 1.16) or phosphate buffer pH 7.45.

**2.2.4.1. Drug analysis.** Analytical techniques for determination of the amount of drugs present in each dissolution sample have been previously reported (Ebube et al., 1997b). For the formulations that contained only APAP, the drug concentration in each sample was determined using a diode array spectrophotometer (Model 8452A, Hewlett Packard Instruments, Avondale, PA, USA) at 244 nm. An HPLC multicomponent analytical method was used for the simultaneous determination of PE and APAP in the formulations containing both drugs. A 5  $\mu$ m Zorbax SB phenyl 250 mm  $\times$  4.6 mm column and a diode array multi-wavelength detector were used for the assay. The dual wavelength UV spectrophotometer was set at wavelength of 216 nm for the detection of PE and 280 nm for APAP. The mobile phase consisted of 80:20 water:acetonitrile, 0.0015% sodium lauryl sulfate (SLS), and 0.05 M monobasic potassium phosphate buffer.

A standard consisting of APAP and PE was used for quantification of the amounts of both drugs present in each dissolution sample. Built-in software inter-controller was used to determine the percent drug contained in each sample based on the average peak area obtained for each of the drug standards. This software enabled corrections for the sample volume removed (without replacement) to be included in the computation. The percent drug released at a given time interval was expressed as mean  $\pm$  S.D.

**2.2.4.2. Statistical analysis.** A one-way ANOVA with a Scheffe's post hoc test was used to analyze the dissolution data obtained for each batch of formulations in order to compare the rate of drug release from the matrix tablets. The confidence limit was set at 95%.

#### 2.2.5. Water uptake and tablet erosion studies

Water uptake and tablet erosion studies were performed according to the method reported by Ebube et al. (1997b). The water sorption or erosion characteristics of the matrix tablets were expressed as either percent water uptake or percent weight loss. All experiments were carried out in triplicate and the results were expressed as the mean  $\pm$  S.D.

### 3. Results and discussion

Table 2 shows the effect of changes in compression force on the initial release of APAP from the compressed matrix tablets. Increasing the compression force from 2000 to 3000 lb slightly decreased the initial rate of APAP released after 60 min. Tablets compressed beyond 3000 lb showed tendency to cap and were not tested for in vitro drug release. Previous investigations have also indicated that changing the compression force had little effect on the dissolution rate of drugs from HPMC matrices (Ford et al., 1987; Ebube et al., 1997b; Mitchell et al., 1993c). In our present study, some formulations (e.g., B and F) showed an initial burst of drug release from matrices compressed at 2000 lb. Therefore, the rest of the in vitro drug release studies were performed only on tablets compressed at a compression force of 3000 lb.

The effect of co-active (PE) on the release of APAP from HPMC:HPC matrices was examined. Fig. 1 shows the release profiles of APAP from HPMC:HPC

Table 2

Effect of compression force on the initial release of APAP from matrix formulations consisting of various blends of HPMC and HPC

Matrix formulation <sup>a</sup>	Compression force (lb)	APAP release	
		% Release at <i>t</i> = 60 min	Initial rate <sup>b</sup> (mg/min)
A	2000	27.1	3.39
	3000	23.5	2.94
B	2000	44.4	5.55
	3000	24.5	3.06
C	2000	34.4	4.30
	3000	31.3	3.91
D	2000	65.6	8.20
	3000	55.0	6.88
E	2000	65.4	8.18
	3000	64.0	8.00
F	2000	61.5	7.69
	3000	39.5	4.94
G	2000	20.4	2.55
	3000	16.3	2.04
H	2000	17.7	2.21
	3000	14.4	1.80
I	2000	22.6	2.83
	3000	17.6	2.20

<sup>a</sup> Formulas for the specified formulations are contained in Table 1.

<sup>b</sup> Rate (amount of drug released/time) calculated from drug release data obtained between 0 to 60 min.

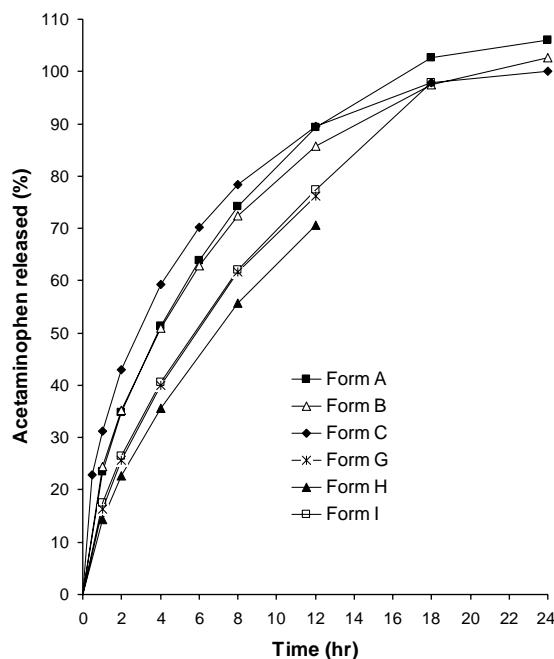


Fig. 1. APAP release from matrix tablets consisting of APAP (A, B, C) or APAP and PE (G, H, I), and 2:1 (A, G), 4:1.5 (B, H), or 5:1.3 (C, I) HPMC:HPC blends. Total polymer loading was 6.3%.

matrix tablets. The release of APAP from matrix tablets formulated with both PE and APAP (formulations G, H, I) was slower than APAP release from similar formulations (A, B, C) which contained APAP as the only model active. This is because PE in the formulations interfered with the hydration characteristics of the polymers and produced granules with smaller mean particle size than those containing only APAP, thus facilitating rapid hydration of the matrix (Ebube et al., 1997a,b). The result of this study is consistent with a previous report by Pham and Lee (1994), which indicated that “the presence of a highly water-soluble compound, fluorescein, in the HPMC matrix generates an additional osmotic gradient, thereby resulting in a faster rate of polymer swelling and a larger increase in gel thickness”. In the presence of a solvent, the mobility of polymer chain is enhanced, resulting in a gradual transformation of a glassy matrix into a rubbery swollen gel (Pham and Lee, 1994). In our present study, a gel layer with considerable consistency was formed rapidly around the tablet core, thus creating a viscous barrier between the tablet core and

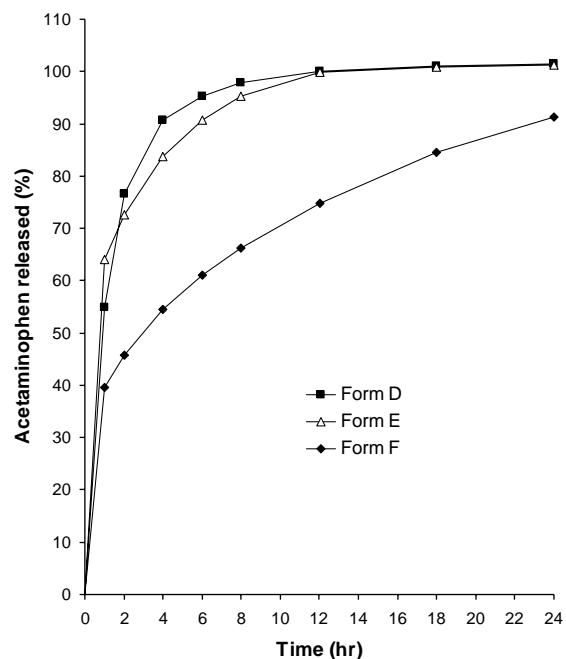


Fig. 2. APAP release from HPMC:HPC matrix tablets as a function of polymer loading—3.5% (D), 9.6% (E), and 19.2% (F). Total polymer consists of 4:1.5 HPMC:HPC blends.

the dissolution medium, and retarded APAP release. Our previous report discussed in details the mechanism of this interference (Ebube et al., 1997a).

APAP release from matrix tablets formulated with either APAP alone (A, B, C) or APAP + PE (G, H, I) was not significantly ( $P < 0.05$ ,  $F = 3.10$ ) influenced by changes in HPMC to HPC ratios (Fig. 1). The ratios of HPMC to HPC in the matrix formulations are presented in Table 1.

Fig. 2 shows the results of HPMC:HPC loading on APAP release for matrix tablets containing only APAP as model drug. The total polymer content of the matrix tablets consisted of 3.5% (formulation D), 9.6% (formulation E), and 19.2% (formulation F). In general, increasing the total polymer content of the tablets from 3.5% (D) to 19.2% (F) decreased the rate of APAP release. However, a relatively fast drug release was observed for formulations (D and E) containing  $\leq 9.6\%$  HPMC:HPC loading. At higher polymer loading, the viscosity of the gel matrix is increased which results in a decrease in the effective diffusion coefficient of the drug (Skoulios et al., 1993). Wan et al. (1993) have

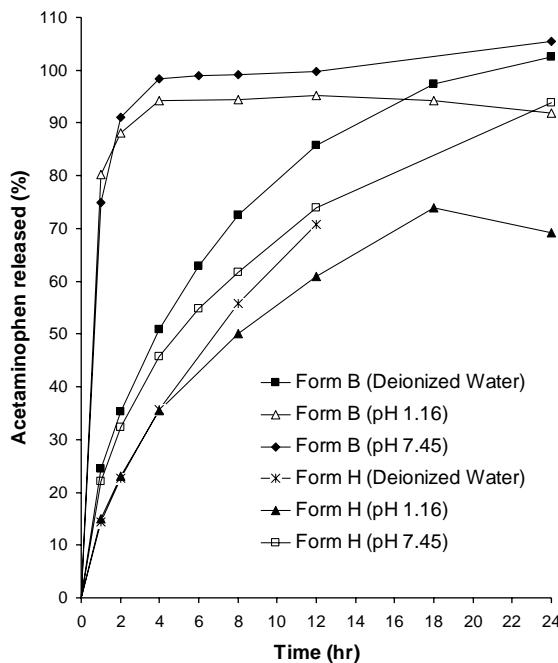


Fig. 3. Effect of pH on APAP release from matrix tablets containing APAP (B) or both APAP and PE (H). Each formulation consists of 4:1.5 HPMC:HPC blends and 6.3% total polymer loading.

also reported that other factors that may contribute to differences in drug dissolution profiles as a function of changes in total polymer concentration include differences in water penetration rate, water absorption capacity, and polymer swelling.

An initial burst of APAP release was observed in formulation F, after which the drug release was considerably retarded (Fig. 2). This phenomenon may be attributed to surface erosion or initial disaggregation of the matrix tablet prior to a gel layer formation around the tablet core (Ebube et al., 1997b).

The effect of pH on APAP release from the matrix tablets is shown in Fig. 3. Drug release from tablets containing APAP + PE (formulation H) was slower than that formulated with APAP alone (formulation B). Formulation B consisting of APAP only showed faster rate of drug release at pH 1.16 or 7.45, compared to drug release in deionized water (pH 5.9). A rapid burst of APAP release from formulation B at pH 1.16 or 7.45 was observed. This may be attributed to depolymerization of HPMC at low pH and/or decreased macromolecular association of the matrix components,

thus resulting in decreased consistency of the gel layer formed around the tablet core (Mitchell et al., 1993a). Thus, the gel layer on the tablet core with reduced viscosity is more susceptible to erosion and diffusion processes, resulting in rapid drug release. The faster drug release observed at pH 7.45 may be attributed to complexation. APAP has been shown to form complexes with polyethylene glycol 4000 (PEG 4000) and polyvinyl pyrrolidone (PVP) (Eide and Speiser, 1967; Eide, 1973). This complexation increased the water solubility and dissolution rate of APAP. A decline in percent of APAP released occurred after 18 h at pH 1.16 and this can be attributed to the hydrolysis of APAP to *p*-aminophenol at low pH (El-Obeid and Al-Badr, 1985). This phenomenon was not observed at pH 7.45. Similar observations have been reported in our previous studies (Ebube et al., 1997b). Further studies have been initiated to fully understand the mechanism of the observed pH effect on APAP dissolution from the polymeric matrices.

### 3.1. Kinetics of the *in vitro* drug release

The drug release data show a good fit to the Power Law Model (Spiepmann and Peppas, 2001) (Eq. (1)):

$$\frac{M_t}{M_\infty} = Kt^n \quad (1)$$

where  $M_t$  is the amount of drug released at time,  $t$ , and  $M_\infty$  is the amount of drug released after infinite time;  $K$  is a constant incorporating structural and geometric characteristics of the tablets, and  $n$  is a diffusional exponent indicative of the mechanism of drug release. The values of the kinetic constant ( $K$ ) and the release exponent ( $n$ ) determined from the drug release data are presented in Table 3. An  $n$  value of 0.5 is consistent with diffusion-controlled release, whereas a value of 1.0 indicates a zero order release. A detailed description of the *in vitro* kinetic model has been presented elsewhere (Ebube et al., 1997b).

The values of  $n$  determined for the various matrices studied ranged from 0.116 to 0.625 and the  $K$  values ranged from 1.04 to 50. The values of  $n$  and  $K$  are inversely related. A high  $K$  value may suggest a burst drug release from the matrix. The kinetic of drug release from HPMC:HPC matrices is consistent with a complex behavior.

Table 3

Values of release exponent ( $n$ ) and kinetic constant ( $K$ ) derived from Power Law Model for APAP release from the matrix tablets

Matrix formulation <sup>a</sup>	Kinetic constant ( $K$ )	Release exponent ( $n$ )	Regression coefficient ( $R$ )
A	2.44	0.554	1.00
B	2.88	0.524	1.00
	50.00 <sup>b</sup>	0.116 <sup>b</sup>	1.00
	23.60 <sup>c</sup>	0.282 <sup>c</sup>	1.00
C	4.86	0.455	1.00
D	12.80	0.362	0.98
E	28.60	0.196	1.00
F	13.00	0.265	1.00
G	1.28	0.625	1.00
H	1.04	0.643	1.00
	1.53 <sup>b</sup>	0.565 <sup>b</sup>	1.00
	2.97 <sup>c</sup>	0.495 <sup>c</sup>	1.00
I	1.50	0.601	1.00

<sup>a</sup> Formulas for the specified formulations are contained in Table 1.

<sup>b</sup> Kinetic constant ( $K$ ) and release exponent ( $n$ ) at pH 1.16.

<sup>c</sup> Kinetic constant ( $K$ ) and release exponent ( $n$ ) at pH 7.45.

The time taken to release 30% ( $T_{30}$ ) and 50% ( $T_{50}$ ) of APAP content from the matrix tablets were determined (Table 4). Tablets containing APAP + PE produced relatively higher  $T_{30}$  (146–186 min) and  $T_{50}$  (342–411 min) values than those containing APAP alone ( $T_{30} = 1$ –92 min;  $T_{50} = 17$ –233 min), thus indicating a slower drug release. No particular trend in  $T_{30}$  and  $T_{50}$  values were observed with changes in HPMC:HPC loading.

Table 4

Time taken for 30 and 50% of APAP release in deionized water (pH 5.9) from matrix tablets formulated with HPMC and HPC as polymeric excipients

Matrix formulation <sup>a</sup>	APAP release	
	$T_{30}$ (min)	$T_{50}$ (min)
A	92	232
B	88	233
C	55	168
D	11	43
E	1	17
F	23	161
G	156	353
H	186	411
I	146	342

<sup>a</sup> Formulas for the specified formulations are contained in Table 1.

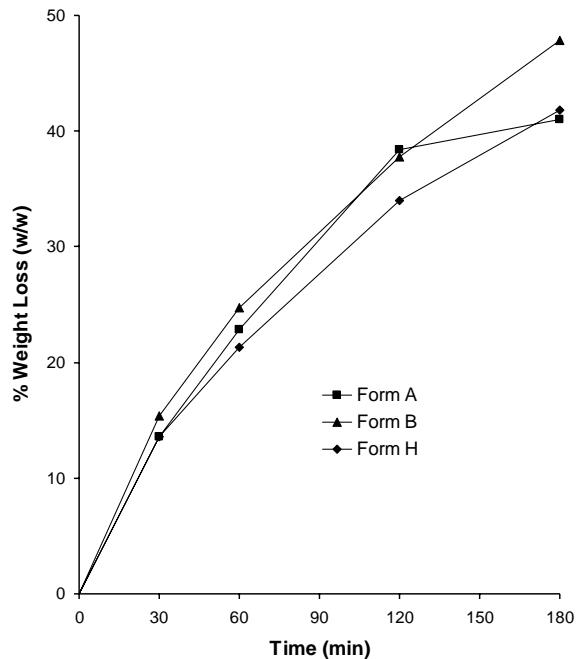


Fig. 4. Weight loss (%) of matrix tablets as a function of erosion time for HPMC:HPC systems containing APAP and 2:1 (A), 4:1.5 (B) polymer blends, or both APAP and PE, and 4:1.5 (H) polymer blends.

Tablet erosion studies show a progressive weight loss of the total tablet with erosion time (Fig. 4), and this is linearly related to the amount of APAP released. The effects of HPMC:HPC ratio, co-active and polymer loading on tablet erosion were not considerable. The tablet water uptake data show a good fit to the Vergnaud model (Vergnaud, 1993) (Eq. (2)) and the Schott second order model (Schott, 1992) (Eq. (3)), respectively, and the kinetics of tablet swelling was determined (Ebube et al., 1997b) (Table 5):

$$M_t = kt^n \quad (2)$$

$M_t$  is amount of liquid transferred at time,  $t$ , and  $k$  is a constant which depends on the amount of liquid transferred after infinite time, the porosity of the matrix and diffusivity. The exponent  $n$  indicates the mechanism of liquid uptake.

$$\frac{t}{W} = A + \frac{t}{W_\infty} \quad (3)$$

where  $W$  is the amount of water uptake at time,  $t$ , and  $A$  is a constant.  $W_\infty$  is the amount of water uptake

Table 5

Comparison of the characteristics of two kinetic models used to fit the matrix tablets water uptake data

Matrix formulation <sup>a</sup>	Kinetic model					
	Vergnaud model			Schott model		
	<i>k</i>	<i>n</i>	<i>R</i> <sup>b</sup>	<i>A</i>	<i>W</i> <sub>∞</sub>	<i>R</i> <sup>b</sup>
A	5.935	0.5555	0.99	0.5011	135.14	0.99
B	5.983	0.5857	1.00	0.5422	196.08	0.95
C	5.860	0.5713	1.00	0.5411	163.93	0.98

<sup>a</sup> Formulas for the specified formulations are contained in Table 1.

<sup>b</sup> *R* is the correlation coefficient for the regression line.

at infinite time and this is attained when the swelling pressure approached the elastic recovery tension of the swollen network.

The values of the exponent *n* for the HPMC:HPC systems (formulations A, B, H) ranged from 0.55 to 0.58. The results, as shown in Table 5, indicate that the kinetics of swelling for the HPMC:HPC matrices studied is both diffusion and stress relaxation controlled.

#### 4. Conclusions

The release of APAP from a heterogeneous hydrophilic matrix consisting of HPMC and HPC was significantly influenced by pH of the dissolution media, polymer loading, and the presence of a co-active, PE. Changes in the HPMC:HPC ratio or compression force did not appreciably affect the rate of drug release. The mechanism of drug release from these hydrophilic matrices is very complex.

The rate of APAP release and the physicochemical attributes of the matrix formulations were considerably altered when PE is present in the formulation as co-active. The presence of a highly soluble compound, such as PE, in an HPMC matrix can generate an additional osmotic gradient, which results in a faster rate of polymer swelling and increase in gel thickness (Pham and Lee, 1994). The mobility of the polymer chain is enhanced with gradual transformation of a glassy matrix into rubbery swollen gel, thereby creating a viscous barrier between the tablet core and dissolution medium (Pham and Lee, 1994). Thus, drug release from the matrix tablet is retarded considerably in the presence of PE.

The kinetics of tablet water uptake was consistent with diffusion and stress relaxation mechanism. The rate of tablet erosion correlates linearly with the amount of APAP release from the matrix tablets. Future studies will focus on fully understanding the complex relationship between the drug(s)–matrix polymers–water as well as processing conditions in order to predict drug release.

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