Effect of Ionic Strength on the Temperature-Dependent Behavior of Hydroxypropyl Methylcellulose Solution and Matrix Tablet

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ABSTRACT: The focus of the present study is on the temperature-dependent behavior of hydroxypropyl methylcellulose (HPMC) solutions at various ionic strength levels. Such behavior is then introduced into the study of tablet dissolution with the aim of explaining why ionic strength could vary the dissolution rate or cause the tablets to disintegrate. The results show that increasing the concentration of solute in the dissolution media will affect the thermal property of hydrated HPMC and then have an effect on the matrix tablets dissolution process. Of the thermal property, reduction of the cloud point is believed to have some relationship with the decrease of the dissolution rate, and decline of the thermal gelation temperature (TGT) might be responsible for the disintegration of the matrix tablets. A ''gel out'' process concerning the mechanism of the disintegration has been put forward, and a rheological method to test the lower critical solution temperature (LCST) is also presented. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 102: 4066–4074, 2006

Key words: water-soluble polymers; rheology; thermal properties; gel out; burst release

INTRODUCTION

Hydroxypropyl methylcellulose (HPMC) is frequently used as the hydrophilic matrix system for controlled drug delivery. Its property and application have been widely studied. Four types of HPMC have been classified by the USP according to the chemical substitution of the ether: A, F (HPMC 2906), E (HPMC 2910), and K (HPMC 2208) with different specialization in applications. Type K grade is usually used in controlled release, because it has relatively low content of methyl groups and high content of hydroxypropyl groups which would present a more rapid hydrating rate compared with other types.

In the aqueous solution state, HPMC has two characteristic temperatures: (1) a lower critical solution temperature (LCST) where the polymer solution shows clouding or precipitation, and (2) a thermal gelation temperature (TGT) at which polymer solution exhibits a sol-to-gel phase transition.[1] The first transition temperature, LCST, which assesses the reduction of polymer solubility with increased temperature,[2] reflects the dehydration process of the polymer. The second transition temperature, TGT, reflects an uprising internal interaction between the polymer molecules mostly governed by hydrophobic interaction rather than hydrophilic interaction between water and polymer molecules.[3] At low temperatures, the cellulose molecules are hydrated and there is little polymer–polymer interaction apart from entanglement.[2] As the temperature rises, the viscosity of the solution decreases and before a complete dehydration the polymer–polymer association occurs leading to an increase in viscosity.[3] However, the interrelationship between clouding, precipitation, and gelation remains relatively poorly understood; indeed, the definitions used for these processes have not been assigned to universal agreement.[4] Therefore, in this study, we conducted a series of experiments with the aim to elucidate their interrelationships.

The first transition temperature (LCST) of the polymer solutions is widely described by the Cloud point. Besides, a precipitation process has generally been noted at the LCST. In the present work, a rheological method that was originally used to test the TGT of the polymer is introduced to study the precipitation process. In this process, we have noted an intensive transition on viscosity–temperature curve. By mathematically differentiating the data curve, we acquired a transition point called the precipitation point in the present study, to characterize the precipitation process.

In general, when water-soluble polymers such as HPMC are used as controlled release matrix, the following process should be observed: when polymer matrix is in contact with the thermodynamically compatible solvent, the latter begins to diffuse molecularly into the former. Swelling of the polymer then occurs and a gel-like layer that acts as a protective viscous

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part[2] will be formed adjacent to polymer–solvent interface due to plasticization of the polymer by the solvent. Failure to form a uniform and coherent ''gel layer'' may lead to immediate drug release. After an induction time, the polymer is dissolved.[5] Thereafter, diffusion of water-soluble drugs and release of water-insoluble drugs by erosion (dissolution) of the polymer will occur, forming the basis of controlled release mechanism.

Despite its wide application in controlled drug delivery for decades, HPMC matrix sometimes still show some ''burst release'' cases in tablets dissolution process onto which doubt about its safety during the drug delivery in human bodies might be cast.[6–8] Salts were believed to have some relationships with such phenomenon. Therefore, in the present work, the salt effect on the thermal property of the HPMC has been intensively studied, and a reasonable mechanism concerning the ''burst'' process has been presented.

EXPERIMENTAL

Materials

HPMC Methocel K15M was a gift from the Colorcom Company supplied by the Dow Company (22% methoxyl and 8.1% hydroxypropyl; $M_w = 4.252 \times 10^5$, $M_n = 8.6356 \times 10^4$, $M_w/M_n = 4.9238$). Dom K15M was gifted by the Ruitai Company in China (25.3% methoxyl and 9.1% hydroxypropyl; $M_w = 6.0579 \times 10^5$, $M_n = 9.321 \times 10^4$, $M_w/M_n = 6.4993$). Sodium chloride, disodium hydrogen phosphate, sodium sulfate, potassium chloride, sodium citrate, sodium phosphate, sodium dihydrogen phosphate, sodium acetate, and sodium bicarbonate were all of laboratory reagent standard from Nanjing Chemical Reagent No. 1 Factory. Propranolol hydrochloride was C.P. standard.

Cloud point studies

A 2% w/v HPMC solution was prepared by dispersing the pre-weighed polymer into approximately one-third of the total amount of distilled water previously heated to 90°C. After completed dispersion, some more distilled water or distilled water containing the required amount of dissolved electrolyte was added until the required weight. The solutions were stored overnight in a refrigerator to achieve full hydration. Samples were transferred to 1-cm^2 cuvettes before testing and any air bubbles entrapped in the gels were removed by ultrasonication. The samples were then placed in water bath with temperature regulator and the temperature gradually increased. Initially, readings were taken at 5°C intervals, which were reduced to 1-°C increments near the transition point. The samples were measured spectrophotometrically at 800 nm against a 2% distilled water solution of the HPMC maintained at room temperature. The cloud point was taken to be the temperature at which the light transmission was 50% of the reference.

Precipitation point studies

Preparation method of 2% w/v HPMC solution was same as above. The samples were placed in a water bath with a temperature regulator to hold at a certain starting temperature of preferably 15°C. When the temperature remains constant for 10 min, the heating process begins using the temperature regulator. The heating rate is ~ 1°C/min. The viscosity of the gel solution was recorded at 2°C increments, which were then reduced to 1°C near the transition point using the rheometer (DVIII Ultra, Brookfield Engineering Institute) with computer control. Because HPMC solution is a non-Newtonian fluid, its viscosity varies under different shearing rate conditions. For this reason, in our tests, if a change in spindle rotation speed is needed, an extra recording would be made closely before and after the speed change with the aim to eliminate the instrument's effect on the viscosity change. After the recording, a viscosity–temperature curve was first made using the data acquired; this curve was then differentiated mathematically in Origin 7.0. The software will calculate the slope values of the curve and yield a derivative curve that represents the slope change of the original data. Generally, a derivative curve may reflect the changing rate of the original curve; we used this method in the present study to see the temperature at which the viscosity varied most. The precipitation point was taken as the temperature in the derivative curve at which the viscosity changing rate reached a peak value after the overall viscosity was lowered to a certain degree (see details in the Discussion section).

Thermal gelation temperature studies

This study followed the precipitation point determination during the heating process on the rheometer. After the viscosity of the solution decreased to a minimum level and remained that value for some moment, the viscosity increased sharply and intensively at a certain temperature. The TGT was taken to be the temperature in the derivative curve at which the viscosity changing rate increase sharply above the cloud point (see details in discussion part).

Dissolution studies

Tablets (10-mm diameter) containing 24% propranolol hydrochloride, 54% HPMC, 19% lactose, and 1% magnesium stearate were prepared by wet granulation and then compression with crushing strength of ~ 10 kg. Three tablets were tested using the ZRS-8G Intelligent Dissolution Tester (Tianjin University, Radio Factory,

Tianjin, China) into various dissolution media maintained at 37°C. The USP27 dissolution apparatus I (basket method) was used, rotating at 100 rpm, and samples were collected at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 h, which were then assayed spectrophotometrically at 319 nm. All media in these tests were prepared in molar concentrations according to pre-calculated ionic strength; all of the media contained only the electrolyte stated.

RESULTS AND DISCUSSION

Effect of ionic strength produced by various electrolytes on the cloud point of 2% HPMC solutions

Several electrolytes were chosen to produce a wide range of ionic strength separately to determine their effect on the cloud point of 2% HPMC gels. The results showed that as the ionic strength increased, the cloud point decreased with an intensive negative linear correlation as shown in Table I. The value of CP_0 calculated for HPMC solution with various electrolytes averaged at 68.48°C ($\log CP_0 = 1.835$) where the tested value for the aqueous solution was 70.9°C. The ability of an electrolyte to salt out a polymer from its solution generally followed the salts order in the lyotropic series.[9] In our test, this order was: $Cl^- <$ acetate $<$ citrate $< PO_4^{3-} < HCO_3^- < SO_4^{2-} < PO_4^{3-} < HPO_4^{2-} < H_2PO_4^-$. The cloud point reduction is explained by ions that have a greater affinity for water than HPMC removing water of hydration from the polymer and thus dehydrating or ''salting out'' the polymer.[9]

It is well known that the molecules of a certain substance will accelerate its moving rate when giving a heating supply. Because the polymer molecule size and the water molecule size differ from each other greatly, they will behave quite differently when receiving such a heating supply. The smaller ones turn to move quickly while the bigger ones turn to move slowly. Such a discrepancy in moving velocity will dispatch them from each other therefore. The presence of any electrolytes will promote this reduction in water–polymer interaction because of the competing of the water by salts which exhibit to us a decrease of the cloud point.

Determination of precipitation point and TGT using rheological method

Viscosity serves as a fundamental parameter in discussing a property of the polymer, in that it has a close relationship with the molecular weight and distribution of the polymer. Also when a polymer solution undergoes such a heating process or experiences such an adding of some electrolytes in it, its viscosity will display various values under different circumstances for the internal interaction of the system (polymer–

TABLE I
Cloud Point Value of 2% Methocel K15M Solution under Different Ionic Strength Levels for Various Electrolytes ($n = 3$)*

Electrolytes	Ionic strength (mol/L)							Regression equation ($\log CP = K_{cp} I + \log CP_0$)	K_{cp}	r
	0.1	0.2	0.3	0.4	0.5	0.6	0.8			
NaCl	67.3 ± 0.1	64.0 ± 0.1	61.5 ± 0.2	59.3 ± 0.2	58.0 ± 0.3	56.3 ± 0.1	51.4 ± 0.2	$y = -0.15x + 1.84$	−0.15	0.9907
KCl	67.1 ± 0.0	63.9 ± 0.2	60.7 ± 0.2	58.8 ± 0.0	56.9 ± 0.1	56.0 ± 0.0		$y = -0.16x + 1.84$	−0.16	0.9843
CH_3COONa		60.5 ± 0.0		55.2 ± 0.3		49.8 ± 0.1		$y = -0.21x + 1.82$	−0.21	0.9997
$Na_3C_6H_5O_7$	65.2 ± 0.0	60.7 ± 0.3	57.2 ± 0.1	54.4 ± 0.2	51.1 ± 0.0	48.0 ± 0.2		$y = -0.26x + 1.84$	−0.26	0.9990
Na_3PO_4	63.5 ± 0.0	59.2 ± 0.1	56.3 ± 0.2	52.6 ± 0.0	49.6 ± 0.0	45.7 ± 0.1	38.9 ± 0.1	$y = -0.28x + 1.83$	−0.28	0.9982
$NaHCO_3$		59.0 ± 0.1		50.8 ± 0.0		44.3 ± 0.3		$y = -0.31x + 1.83$	−0.31	1.0000
Na_2SO_4	62.6 ± 0.2	58.7 ± 0.2	52.2 ± 0.1	48.1 ± 0.1	43.3 ± 0.1	39.7 ± 0.4	29.6 ± 0.2	$y = -0.41x + 1.84$	−0.41	0.9982
Na_2HPO_4	63.3 ± 0.2	57.5 ± 0.1	52.8 ± 0.0	47.7 ± 0.3	43.4 ± 0.2	39.1 ± 0.1	28.9 ± 0.1	$y = -0.42x + 1.84$	−0.42	0.9996
NaH_2PO_4	60.2 ± 0.0	52.3 ± 0.1		39.8 ± 0.0	32.8 ± 0.1			$y = -0.60x + 1.84$	−0.60	1.0000

* K_{cp} in the equation stands for salting ability for certain electrolyte. The higher the absolute value, the more influential it is.

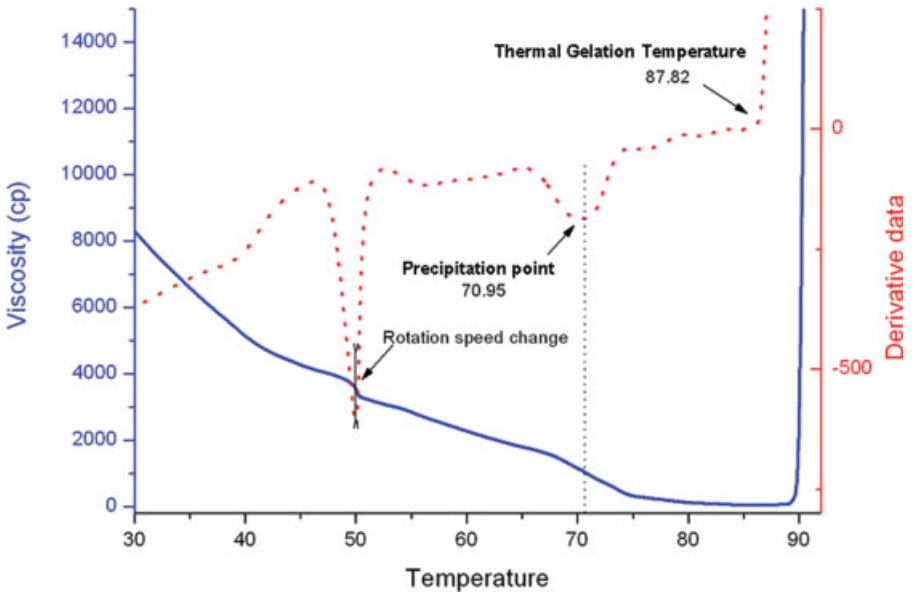

Figure 1 Viscosity–temperature curve and its derivative curve for 2% Methocel K15M in aqueous solution. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

solvent–electrolytes) will change accordingly. Therefore, by using rheological method to monitor the viscosity change, there is the possibility to further our information about the internal interaction transformation of the system at various conditions.

Figure 1 shows a typical viscosity changing profile in such a heating process for a 2% HPMC solution. The solid line is drawn according to the data obtained by the rheometer; the dot line represents the derivative value of the curve calculated by Origin 7.0 software where a peak or valley stands for a sharply change in slope of the curve.

As shown in this graph, as the temperature rises, the viscosity of HPMC solution first decreases, this could be partly explained by the dehydration of the polymer caused by the absorption of translational energy by the polymer molecules,[10] which leads to a discrepancy in moving velocity of the polymer and water molecules. Then, the decline of the viscosity reaches a certain level that the polymer–water binding force lowered to minimum (at $\sim$ 68°C), thereafter HPMC precipitate from the solution (68–74°C). Continuing heating will promote the binding between polymer molecules. And at a certain temperature, the viscosity of the newly formed polymer gels increase abruptly.

On the dotted line, which represents the slope of the viscosity–temperature curve, several valleys could be found, each indicating that the existence of an abrupt slope change. The first big valley at $\sim$ 50°C in this graph is caused by the changing of the spindle rotation speed on the DVIII rheometer, which could be ignored because of the instrument reason. At $\sim$ 88°C, there is an abrupt change in slope where the viscosity increases sharply. Normally, it is believed to be the TGT. At $\sim$ 71°C, another valley is found and is named as precipitation point based on the precipitation of the polymer molecules from the solution. It is very interesting that the precipitation point on this graph coincides with the cloud point for the same solution (Fig. 2). It suggests that at this temperature, the turbidity change of the solution is accompanied by the viscosity change. Therefore, the precipitation point and the cloud point might be regarded as indeed one transition point, and that is LCST. Consequently precipitation of the polymer from

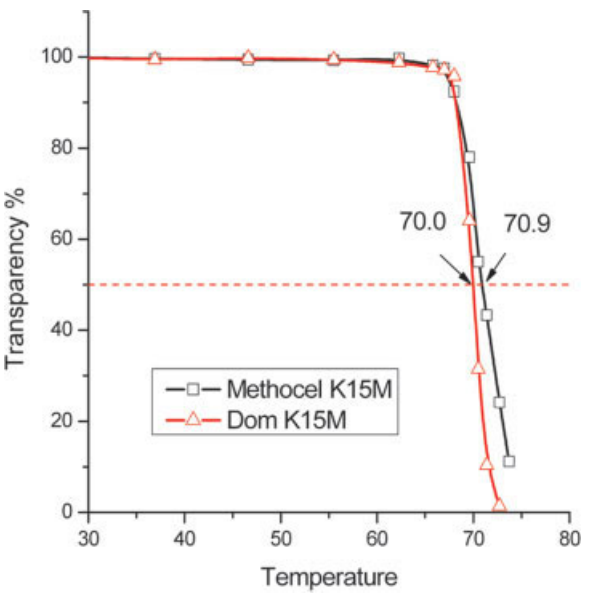

Figure 2 Transparency–temperature curve for 2% Methocel K15M and Dom K15M in aqueous solution. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

the solution gives the reason to why solution clouds under heating.

Moreover, the precipitation occurs at the end of the dehydration process but differs from that in viscosity changing rate (as shown on the derivative curve). Therefore, a phase-separation process, as some researchers have noted,[1,4] might exist. The phase separation is caused by precipitation, and it leads to the formation of dense aggregates which reduce the mobility of the system leading to gelation.[11] On our graph this gelation process occurs at TGT.

More examples are displayed in Figure 3 and all prove that using a rheological method to assess the LCST is both reasonable and accurate. As is well known, a rheological method was originally used in the test of the TGT, while in our study we introduce it into the determination of the precipitation point, a type of LCST. The advantage of doing this lies in that two transition temperatures of the polymer solution (LCST and TGT) could thus be successfully integrated by just one test, and might be compared simultaneously and comprehensively. Thus, the interrelationship between them might be much clearer.

Salts effect on the precipitation point and the TGT

Based on the rheological method discussed above, several tests with the aim of studying the salts effect on the precipitation point and the TGT are then conducted (Table II). The precipitation point decreases with increased ionic strength. After comparing the precipitation point and the cloud point at various levels of ionic strength, it is found that the two values are equal at almost all levels, further confirming that clouding and precipitation indeed occur simultaneously at LCST for the polymer solution under heating, whether salts are added or not. If no salt is added in, heating then becomes the driving force of dehydration, and at LCST the polymer will precipitate from the solution accompanied by clouding. If salts exist, the LCST might be reduced when the salts exhibit the water-competing effect just as occurred in our tests.

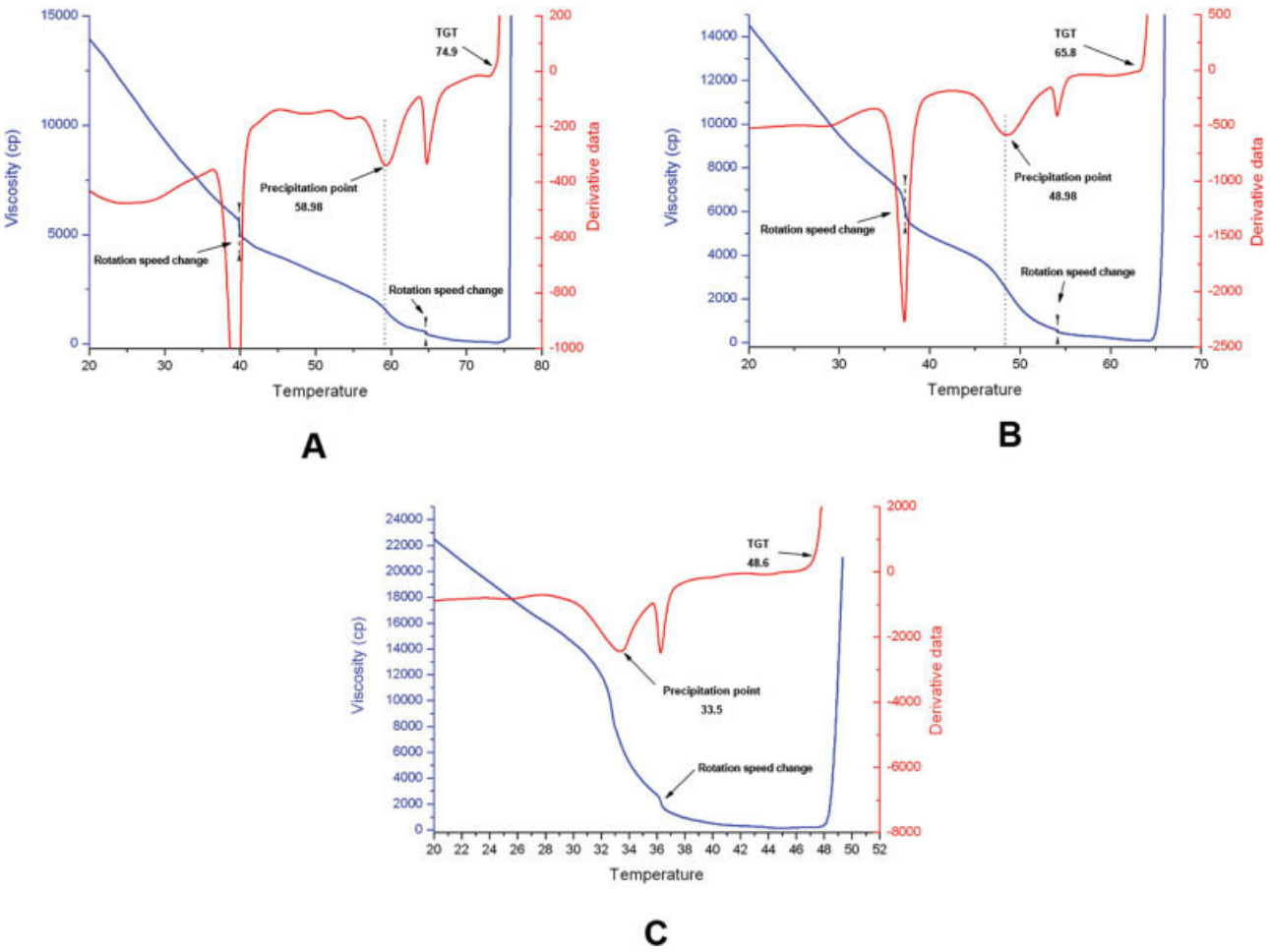

Figure 3 Effect of ionic strength produced by disodium hydrogen phosphate on the rheological behavior of 2% Methocel K15M solution. (A) I = 0.2 mol/L; (B) I = 0.4 mol/L; (C) I = 0.6 mol/L. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE II
Cloud Point, Precipitation Point, and Thermal Gelation Temperature (TGT) Obtained under Different Ionic Strength for Two Kinds of HPMC 2% Solution

HPMC type	Solution type	Ionic strength (mol/L)	Cloud point (°C)	Precipitation point (°C)	TGT (°C)	Retained gelling temperature*
Methocel K15M	Distilled water	0	70.9	70.95	87.82	16.87
	Na_2HPO_4	0.2	57.5	58.98	74.90	15.92
		0.4	47.7	48.98	65.80	16.82
		0.6	39.1	33.50	48.60	15.10
	NaH_2PO_4	0.2	52.3	50.87	66.64	15.77
Dom K15M	Distilled water	0	70.0	69.98	77.12	7.14
	Na_2HPO_4	0.2	57.4	56.44	63.75	7.31
		0.4	48.2	51.98	59.03	7.05

* Retained gelling temperature is defined as the temperature gaps between precipitation point and thermal gelation temperature (TGT).

Similarly, the TGT decreases as the ionic strength goes up. And it is interesting that the temperature gap between the precipitation point and TGT in each run remain constant at various ionic strength levels. This gap is defined as ''retained gelling temperature'' in the present work and based on our experiments, this value should be constant for certain type of HPMC. For Methocel K15M (Dow), this value is $\sim 16^{\circ}C$, while for Dom K15M (Ruitai), it exhibits a $7^{\circ}C$ temperature gap. Based on this gap, it is suggested that the salts only have an impact on the dehydration process or precipitation process but not on the gelation process. This means the interaction between water and polymer molecules in the solution under heating will be affected by the salts, but the hydrophobic interaction between polymer molecules after phase separation that then will lead to gelation will not be affected by the salts. It is highly possible that the latter interaction will only depend on the chemical constitution of the HPMC.

Effect of ionic strength on the dissolution of propranolol from HPMC K15M matrices tablets

A series of experiments carried out to determine the influential ability of the various salts at specific ionic strength on drug dissolution were conducted. Propranolol hydrochloride was chosen as the model drug in HPMC matrix.

A three-dimensional-graph is then made so that the changing trend of the release rate could be clearly noticed and typified (Fig. 4). In all cases, the release rates decreased initially from the control (distilled water) with an increase in ionic strength of the electrolytes, until a minimum release rate was obtained ($I = 0.4$ mol/L). As the ionic strength continued to increase (above $I = 0.5$ mol/L), a ''burst release,'' defined as that release ratio within 3 h exceed 70%, appeared and the release behavior changed significantly. Drug release data from the tablets in various dissolution media are summarized in Table III.

If the decreasing release rate of the drug caused by the uprising of the ionic strength was compared with the decreasing cloud point value of the sole HPMC solution, the decline trend of the two coincided with each other perfectly. As shown in Figure 5, which represents the dissolution profile of same propranolol HPMC matrix in three types of dissolution media (identical ionic strength of 0.2 mol/L), the release rate of the drug in three solutions follows the below sequence: $NaCl > Na_2SO_4 > Na_2HPO_4$, which amazingly paralleled with the cloud point reducing of the three at ionic strength of 0.2 mol/L: NaCl (64.0°C) $> Na_2SO_4$ (58.7°C) $> Na_2HPO_4$ (57.5°C).

Therefore, the reducing of the dissolved HPMC's solubility caused by the water-competing effect of the electrolyte appears to be one explanation for the

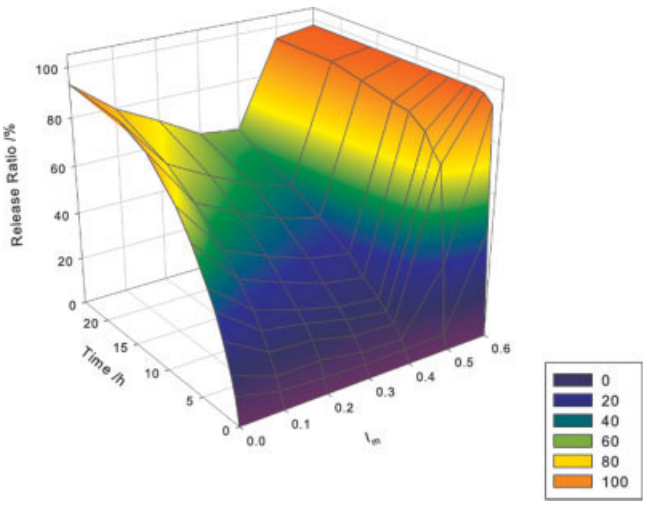

Figure 4 Three-dimensional graph of dissolution profile for propranolol hydrochloride with HPMC K15M as matrix under different ionic strength levels produced by disodium hydrogen phosphate. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE III
Comparison of the Dissolution Rate and Cloud Point of 2% Methocel K15M under Different Ionic Strength Solutions

Electrolytes	Ionic strength (mol/L)	Higuchi release rate (% · $min^{-1/2}$)	Cloud point (°C)
None	0	2.7693	70.9
Na_2HPO_4	0.1	2.3498	63.3
	0.2	2.0300	57.5
	0.3	1.7929	52.8
	0.4	1.6380	47.7
	0.5	Burst release	43.4
	0.6	Burst release	39.1
NaCl	0.2	2.6753	64.0
	0.3	2.4393	61.5
	0.4	2.4144	59.3
	0.6	2.8838	56.3
	0.7	2.9592	53.5
	0.8	Burst release	51.4
Na_2SO_4	0.2	2.4761	58.7
	0.4	2.3471	48.1
	0.8	Burst release	29.6
KCl	0.2	2.6197	63.9
	0.4	2.4066	58.8
	0.8	Burst release	

decline of the dissolution rates.[7] Karen Mitchell introduced the pore tortuosity, τ, to explain this process, as it is related to the apparent diffusion coefficient in the hydrated matrix, and the actual diffusion coefficient of the drug in the release media.

The above is most concerned with the hydrated or dissolved HPMC particles, for unhydrated particles in the matrix the existence of some electrolytes could also vary the dissolution rate of the drug in another way. As noted at the beginning of this study, drug dissolution is governed by the diffusion of the water and the dissolution of the polymer. Because the electrolyte will compete with HPMC for binding with water, an increase in concentration of electrolyte could be understood as that the free-binding water for the hydration of HPMC have been reduced; therefore, the hydration process will be retarded compared with solo aqueous solution. A retard in hydration will result in delayed drug release. As the concentration (ionic strength) of the electrolyte increases, the retard of the polymer hydration will be exacerbated which could also render an apparent decreasing release rate. Therefore, to be complete in discussing of the reduced drug dissolution rate, two types of cases should be emphasized, namely for hydrated (dissolved) and unhydrated HPMC, respectively.

Explanation of the ''burst release'' phenomenon

The controlled drug delivery process is to some extent dominated by the hydrating, swelling, and dissolution processes of the polymers, which consist of the matrix. Therefore, change in such factors might result in varied drug release rate or might decide whether a successful drug release could be obtained. A successful drug release process refers to a tablet matrix that maintains its integrity throughout the release course. However, in solutions with high ionic strength electrolytes,

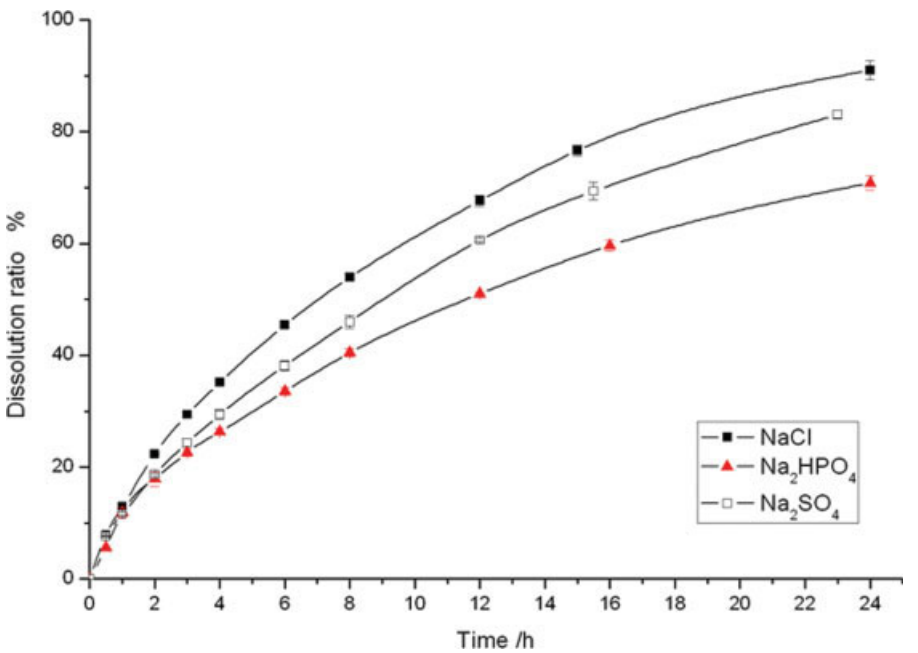

Figure 5 Dissolution profile of propranolol HCl with Methocel K15M matrix tablets in three electrolytes solutions with identical ionic strength of 0.2 mol/L. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE IV
Comparison between Two Kinds of HPMC under Different Ionic Strength Produced by Disodium Hydrogen Phosphate*

Ionic strength (mol/L)	HPMC type	Dissolution rate (% · $min^{-1/2}$)	f_2	Cloud point (°C)	TGT (°C)
None	Methocel K15M	2.7693	93.31	70.9	87.8
	Dom K15M	2.6909		70.0	77.1
0.1	Methocel K15M	2.3498	87.71	63.3	
	Dom K15M	2.4049		63.0	
0.2	Methocel K15M	2.0300	79.91	57.5	74.9
	Dom K15M	2.2449		57.4	63.8
0.3	Methocel K15M	1.7929	74.95	52.8	
	Dom K15M	2.0241		52.4	
0.4	Methocel K15M	1.6380	13.79	47.7	65.8
	Dom K15M	Burst release		48.2	59.0
0.5	Methocel K15M	Burst release	21.16	43.4	
	Dom K15M	Burst release		43.0	
0.6	Methocel K15M	Burst release	43.75	39.1	46.6
	Dom K15M	Burst release		38.1	

* K_{cp} in the equation stands for salting ability for certain electrolyte. The higher the absolute value, the more influential it is.

examples of failure in keeping integrity of the matrix (i.e., the burst release) could be easily found.[6,7,12,13]

Reduction of cloud point to a minimum level at which the polymer precipitate from the solution is generally taken to be the reason for failure in keeping integrity of the matrix.[7] However, in our tests, the matrix tablets composed of two types of HPMC sharing nearly the same cloud point value at various ionic strength circumstances displayed quite separately in dissolution and disintegration as shown in Table IV.

The f_2 value, a similarity factor, is calculated in Table IV according to eq. (2):

$$f_2 = 50 \cdot \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n} W_t(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad (2)$$

where R_t and T_t is the cumulative release ratio of reference sample (Methocel K15M here) and test sample (Dom K15M here) at time t; n is number of the sampling; W_t stands for weight, which is assigned to 1 here. According to FDA, an f_2 value of 50–100 shows that there is no significant difference between the two samples, while a value of < 50 represents significant variation.

For Methocel K15M, the minimum release rate appears at 0.4 mol/L of ionic strength level while for Dom K15M it is 0.3 mol/L (Fig. 6). And ionic strength values for disintegration present a 0.1 mol/L gap between the two. Although below an ionic strength of 0.4 mol/L two types of HPMC act similarly as the matrix for drug dissolution, they display quite differently above ionic strength of 0.4 mol/L (Table IV). Therefore, there might be some other factors besides the precipitation to render the phenomenon. In our study, it is found that the TGT between the two under various solutions exhibits almost a 10°C gap; therefore, the gelation of the polymer seems be such an additional factor.

Based on the above discussion, a ''gel out'' process should be emphasized for the drug release with HPMC as its matrix at high ionic strength solutions. In tablets, the glass-like HPMC particles will hydrate after in contact with water (free water), every hydrated HPMC then possess such two kinds of transition temperatures of solutions: lower critical solution temperature and the thermal gelation temperature (in that order). At certain temperature (take 37°C for example), if it is higher than the first transition temperature for the HPMC solution, the phase separation will occur, the drug dissolution rate will decrease because of the solubility change of the polymers. If it is higher than

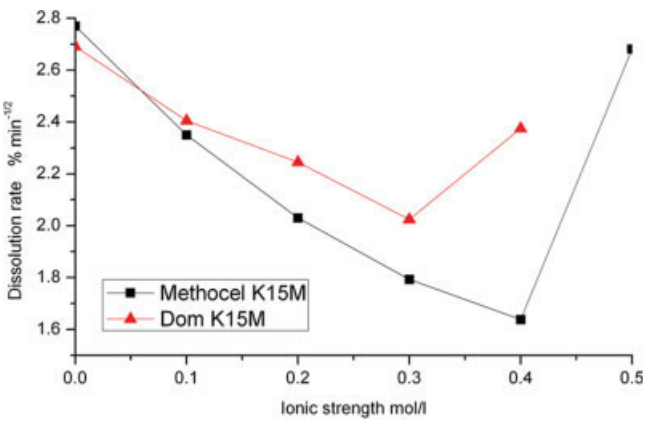

Figure 6 Effect of ionic strength produced by disodium hydrogen phosphate on the dissolution rate of two kinds of HPMC matrix tablets. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

the second transition temperature, the formation of the gel network will begin. It should be emphasized here that the newly formed thermal gel differs from the fully hydrated gel layer for drug diffusion from the tablets. This type of gel is more compact, which cannot act as the diffusion route for drugs. Moreover, in experiments it is found that after the gel network is formed, the s volume of the gel contracts. Therefore, it is highly possible that this volume change of the gel will produce stress variation in tablets and the matrix will become unstable. Consequently, even minor stimulations will break the balance and cause such a ''burst'' phenomenon. As far as this ''gel out'' process is concerned, attention should be attached to such three aspects:

1. *Temperature dependent*: It is easy to understand that such a ''gel out'' process happens only when the temperature has reached the TGT for HPMC in certain solutions. A lower temperature than the TGT will not result in such a ''gel out'' process.
2. *Concentration dependent*: The gel-out process depends on the concentration of the polymers, because concentration of the polymers will affect the gelation process.[4] Higher concentration will lead to lower TGT, which makes such a ''gel out'' process been easily observed.
3. *Ionic effect*: The presence of any electrolytes will accelerate both the phase separation process and the gelation process because of the competition with HPMC for binding of water. As the ionic strength for certain electrolyte increases, two kinds of transition temperature will decrease correspondingly. If the testing temperature is higher than the second transition temperature, such a ''gel out'' process will occur. Therefore, in dissolution media with a high level of electrolytes in it, ''burst release'' may be observed because the ionic effect has lowered the TGT to a certain degree that below testing condition, e.g., 37°C, which will result in the gelation. In contrast, if the dissolution media contains little or no electrolytes in it, the TGT will not be lowered below the testing temperature, which will not render a ''gel out'' process. That is why ''burst release'' could hardly be seen in dissolution process of HPMC matrix in distilled water.

CONCLUSIONS

LCST and TGT, two important transition temperatures of HPMC in the solution state, have been introduced to the study of tablets dissolution with the aim of explaining why ionic strength could vary the dissolution rate or cause the disintegration. The results show that increasing of the concentration of solute in the dissolution media will lower such two kinds of temperatures. Cloud point is believed to have some relationship with the decrease of the dissolution rate while TGT might be responsible for the disintegration of the matrix tablets. Therefore, for the product's development, especially in controlled release systems, additional attention should be attached to the effect of the salt on the thermal property of the matrix polymers in the releasing process. Because the variation of that property might also occur in the human gastrointestinal tract because of the complication caused by intake of the foods, minerals, salts etc. And that will bring VIVIC problems or application risks. And based on the present study, HPMC with a higher TGT value will exhibit a stronger resistance to the effect of the salt during the dissolution process.

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