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Effect of source variation on drug release from HPMC tablets: Linear regression modeling for prediction of drug release

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ABSTRACT

The aim of this study was to investigate the effect of source variation of hydroxypropyl methylcellulose (HPMC) raw material on prediction of drug release from HPMC matrix tablets. To achieve this objective, the flow ability (i.e., angle of repose and Carr's compressibility index) and apparent viscosity of HPMC from 3 sources was investigated to differentiate HPMC source variation. The physicochemical properties of drug and manufacturing process were also incorporated to develop the linear regression model for prediction of drug release. Specifically, the *in vitro* release of 18 formulations was determined according to a $2 \times 3 \times 3$ full factorial design. Further regression analysis provided a quantitative relationship between the response and the studied independent variables. It was found that either apparent viscosity or Carr's compressibility index of HPMC powders combining with solubility and molecular weight of drug had significant impact on the release behavior of drug. The increased drug release was observed when a greater in drug solubility and a decrease in the molecular weight of drug were applied. Most importantly, this study has shown that the HPMC having low viscosity or high compressibility index resulted in an increase of drug release, especially in the case of poorly soluble drugs.

1. Introduction

Drug release from the dosage form is controlled mainly by the properties of polymer and drug used in the preparations. Since the physicochemical properties of powder excipients play a critical role in the formulation, processing, *in vitro* and *in vivo* performance of the finished dosage forms (Doelker et al., 1987; Whiteman and Yarwood, 1988; Parker and Rowe, 1991; Landin et al., 1992, 1993, 1995; Sriamornsak et al., 2007), the determination of critical properties of drug formulation become necessary to obtain the product with desired and reproducible attributes. The properties may show inter-vendor, and even inter-lot, variation. In some cases, physical characterization of powder excipients indicated that the materials are identical, however, their behavior during processing and in the finished product may vary (Chatlapalli and Rohera, 2002). This is due to the fact that the process and the product are sensitive to the physicochemical and morphological variation of the excipient that cannot be detected by routine physical characterization.

The most frequently used polymer for preparation of hydrophilic matrix tablets is hypromellose or hydroxypropyl methylcellulose (HPMC). HPMC is a cellulose derivative consisting of a backbone of cellulose with methoxylic and hydroxypropoxylic moieties substituted onto the glucose units. In commercial, pharmaceutically approved HPMC is available in different viscosities and substitution grades within certain specification limits (European Pharmacopoeia, 2005; United States Pharmacopeia, 2008). This implies that two sources of the same HPMC grades, which both meet the pharmacopoeia specifications, are expected to have a similar functionality and behavior. However, the specifications are broad and provide only average values of the polymer properties. The consequence of the broad specifications has been demonstrated in a previous study (Dahl et al., 1990) in which tablets composed of excipients with the same pharmaceutical grade, behaved differently. More importantly, the detected variability between the polymers was sufficient to have relevant effects on drug release. Recently, Chatlapalli and Rohera (2002) demonstrated the effect of excipient source variation on rheological behavior of diltiazem HCl–HPMC wet masses. The effect of chemical heterogeneity of HPMC on polymer release from matrix tablets was also studied by Viridén et al. (2009).

The application of an optimization technique consisting of statistical design to pharmaceutical formulation development would provide an efficient and economical method to acquire the necessary information to understand the relationship between formulation variables or causal variables and dependent variables or resulting responses and in order to realize the effects of causal

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variables and to obtain the appropriate formulation with target goal (Stetsko, 1986; Wanchana, 2003). In recent years, the pharmaceutical industry has used experimental design and *in silico* modeling more for the optimization of development of dosage forms (Dayal et al., 2005; Zaghloul et al., 2001; Elkheshen et al., 1996; Prakobvaitayakit and Nimmannit, 2003; Takayama et al., 1999), pharmacokinetics (Yamashita et al., 2006) and drug release (Li et al., 2003; Piriyaprasarth et al., 2009, 2010). However, the use of statistical design to investigate the effect of HPMC source variation on drug release has not been reported. Therefore, the objective of this study was to investigate the effect of HPMC source variation on prediction of drug release from HPMC tablets using statistical design. The crucial physical characterization was determined to differentiate HPMC source variation and used as independent variables combining with physicochemical properties of drug and manufacturing process to develop the mathematic model for prediction of drug release.

In many instances, quality control checks must be performed on powders to determine of certain attributes of the powder fall within a predefined range. These attributes include chemical composition, particle size, color, moisture and flow properties. In this study, the flow properties (e.g., angle of repose, Carr's compressibility index (CI) and Hausner ratio) and apparent viscosity of HPMC from three different sources were investigated. The flow properties and viscosity were determined and used as the independent (polymer) variables. Two compression forces for matrix tableting were used to represent the independent (process) variables and the physicochemical properties of drug such as molecular weight and solubility were used as the independent (drug) variables. Dependent variables studied included the percent of drug released at 1, 2, 4 and 8 h. Specifically, the *in vitro* release of 18 formulations was determined according to a $2 \times 3 \times 3$ full factorial design. Further regression analysis provided a quantitative relationship between the response and the studied independent variables.

2. Materials and methods

2.1. Materials

Theophyline anhydrous (lot number A00725) and caffeine (lot number 00099360-A) were obtained from BASF (Thailand) and theobromine (lot number 105K2510) was purchased from Sigma (St. Louis, MO, USA). Hydroxypropyl methylcellulose (HPMC) was purchased from three widely used sources, namely Methocel® E15LV (lot number WB27012407, Dow Chemical Co., Plaquemine, LA, USA), Pharmacoat® 615 (lot number 404183, Shin-Etsu Chemical Co., Naiigata, Japan) and Rutocel® E15 (lot number 20080446, Taiun Ruitai Cellulose Co., Shandong Province, PR China) and referred as HPMC-USA, HPMC-JP and HPMC-CH, respectively. All other chemicals were of analytical grade or pharmaceutical grade.

2.2. Measurement of flow ability of HPMC from various sources

2.2.1. Measurement of angle of repose

When HPMC powders were poured onto a horizontal surface, a conical pile was formed. The internal angle between the surface of the pile and the horizontal surface, known as the angle of repose, was measured. It is related to the density, surface area and shapes of the particles, and the coefficient of friction of the HPMC.

2.2.2. Determination of Hausner ratio and Carr's compressibility index (CI)

The bulk and tapped densities of HPMC from various sources were determined as the volume before and after 100 taps, respectively. The Hausner ratio was determined as the ratio of the bulk density to the tapped density (Eq. (1)) (Well and Aulton, 1988).

$$\text{Hausner ratio} = \frac{\rho_T}{\rho_B} \quad (1)$$

where ρ_T is the tapped density of the powder and ρ_B is the bulk density of the powder.

CI was determined as the percentage ratio at which the HPMC is packed down to the tapped density (Eq. (2)) (Well and Aulton, 1988).

$$CI = 100 \times \left(1 - \frac{\rho_T}{\rho_B}\right) \quad (2)$$

The Hausner ratio may be related to the compressibility of powder and values of <1.25 are indicative of good compressibility. The CI may be indicative of flowability and degree of packing of the material, which are relevant properties when filling the matrices of the tablet press. CI of <15% indicates an adequate flow of powders and stable packing, while values of >25% are characteristic of poor flow properties.

Table 1
Properties of drugs examined in the study.

Drug	Molecular weight (Da)	Solubility at 37 °C[a] (mg/mL)
Theobromine	180.17	0.7
Theophylline	180.16	11.8
Caffeine	194.19	37.5

[a] Data were obtained from Sriamornsak and Kennedy (2007).

2.3. Measurement of apparent viscosity

HPMC was dispersed in deionized water with gentle stirring at room temperature. Different concentrations (2 or 4%, w/v) of all HPMC were prepared. The apparent viscosity of all formulations was measured using a Brookfield digital viscometer (model RVD, Brookfield Engineering Laboratories, Inc., USA) with ultra low adaptor at 25 °C and a speed of 20 rpm. The measurements were made in triplicate.

2.4. Preparation of matrix tablets

2.4.1. Tablet preparation

Matrix tablets were prepared by weighing 300 mg (drug 100 mg and HPMC 200 mg) and directly compressed using a hydraulic press (Model 15011, Specac, USA) with 9.5-mm diameter flat-faced tooling. Drugs used in this studied were theophylline, theobromine and caffeine which have various solubilities (Table 1). The compression force was fixed at 2 and 5 kN.

2.4.2. Determination of tablet hardness and thickness

Six matrix tablets were sampled and individually subjected to test for hardness using Texture Analyzer (TA.XT Plus, Stable Micro Systems, UK). The mean and standard deviation of the tablet hardness were calculated. The thickness of the matrix tablets was determined using a caliper (Mitutoyo Dial Thickness Gauge, Mitutoyo, Japan) and the results were expressed as mean values of ten determinations.

2.5. Experimental design

To explore the effect of flowability and apparent viscosity of HPMC, drug properties and process variable (compression force) on drug release from matrix tablet, the experimental design was generated. The formulations were fabricated according to a $2 \times 3 \times 3$ full factorial design, allowing a simultaneous evaluation of polymer and drug variables, process variable and their interactions.

Table 2
Tablet formulations studied according to the factorial design.

Formulation code	Drug	Source of HPMC	Compression force (kN)
F1	Theobromine	HPMC-CH	2
F2	Theobromine	HPMC-CH	5
F3	Theobromine	HPMC-JP	2
F4	Theobromine	HPMC-JP	5
F5	Theobromine	HPMC-USA	2
F6	Theobromine	HPMC-USA	5
F7	Theophylline	HPMC-CH	2
F8	Theophylline	HPMC-CH	5
F9	Theophylline	HPMC-JP	2
F10	Theophylline	HPMC-JP	5
F11	Theophylline	HPMC-USA	2
F12	Theophylline	HPMC-USA	5
F13	Caffeine	HPMC-CH	2
F14	Caffeine	HPMC-CH	5
F15	Caffeine	HPMC-JP	2
F16	Caffeine	HPMC-JP	5
F17	Caffeine	HPMC-USA	2
F18	Caffeine	HPMC-USA	5

The experimental design with corresponding formulations is outlined in Table 2. In this study, the apparent viscosity of 2 and 4% (w/v) HPMC and the flowability were used as polymer variables. The parameter for the flowability included angle of repose, Hausner ratio and CI. The solubility and molecular weight were used as parameters for drug properties. The compression force at either 2 or 5 kN was the only process parameter studied. The dependent variables, which were tested, included the following: Y_1, Y_2, Y_3, Y_4 were the percent drug released at 1, 2, 4, 8 h, respectively.

2.6. In vitro drug release studies

An *in vitro* release of theophylline, theobromine and caffeine from matrix tablets was studied using USP dissolution apparatus II (model DT 70, Erweka, Germany). Nine hundred milliliters of phosphate buffer pH 6.8, as the dissolution medium, was placed in the glass vessel, the apparatus assembled, and the dissolution medium equilibrated to 37 ± 0.5 °C. The rotation speed of paddle was 50 rpm. At predetermined time intervals, the dissolution medium was removed for determining a drug concentration and fresh medium was replaced. The amount of drug released in the dissolution medium was measured using a UV spectrophotometer (model Lambda 2, Perkin-Elmer, USA) at the wavelength of 271 nm for theophylline and 273 nm for theobromine and caffeine. The studies were carried out in six vessels. The cumulative percentage of drug release was calculated and plotted against time.

2.7. Statistical analysis

Data were expressed as the mean ± standard deviation (SD). Analysis of variance (ANOVA) and Levene's test for homogeneity of variance were performed using SPSS version 9.0 for Windows (SPSS Inc., USA). *Post hoc* testing ($P < 0.05$) of the multiple comparisons was performed by either the Scheffé or Games–Howell test depending on whether Levene's test was insignificant or significant, respectively. The data were also analyzed using Unscrambler® software (CAMO Software India Pvt. Ltd., Bangalore, India). The mathematical model used was a linear model, which bears the form of Eq. (3).

$$Y_i = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3 \quad (3)$$

where Y_i is the level of response variables, b_j is the regression coefficient, X_i and X_j represent the main effect of the formulation variables and their interactions.

Table 3
Physical properties of HPMC from various sources.

Properties	Sources of HPMC		
	HPMC-CH	HPMC-JP	HPMC-USA
Angle of repose (°)	62.68	61.85	60.26
Bulk density (g/mL)	0.41	0.36	0.41
Tapped density (g/mL)	0.54	0.53	0.56
Hausner ratio	1.32	1.47	1.37
Carr's compressibility index (%)	23.0	31.0	27.3
Viscosity of 2% (w/v) HPMC (cps)	13.55 ± 0.18	12.27 ± 0.49	15.89 ± 2.36
Viscosity of 4% (w/v) HPMC (cps)	90.99 ± 2.27	62.61 ± 2.97	83.41 ± 1.88

3. Results and discussion

3.1. Flowability of HPMC from various sources

Flowability is a factor for several processes in pharmaceutical industry, including compaction process. However, much proven scientific understanding of powder flow has not been used fully by the pharmaceutical industry. In this study, the powder flowability in the context of various sources was used as independent variables. Table 3 shows flow properties of HPMC from different sources. The characterization revealed some differences in the angle of repose and bulk/tapped densities of HPMC from 3 sources. HPMC-USA and HPMC-CH exhibited higher bulk and tapped densities than HPMC-JP. In contrast, HPMC-JP yielded the highest CI and Hausner ratio whereas HPMC-CH yielded the lowest compressibility index and Hausner ratio. This indicated that HPMC-JP had a high degree of consolidation but higher angle of repose as compared with HPMC-USA (Table 3). The bulk and tapped densities of the HPMC were in a good agreement with the previous reports (Chatlapalli and Rohera, 2002; Rowe et al., 2006). The CI of the HPMC also influenced the thickness of compressed HPMC matrix tablets. For instance, HPMC-CH with the lowest CI produced the thickest tablets (data not shown).

3.2. Apparent viscosity of HPMC from various sources

The apparent viscosity of 2 or 4% (w/v) HPMC from different manufacturing sources, at 25 °C, determined with a rotational viscometer is also shown in Table 3. The apparent viscosity of 2% (w/v) HPMC from different sources was not significant different ($P > 0.05$) and have passed the viscosity specification limit (i.e., 12–18 cps). The specifications are broad and provide only average values of the polymer properties. Dahl et al. (1990) also reported that the broad specifications demonstrated different behaviors although the tablets composed of HPMC (type 2208) with the same pharmaceutical grade. In this study, however, the apparent viscosity of 4% (w/v) HPMC which is not suggested as specification was significantly different ($P < 0.05$) among HPMCs from different sources. The rank order of the apparent viscosity of 4% (w/v) HPMC is HPMC-CH > HPMC-USA > HPMC-JP. This is responsible for many complications associated with the use of HPMC in matrix tablet formulations. Therefore, the apparent viscosity of 4% (w/v) HPMC was proposed to be used as another polymer variable.

3.3. In vitro drug release studies

In vitro drug release from the HPMC matrix formulations using various sources of HPMC is depicted in Fig. 1. Three xanthine drugs, i.e., theobromine, theophylline and caffeine, with different solubilities were used. Each data point represents the mean of six measurements of each formulation. The properties of drug examined in the study, including molecular weight and aqueous

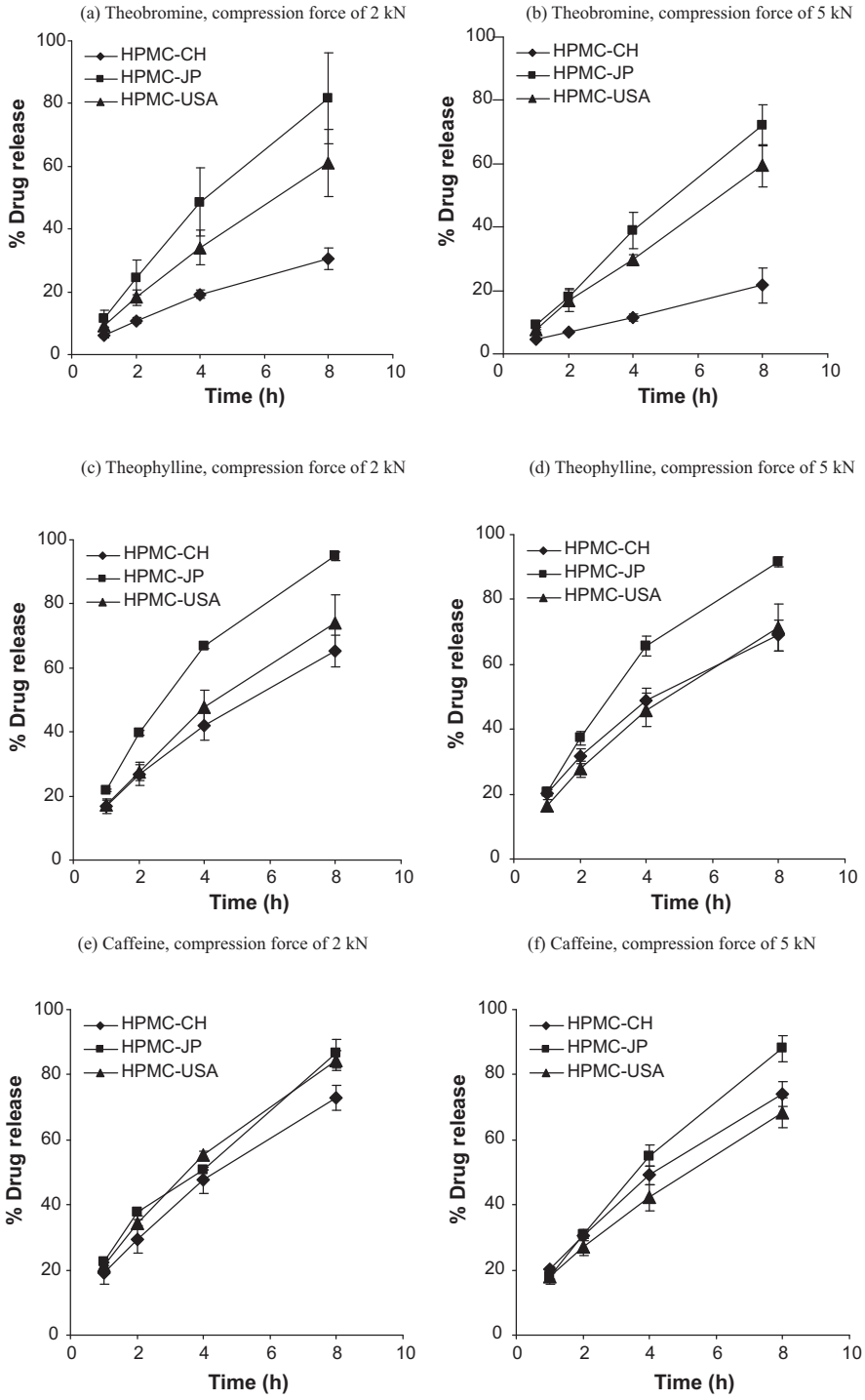

Fig. 1. Percent cumulative drug release prepared from various sources of HPMC for the matrix tablet formulations; (a) theobromine, (b) theophylline, and (c) caffeine, with the compression force of 2 and 5 kN ($n = 6$).

solubility at 37 °C (Sriamornsak and Kennedy, 2007), were shown in Table 1. In the case of theobromine, which is a poorly soluble drug (Table 1), the drug release from HPMC-JP tablets was faster than those from HPMC-USA tablets and HPMC-CH tablets. The drug release from HPMC-CH tablets was the slowest (Fig. 1a). This is in an excellent agreement with their flowability and viscosity results in this study. HPMC-CH having the highest apparent viscosity (4%, w/v HPMC) and the lowest CI and Hausner ratio (Table 3) demonstrated the slowest drug release from matrix tablets. When the compression force was increased from 2 to 5 kN, the performance of drug release from various sources of HPMC was not significantly different. However, the percentage of drug release decreased slightly with the increased compression force. This might be due to the influence of compression force on the hardness of the tablets (hardness of tablets was about 10–17 kP and 13–19 kP for tablets compressed with 2 and 5 kN, respectively), resulting in the decrease of drug release. Similar trend was observed in the case of theophylline (Fig. 1c and d) and caffeine (Fig. 1e and f). However, the effect of HPMC source variation was not obviously noticed in theophylline and caffeine. This may be due to a higher solubility of

Table 4
ANOVA table for different combining parameters of regression modeling of percent drug release from matrix tablets at 1 h; X_1 = Carr's compressibility index, X_2 = angle of repose, X_3 = solubility, X_4 = molecular weight, X_5 = compression force and X_6 = apparent viscosity of 4% (w/v) HPMC.

Source	d.f.	Sum square	Mean square	*F* value	Probability
$X_1 + X_2 + X_3 + X_4 + X_5 + X_6$					$r^2 = 0.9278$
Regression	6	547.46	91.24	23.55	<0.0001
Residual	11	42.62	3.87		
Total	17	590.08			
$X_1 + X_2 + X_3 + X_4 + X_5$					$r^2 = 0.9278$
Regression	5	547.46	109.49	30.83	<0.0001
Residual	12	42.62	3.55		
Total	17	590.08			
$X_1 + X_2 + X_3 + X_4$					$r^2 = 0.9177$
Regression	4	541.50	135.37	36.23	<0.0001
Residual	13	48.58	3.74		
Total	17	590.08			
$X_1 + X_3 + X_4 + X_6$					$r^2 = 0.9177$
Regression	4	541.50	135.37	36.23	<0.0001
Residual	13	48.58	3.74		
Total	17	590.08			
$X_1 + X_3 + X_4$					$r^2 = 0.9104$
Regression	3	537.22	179.07	47.43	<0.0001
Residual	14	52.86	3.78		
Total	17	590.08			
$X_2 + X_3 + X_4$					$r^2 = 0.8724$
Regression	3	514.76	171.59	31.90	<0.0001
Residual	14	75.31	5.38		
Total	17	590.08			
$X_3 + X_4 + X_6$					$r^2 = 0.9172$
Regression	3	541.23	180.41	51.70	<0.0001
Residual	14	48.85	3.49		
Total	17	590.08			

theophylline and caffeine than theobromine (Table 1). Generally, a highly soluble drug would have a faster drug release than a poorly water-soluble drug. Particularly, the drug release from the HPMC-USA matrix tablets, using 2 kN compression force, at 1 and 8 h was 9% and 61% for theobromine, 17% and 74% for theophylline and 21% and 84% for caffeine.

3.4. Effect of flowability and apparent viscosity of HPMC and drug properties on drug release from matrix tablets

Design of experiment (DOE) has been widely used in pharmaceutical field to study the effect of formulation variables and their interactions on response variables (Chu et al., 1991; Garcia-Gonzalez et al., 1993). In this study, a $2 \times 3 \times 3$ full factorial design (Table 2) was used. The flowability of HPMC of the same degree of substitution (type 2910, according to US Pharmacopeia) and viscosity grade (12–18 cps for 2% (w/v) HPMC according to specification) from 3 sources (HPMC-JP, HPMC-CH, HPMC-USA) and the properties, i.e., molecular weight and solubility of three drugs were used as independent variables. The other independent variables were manufacturing process, i.e., compression force at 2 and 5 kN. The ratio of HPMC to drug was fixed to 2:1. The results of drug release from different formulations, fabricated according to the factorial design, are presented in Fig. 1. There is a clear difference in the drug release pattern between the polymers from different sources as mentioned above. The percent cumulative drug release was high in the case of matrix tablets prepared from HPMC-JP (Fig. 1) while the use of HPMC-CH appeared to decrease the overall drug release from the matrix tablets, especially in the case of poorly soluble drug such as theobromine. The higher drug release observed from HPMC having higher CI (i.e., poor flowability) may result from the tablets with high weight variation and lower tablet strength (data not shown).

ANOVA test of the drug release indicated that the drug properties, apparent viscosity and flowability (such as angle of repose and CI) were crucial variables ($P < 0.05$) while the compression force and their interaction had no significant effect on drug release from matrix tablets. Table 4 shows ANOVA table for different combining parameters of regression modeling of percent drug release from matrix tablets at 1 h in which X_1 to X_6 was CI, angle of repose, solubility, molecular weight, compression force and apparent viscosity of HPMC (4%, w/v), respectively. The statistical results of the best obtained mathematic model based on the highest correlation coefficient (r^2), which corresponded to the smallest root mean square error (RMSE) value. When all parameters (X_1–X_6) were used for regression model, the r^2 of 0.9278 ($P < 0.001$) and the RMSE of 1.968 ($P < 0.001$) were achieved. However, only coefficient values obtained from molecular weight and solubility were significant (data not shown). When the apparent viscosity was removed from the model, the r^2 and the RMSE were not changed. ANOVA results revealed that the compression force (X_5) was not significant parameter for the release model, therefore, this parameter was eliminated from the regression model. The r^2 became 0.9177 and RMSE was 1.934 ($P < 0.01$) when X_1–X_4 were used as independent parameters. This result was comparable from those obtained from the combination of solubility, molecular weight and apparent viscosity (X_3, X_4, X_6; r^2 of 0.9172 and RMSE of 1.868, $P < 0.01$). Considering that both CI and angle of repose represented the flowability of HPMC; however, the correlation (r) between these two parameters was quite low ($r = -0.382$). Thus, the regression models containing 3 independent parameters; molecular weight, solubility and CI or angle of repose were developed. Interestingly, the combination of CI, solubility and molecular weight gave the comparable r^2 (0.9104, $P < 0.01$) to the combination of three parameters (X_3, X_4, X_6; $r^2 = 0.9177$, $P < 0.01$). The incorporation of angle of repose with solubility and molecular weight resulted in the decrease in the r^2 (0.8724, $P < 0.01$). In addition, the high correlation between CI and the apparent viscosity of 4% of HPMC was found ($r = -0.952$). Therefore, the regression model using these two parameters combined with molecular weight and solubility did not provide a better model compared with using three parameters (X_1, X_3, X_4 or X_3, X_4, X_6). Previous works (Ranga Rao et al., 1988; Hiremath and Saha, 2008; Siepmann and Peppas, 2001; Grassi et al., 2004) reported that various formulation factors such as polymer viscosity, polymer particle size, drug/polymer ratio, drug solubility, compression

Table 5
Regression analysis data for percent cumulative drug release from matrix tablets at various times using solubility (X_3), molecular weight (X_4) and apparent viscosity of 4% (w/v) HPMC (X_6) as formulation parameters.

Parameters	% Cumulative drug release							
	1 h		2 h		4 h		8 h	
		P-value		*P*-value		*P*-value		*P*-value
Model	$F = 51.703$	<0.0001	$F = 31.926$	<0.0001	$F = 21.761$	<0.0001	$F = 17.772$	<0.0001
Intercept	325.96	<0.0001	510.91	<0.0001	778.34	<0.0001	801.62	0.0017
X_3	0.978	<0.0001	1.427	<0.0001	2.019	<0.0001	2.088	0.0009
X_4	−1.724	<0.0001	−2.621	<0.0001	−3.887	0.0002	−3.717	0.0063
X_6	−0.101	<0.0001	−0.301	0.0007	−0.621	0.0003	−1.000	0.0001
r^2	0.917		0.872		0.823		0.792	
Standard error	1.87		3.59		6.54		9.57	

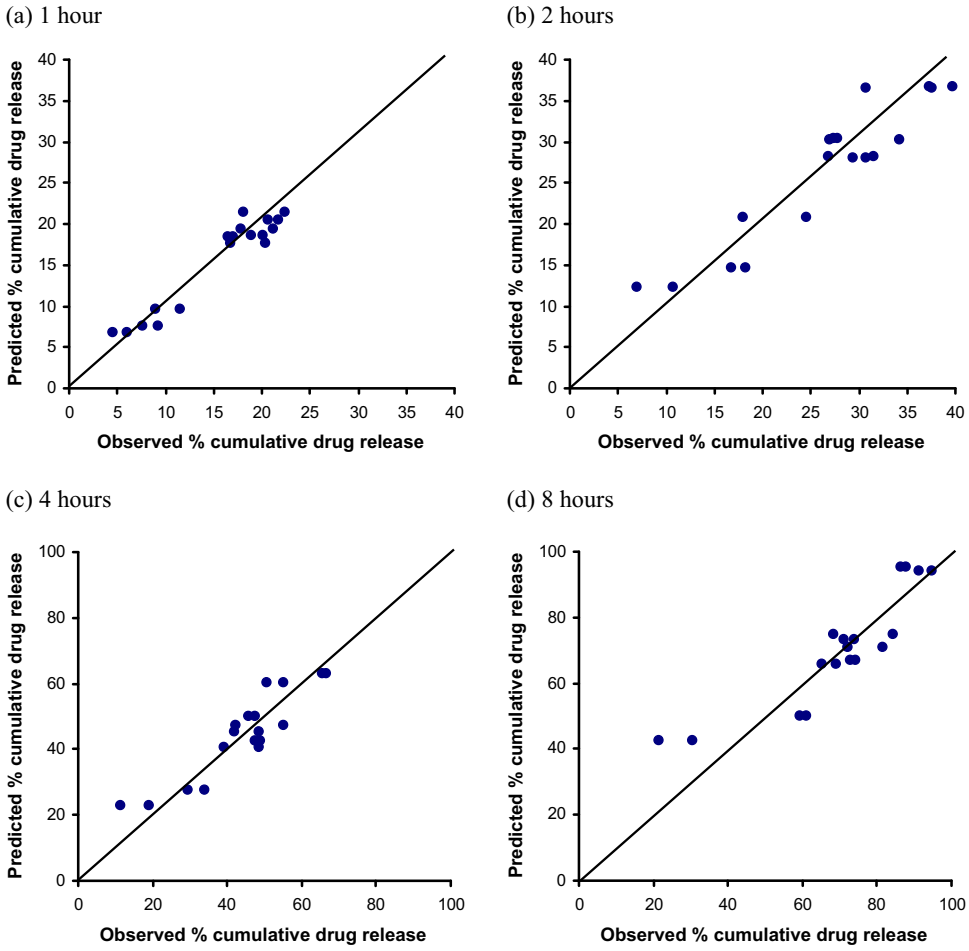

Fig. 2. The relationship between observed percent cumulative drug release and predicted percent cumulative drug release; (a) 1 h, (b) 2 h, (c) 4 h, and (d) 8 h.

force and testing medium influenced the drug release from HPMC matrices. In this study, various formulation factors such as polymer particle size, drug/polymer ratio and testing medium were controlled. Drug solubility, molecular weight of drug and the polymer viscosity or the simple flowability factor such as CI were found to be the critical factors for prediction of the drug release from HPMC matrix tablets. However, in this study, the contribution of compression force in the improvement of r^2 is quite small. This might be due to the compression force used in this study was not significantly different. Table 5 shows the regression analysis data for percent cumulative drug release from matrix tablets at various intervals using solubility, molecular weight and apparent viscosity as formulation parameters. Fig. 2 shows the relationship between observed percent cumulative drug release and predicted percent cumulative drug release at various time intervals. The r^2 was in the range of 0.792–0.917 and RMSE was in the range of 11.647–8.441. Therefore, the proposed mathematic model, in which drug solubility, molecular weight and apparent viscosity of HPMC were used as formulation parameters, was able to predict the percent cumulative drug release at various times with a reasonable degree of accuracy.

4. Conclusion

This study revealed the effect of HPMC source variation and physicochemical properties of drug on prediction of drug release from HPMC tablets. The source of HPMC could be differentiated by their physical properties such as CI, bulk and tapped densities

and apparent viscosity. Most importantly, it was found that the HPMC having low viscosity or high CI resulted in an increase in drug release, especially in the case of poorly soluble drugs. Interestingly, the aqueous solubility and molecular weight of drug as well as apparent viscosity and CI of each HPMC were found to be the critical factors for prediction of drug release from matrix tablets. However, other properties which are not present here may also be the factors influencing the prediction of drug release, for example, surface characteristics of polymer powder, swelling properties of polymer, the rate of water uptake into the matrices, etc. From the results obtained from this study, it can be concluded that computer models developed could be applied in pharmaceutical industry to assist in decision making and to select quality materials and manufacturing processes in order to ensure the pharmaceutical characteristics desired.

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