The Influence of Agitation Sequence and Ionic Strength on *in-vitro* Drug Release from Hypromellose (E4M and K4M) ER Matrices - The use of the USP III Apparatus

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Abstract

Theophylline extended release (ER) matrices containing hypromellose (hydroxypropyl methylcellulose (HPMC) E4M and K4M were evaluated in media with a pH range of 1.2-7.5, using an automated USP type III, Bio-Dis dissolution apparatus. The objectives of this study were to evaluate the effects of systematic agitation, ionic strength and pH on the release of theophylline from the gel forming hydrophilic polymeric matrices with different methoxyl substitution levels. Tribo-electric charging of hypromellose, theophylline and their formulated blends containing E4M and K4M grades has been characterised, along with quantitative observations of flow, compression behaviour and particle morphology. Agitations were studied at 5, 10, 15, 20, 25, 30 dips per minute (dpm) and also in the ascending and descending order in the dissolution vials. The ionic concentration strength of the media was also varied over a range of 0-0.4 M to simulate the gastrointestinal fed and fasted states and various physiological pH conditions. To study the effect of ionic strength on the hydrophilic matrices, agitation was set at 20 dpm. The charge results on individual components imply that the positively charged particles have coupled with the negatively charged particles to form a stable ordered mixture which is believed to result in a more homogeneous and stable system. The particle shape analysis showed the HPMC K4M polymer to have a more irregular morphology and a rougher surface texture in comparison to the HPMC E4M polymer, possibly a contributory factor to the gelation process. The results showed gelation occurred quicker for the K4M tablet matrices. Drug release increased with increased agitation. This was more pronounced for the E4M tablet matrices. The ionic strength also had more of an effect on the drug release from the E4M matrices. The experiments highlighted the resilience of the K4M matrices in comparison with the E4M matrices. The results thus show that despite similar viscosities of E4M and K4M, the methoxyl substitution makes a difference to their control of drug release and as such care and

consideration should be given to the choice of polymer used for extended release. The use of systematic change of agitation method and ionic strength may indicate potential fed and fasted effects on drug release from hydrophilic matrices.

Keywords: Agitation, Ionic concentration strength, HPMC, Similarity factor, Kinetics of drug release, DSC, Particle size, Triboelectrification, Theophylline, USP III

1. Introduction

Tablets made with HPMC swell in contact with water forming a gel layer around the matrix. The release of the drug from the matrix thus depends on the possible interactions between aqueous medium, polymer, drug and other tablet ingredients [1]. It is well known that food administration can affect the bioavailability of oral dosage forms as a result of interactions which may occur between the formulation and the food [2, 3]. Researchers have demonstrated that the gel layer formed around hydrophilic matrices, upon its contact with gastro-intestinal (GI) fluids, is eroded allowing drug release. This erosion is the dominant release mechanism for poorly soluble drugs **[2-6]**. The other mechanistic approach is that the soluble portion of drug is released by diffusion through the gel layer [4-6]. The non-ionic nature of HPMC means that when drug solubility is pH-independent, the matrices also exhibit pH-independent drug release profiles. Generally, the higher the solubility of the drug, the faster its release; this is due to a higher diffusional driving force.

Two major characteristics of the GI fluids are pH and ionic strength. They vary greatly along the GI tract under both fasting and fed conditions [7, 8] and can affect the rate at which a drug is released from hydrophilic ER matrices [9-11]. The ionic strength of the fluids of the GI tract in man under both fasted and fed states and various physiological pH conditions cover a range of 0-0.4 M [9]. Sodium chloride is the midrange of the lyotropic series and has

the ability to salt out polymers, hence is often used as the agent for ionic regulation of dissolution media [9, 14].

The high molecular weight METHOCEL^{TM} Premium K (hypromellose 2208, USP) and E (hypromellose 2910, USP) chemistries are the most widely used polymers in ER matrix formulations. The difference in methoxyl content for the HPMC E4M and K4M grades means a variation occurring chemically and physically. These properties affect thermal gelation and polymer solubility amongst other properties. The gelation temperatures of HPMC polymers E and K are 56 ^{o}C and 70 ^{o}C respectively. As the HPMC substitution type and molecular weight also has an effect on the amount of water bound to the polymer, McCrystal et al., [15] noted that the relative amount of water in the different distinct states of the polymer was altered with the addition of drugs. The self-diffusion coefficient (SDS) of water in the pure gels of HPMC E4M and K4M showed the K4M being significantly lower than the E4M polymer. This meant the K4M polymer was more resistant to the effects of erosion as compared to the E4M polymer, leading to a reduction in drug diffusivity out of a tablet matrix [16].

Pharmaceutical powders are often small in particle size (less than 100 µm) and irregularly shaped and have low bulk density. They are prone to electrostatic charging because they normally have a high electrical resistance, preventing charge dissipation. The ability to control the charging of pharmaceutical powders is essential in improving the quality of the end product and minimising deposition and powder loss. Tribo-electrification is used to help with the mixing operations in industry [17]. Fine particles charge opposite to coarse particles during particle collisions with material surfaces. This results in fine particles adhering to larger carrier particles, known as ordered mixing. Charging of particles with the opposite polarity has been utilised in the formation of stable ordered mixtures which have been proven to minimise segregation [18].

In a recent study the influence of changing the agitation sequence during dissolution testing in a USP III Apparatus as a model for fed and fasted conditions on drug release from HPMC matrices were studied [13]. The methodology used was further explored to investigate the effect of ionic strength and pH of the media on theophylline release from HPMC matrices using the USP III Apparatus [12]. As the high molecular weight METHOCEL Premium K (hypromellose 2208, USP) and E (hypromellose 2910, USP) chemistries are the most widely used polymers in ER matrix formulations, physical characterisation of Methocel, theophylline and their formulated blends was quantified by triboelectrification, flowability and particle morphology to ensure reliable flow is attained. The present work explores the two methodologies developed by the same authors to investigate the effect of agitation sequence, ionic strength and pH of the media on theophylline as a model drug release from HPMC K4M and E4M matrices using USP III Apparatus. This study investigates the influence of HPMC substitution level on drug release using USP III apparatus to discriminate between the performances of the two polymers. The approach used in the present study can be used to differentiate poor sustained release formulation from robust formulations.

2. Materials and methods

2.1. Materials

HPMC grades METHOCEL™, K4M and E4M supplied by Colorcon UK were used as the hydrophilic matrix former. Anhydrous theophylline (Sigma, USA) was used as the model drug. Dissolution buffers were prepared according to the USP 2003 using the following materials: potassium chloride (Acros Organics, UK) and hydrochloric acid (Fisher Scientific, UK) for pH 1.2 and pH 2.2 and potassium phosphate monobasic-white crystals (Fisher BioReagents, UK) and sodium hydroxide (Fisher Scientific, UK) for pH 5.8, 6.8, 7.2 and 7.5 media.

2.2. Tablet Preparation

Round cylindrical tablets with a diameter of 9.56 mm and the target weight of 250 mg were prepared by blending theophylline with either HPMC E4M or K4M in the ratio of 4:1 for 10 min in a Turbula® (Type T2 C, Switzerland) blender. Tablets compression, true density measurements of the powder mixtures and porosity calculations are detailed in Asare-Addo *et al.*, 2011[12]. The Dr. SCHLEUNIGER tablet tester 8M (Serial No. 02209) was used in the determination of the tablets breaking force. Five readings were taken in order to determine the mean and standard deviation values.

2.3. Powder characterisation

Carr's Index

Bulk and tapped volume of HPMC K4M and E4M polymers and theophylline powders were determined using a mechanical tap density machine (Copley Scientific, UK). Carr's index (CI) was calculated from equations 1:

$$\text{CI}\ (\%)\ \frac{\text{Bulk density}-\text{Tap density}}{\text{Bulk density}} \times 100 \qquad \text{Eq. 1}$$

Electrostatic properties of pure polymers and formulated blends

A tribo-electric device based on a shaking concept, previously described by Šupuk and co-workers [19] was used to investigate the tribo-electrification of bulk powders by determining the charge-to-mass ratio. Charge-to-mass ratio is an important parameter that needs to be determined in order to accurately predict the behaviour of charged particles. The most common device used for charge-to-mass measurement is the Faraday cup and it works on the principle that charge induces an image of itself on a conducting surface. In this work, the charge-to-mass ratio of the bulk powders was measured following shaking using a custom made Faraday cup connected to an electrometer (Keithley Model 6514). The Faraday cup

consists of two conducting cups with an entrance on the top through which powder can enter. The inner cup is isolated from the outer cup by an insulating spacer. The outer cup is used to prevent external charges being measured and to reduce any external noise. If a positively charged particle enters the Faraday cup, a negative charge is induced and distributed on the inner surface of the Faraday cup, whilst a positive charge is distributed over the outer surface of the cup, setting up an electric field and a potential difference between the two cups. The capacitance C between the inner and outer cups acquires a potential, $V = q/C$ which is measured by an electrometer connected to an inner cup. The charge-to-mass ratio is obtained by dividing the net charge measured and the mass of the sample tested.

Tests were carried out under ambient temperature (22 ºC) and humidity (35-47 %RH). This method was used to ensure that a stable and homogeneous mixture of the HPMC E4M and K4M formulation blends was achieved.

2.4. Micrometric properties of polymers

Particle size analysis

Particle size distribution (PSD) analysis was conducted on an aerosolised dry sample using a Sympatec (Clausthal-Zellerfeld, Germany) laser diffraction particle size analyser as described in details elsewhere [20].

Particle shape analysis

Quantitative **absolute** particle shape image analysis was performed using a computerized morphometric **analysing** system (Leica Q Win Standard **Analysing** Software and Leica DMLA Microscope; Leica Microsystems Wetzlar GmbH, Wetzlar, Germany), as adapted from Kaialy *et al*., [20]. Optical image analysis microscopy was employed to quantify shape

of the HPMC E4M and K4M particles using several shape descriptors including roundness [21] and roughness [22].

2.5. Dissolution Test

Effect of pH and Agitation

Drug-release behaviour of the above formulations was investigated in six dissolution media to determine the sensitivity of different methoxyl substitution grades of HPMC to the pH. A series of buffer solutions that simulated the stomach and intestinal conditions in fasted and fed states with the pH values of 1.2, 2.2, 5.8, 6.8, 7.2 and 7.5 were used. The dissolution testing was conducted for 310 minutes for all formulations.

The influence of agitation on drug release was studied as detailed in Asare-Addo *et al.*, [13].

All theophylline HPMC (E4M and K4M) formulations were tested against this developed methodology. This allowed discriminating the effect of the agitation on the formulations where different methoxyl substitution grades of the HPMC were used.

The Influence of Ionic Strength

Drug-release behaviour of the formulations was investigated in six dissolution media to determine the sensitivity of different methoxyl substitution grades of HPMC to the pH with ionic strength. The dissolution testing was conducted for 310 minutes for all formulations. Sodium chloride was used to regulate ionic strength of the media from 0 to 0.4 M in buffers with pH of 1.2, 2.2, 5.8, 6.8, 7.2 and 7.5. Both theophylline-K4M and E4M formulations were tested using the developed method varying media ionic strength by Asare-Addo and co workers [12]. The absorption of the released theophylline was measured at 271 nm using a UV/Visible spectrophotometer (Varian, Cary 50).

2.6. Similarity factor

Similarity factor was calculated as detailed in Asare-Addo *et al.*, 2010 **[13]** for the effect of agitation. Drug release in the water media was used in the determination of *f2* values where ionic strength was concerned as detailed in Asare-Addo *et al.*, [12].

2.7. Dissolution parameters

The mean dissolution time (MDT) is the mean time for the drug to dissolve under *in-vitro* dissolution conditions. This is another approach to obtain a parameter that describes the dissolution rate. This helps to characterize the drug release profile and compare drug release rates from different dissolution data [23]. This is calculated using Equation 2. This MDT is a model-independent method and is suitable for dosage forms having different mechanisms of drug. As this experiment uses different viscosities of HPMC polymers, it provides a way of comparing the dissolution profiles.

$$MDT = \frac{\sum_{j=1}^{n} t_j \Delta M_j}{\sum_{j=1}^{n} \Delta M_j} \qquad \text{Equation 2}$$

Where;

j = sample number

t_j = midpoint of the jth time period (easily calculated with ((t + t-1)/2)

ΔM_j = additional amount of drug dissolved between t_j and t-1.

The mean dissolution rate (MDR) can be calculated according to Equation 3. This is the mean rate for the speed at which the dissolution process occurs. Its unit is $\%min^{-1/2}$.

$$MDR = \frac{\sum_{j=1}^{n} \Delta M_j / \Delta t}{n} \qquad \text{Equation 3}$$

Where;

n = number of dissolution sample times

Δt = time at the midpoint between t and t-1 (easily calculated with [t + (t-1)/2].

The area under the dissolution curve up to the time, t, expressed as the percentage of the area of the rectangle is known as the dissolution efficiency (DE) of a pharmaceutical dosage form [24]. This is mathematically depicted as Equation 4.

$$DE = \frac{\int_0^T Y \times dt}{Y_{100} \times T} \times 100\% \qquad \text{Equation 4}$$

Where;

y =the percentage of drug dissolved at time t.

2.8. Kinetics of drug release

The kinetics of drug release was analysed using Peppas equation [25] as detailed in Asare-Addo et al., [13]. In general, n values close to 0.5 are indicative of the drug release primarily by diffusion. Values of 1 for n mean drug is released by the process of swelling. Anomalous transport is the term given to n values between 0.5 and 1. This is an indicator of the superposition of both processes **[25].** However for cylinders, which were the shape of the tablet matrices made in this experimentation, the n values are slightly different as derived by **[25].** Values of n of up to 0.45 suggest Fickian diffusion, and values of above 0.89 suggest Case-II transport. Values between these two suggests anomalous transport occurring.

3. Results and discussion

3.1. HPMC polymer and formulation characterization

The physical characterization results for the tested E4M and K4M polymer powders and 4:1 drug:HPMC formulations showed that they are robust formulations in terms of tablet hardness (for full details refer to supplementary materials Table S1). The results of the triboelectrification tests are shown in Figure 1. The results show that both grades of Methocel charged positively against the stainless steel container. The magnitude of charge of Methocel E4M was notably high for an excipient and can be characterised on the upper level of excipient chargeability as reported previously [26]. Theophylline charged negatively as did the blends, but to a lesser extent than Theophylline due to the presence of HPMC polymer in the blends. The level of charge on the Theophylline and Methocel E4M was higher than the rest of the samples tested. It may be reasonable to consider in the first instance that the charge on the blend is additive, hence explaining the specific charge on the blends being lower than pure Theophylline. Because the drug and the polymers E4M and K4M get charged oppositely, it is anticipated that polymers could adhere to the surfaces of Theophylline forming an ordered mixture. Ordered mixtures are believed to result in a more homogeneous and stable system compared to that of a random mixture [27]. In this case, drug:HPMC formulations are likely to retain its integrity as the bonds between the particles are strong enough, and thus result in formation of strong compacts. HPMC E4M and K4M polymer powders demonstrated similar PSDs (Figure 2). The particle shape analysis however showed the HPMC K4M polymer to have a more irregular morphology and a rougher surface texture in comparison to the HPMC E4M polymer, as indicated by higher roundness and roughness descriptors (see supplementary materials Figure S1). A conclusion can be drawn that HPMC K4M would have higher surface area in contact with media for hydration when compared to HPMC E4M. Due to the similarity of the porosity values and tablet volumes for the E4M and K4M tablet matrices, its effect on drug release was considered negligible. The K4M tablet formulation produced mechanically stronger tablets compared to E4M tablet formulation (see

supplementary materials Table S1). Table S1 also indicated that all formulations investigated in the study had good Carr's index values indicating good powder flow.

3.2. Effect of pH and Agitation

Once the matrices were introduced into the medium, the polymers quickly hydrated on the tablet surface and formed a gelatinous layer. Generally, agitation had a more significant effect on E4M tablets as compared to the K4M matrices (Figure 3). It was also observed that the drug release patterns for the two polymers, HPMC E4M and K4M were very different despite having similar viscosities as evident in Figure 4. As a result of HPMC K polymers having the highest ratio of hydroxypropoxyl to methoxyl substitution, gelation occurs quickly compared to other HPMC polymer grades [16, 28]. Hydration and thus gelation could also have happened quickly for the HPMC K4M tablet formulation because of its higher irregularity and roughness as compared to the HPMC E4M that increases its surface area (supplementary materials Figure S1) in the hydration medium.

Dip rate was plotted against the drug release in its respective medium (Figure 4). With an increase in agitation, the theophylline release rate from E4M and K4M matrices increased. Figure 4a, representing the drug release after 60 minutes in pH 1.2 with the differing dip rate demonstrates a positive slope which makes the effect of agitation on drug release very clear. The general positive slope shows that there was increased erosion occurring as the dip rate was increased. Also evident here is the proof that erosion was higher for the E4M HPMC polymer. The decrease in the drug release from E4M matrices and thus the decline in the general positive slope in the drug release-dip rate profiles in 7.2 (Figure 4b) is as a result of the decreasing amount of theophylline left as it had gone into solution at the higher dip rates (for full details of the results refer to supplementary materials Figure S2). The K4M matrices

were however more resilient to the effects of agitation in comparison to E4M. The drug release-dip rate graphs showed the linearity of the increased release as agitation was increased until the tablet was placed in pH 7.2. Then it was evident that with 30 dpm, most of the drug had gone into solution discontinuing the observed linearity. Also the gel layer thickness was reduced due to the increase in agitation that prevented the gel from swelling to its full capacity thereby causing the matrix surface to experience a mass transport [29].

A comparison of the two different agitations rates in the ascending order of 5-30 dpm and descending order of 30-5 dpm, showed that a higher amount of the drug was released when agitation started at 30 dpm. In the case of E4M matrices, the entire drug was released in pH 7.2 after 280 minutes with a starting agitation of 30 dpm, with 75 % of the drug released in pH 1.2 alone. When agitation was started at 5 dpm, 76 % of the drug was released after 310 minutes in pH 7.5. For K4M matrices, even when agitation started at 30 dpm and ended at 5 dpm, only 82 % of the drug was released after 310 minutes. When agitation started at 5 dpm and ended at 30 dpm, 64 % of drug was released after 310 minutes in pH 7.5

These results show that controlling drug release in the desired medium is fundamentally important. For formulations that are not robust, the agitation could cause a relatively fast drug release resulting in a possible toxicity or making a drug unavailable at the targeted site. Additionally, different dissolution profiles obtained with different HPMC substitutions grades give the formulator a chance to obtain “a desired” specifically tailored drug release profile.

The statistical analysis of the DE, MDR and MDT from the drug release profiles indicated that an increase in the agitation levels resulted in a general increase in the DE values. For E4M matrices, DE values rose from 61 % (when agitation was at 5 dpm) to 91 % (when agitation was at 30 dpm). For K4M tablets, DE value of 31 % at 5 dpm increased to 63 % at 30 dpm. MDR also followed the same trend (Table 1). The ascending and descending orders of agitation showed DE to be highest for both polymer formulations with theophylline when

agitation started at 30 dpm and ended at 5 dpm. MDT was the highest at the ascending order of agitation for both E4M and K4M matrices with respective values of 102 min and 146 min (Table 1).

3.3. Effect of Ionic strength

Ionic strength of the medium had a more significant effect on theophylline release from E4M matrices (Figure 5). For E4M tablets, drug release in pH media was very similar to that in water media (*f2*=95). For K4M tablets, *f2* (all above 50) indicates that there was a similarity in the drug release profiles despite the ionic strength increment. This behaviour is attributed to their different levels of methoxyl substitution. This methoxyl substitution makes the E4M more prone to the effects of erosion than the K4M polymer [14]. In pH 1.2 only, 67% and 66% of drug has been released from the tablet matrices for the E4M formulation in the water media and the pH media (no salt) respectively. Upon addition of salt, drug release increased to 84 % and 83 % in 0.2 M and 0.4 M media respectively. For K4M matrices, 31 % of theophylline was released in the water media. Drug release increased to 37 % when ionic strength was increased to 0.2 M and a little further increase occurred when ionic strength was increased to 0.4 M. These observations are also depicted in Figures **6** (a-b). These were the amount of drug released from the different matrices in different pH media over a specified time (for full details refer to supplementary materials Figure S3). At the low ionic strengths (pH media, no salt), the polymer hydration was unaffected (*f2* values of 95 and 74). Higher ionic strengths however may have lead to a loss of gel integrity of the E4M matrices hence the increase and difference in their drug release profiles and dissimilarity of the *f2* values.

Table 2 shows that for K4M formulations, anomalous transport was the only kinetics of theophylline release as the n values were above 0.45 [30, 25]. The E4M formulation suggests that Fickian diffusion was the sole dominant kinetics of drug release (*n* values ranging from

0.12 to 0.27) **(Table 2).** One exception was when agitation was changing in ascending order from 5 to 30 dpm resulting in anomalous transport with an n value of 0.50 (Table 2).

The highest *n* value was achieved in the water media for both polymers studied. An increase in the ionic concentration strength to 0.4 M changed the dominating anomalous transport occurring for the K4M tablet matrices to Fickian diffusion with an *n* value of 0.39. In both cases, a decrease in the value of *n* occurred with an increase in the ionic concentration strength.

Due to the similarity values obtained for the K4M tablet matrices, it can be seen that apart from where DE decreased from 56 % in water media to 53 % in pH media, it was hard to establish trends in the values of DE and also for the MDT and MDR values. The E4M tablet matrices had similar DE values in water and pH media (82 % and 79 %) and also in the ionic concentration strength of 0.2 and 0.4 (92 % and 91 %) respectively (Table 2). A significant difference occurs when the ionic strength of the medium increases from as low as in the pH media (actual ionic strength 0.05-0.14 M) to when the use of sodium chloride results in 0.2 M and 0.4 M ionic strength levels in addition to the "pH media". This meant that the actual ionic concentration strength at the 0.2 M level ranged between 0.25-0.34 M and for the 0.4 M ranged between 0.45-0.54 M thus causing dissimilarity to occur when these were compared to the water as the reference standard.

4. Conclusion

Previously conducted experiments showed a decrease of the outer gel layer thickness and thus the erosion constant of tablet matrices as agitations were increased. This experimentation indicated that agitation had a more significant effect on theophylline release from E4M matrices when compared to K4M tablets. Drug release was faster as agitation was increased from 5 dpm to 30 dpm. The experiments also showed that the erosion occurring as a result of the increased agitation was more rapid for the E4M matrices. Ascending and descending

agitation in the different vials with different pH resulted in a significant difference in the theophylline release rate. The results indicate the importance of targeting or controlling drug release in the desired media. For formulations that are not robust, the agitation could cause a relatively fast drug release resulting in a possible toxicity or making drug not available in the required medium or site.

As the ion concentration in a polymer solution is increased, the solubility or hydration of the polymer decreases thus reducing the amount of available water for hydrating the polymer. Evidence from experiments conducted showed that ionic strength had a significant effect on the release patterns of the matrices made from E4M. The K4M was however resilient to the influence of ionic strength. The methoxyl substitution made a difference to the drug release rate from E4M and K4M tablets despite the similarity in polymer viscosity. Particle shape analysis showed HPMC K4M to have rougher and higher irregular surfaces when compared to HPMC E4M thus increasing its surface area for hydration and thus could add to the reasons of its ability to form quicker gels to prevent the "burst" or higher drug release when again compared to HPMC E4M. It was also reasonable to conclude that the polymers E4M and K4M are charged to form stable ordered mixtures by adhering to oppositely charged particles which is believed to result in a more homogeneous and stable formulations. This highlights the importance of choosing the right HPMC polymer for the extended release matrix.

References

[1] B. Sasa, P. Odon, S. Stane, and K. Julijana, Eur. J. Pharm. Sci. 27 (2006) 375-383.

[2] B. Abrahamsson, K. Roos, J. Sjogren, Drug Dev. Ind. Pharm. 25 (1999) 765-771.

[3] W. Phuapradit, S. Bolton, Drug Dev. Ind. Pharm. 17 (1991) 1097-1107.

[4] B. Abrahamsson, D. Johansson, A. Torstensson, K. Wingstrand, Pharm. Res. 11 (1994) 1093-1097.

[5] J. W. Skoug, M. V. Mikelsons, C. N. Vigneron, N. L. Stemm, J. Controlled Release 27 (1993) 227-245.

[6] W. D. Lindner, B. C. Lippold, Pharm. Res. 12 (1995) 1781-1785.

[7] C. G. Wilson, N. Washington, in Physiological Pharmaceutics, Chichester: Ellis Horwood Ltd, (1989) 47-68.

[8] W. N. Charman, C. J. H. Porter, S. Mithani, J. B. Dressman, J. Pharm. Sci. 86 (1997) 269-282.

[9] J. L. Johnson, J. Holinej, M. D. Williams, Int. J. Pharm. 90 (1993) 151-159.

[10] M. C. Bonferoni, S. Rossi, F. Ferrari, M. Bertoni, C. Caramella, Int. J. Pharm. 117 (1995) 41-48.

[11] A. C. Hodsdon, J. R. Mitchell, M. C. Davies, C. D. Melia, J. Controlled Release 33 (1995) 143-152.

[12] K. Asare-Addo, M. Levina, A.R. Rajabi-Siahboomi, A. Nokhodchi, Carbohydrate Polym. 86 (2011) 85-93.

[13] K. Asare-Addo, M. Levina, A.R. Rajabi-Siahboomi, A. Nokhodchi, Colloids Surf. B: Biointerf. 81 (2010) 452-460.

[14] K. Mitchell, J.L. Ford, D.J. Armstrong, P.N.C. Elliott, C. Rostron, J.E. Hogan, Int. J. Pharm. 66 (1990) 233-242.

[15] C.B. McCrystal, J.L. Ford, and A.R. Rajabi-Siahboomi, Thermochim. Acta 294 (1997) 91-98.

[16] A.R Rajabisiahboomi, R.W. Bowtell, P. Mansfield, M.C. Davies, and C.D. Melia, Pharm. Res. 13 (1996) 376-380.

[17] Kaye B.H (1997) Powder mixing, Chapman & Hall, London, UK.

[18] J.N. Staniforth, J.E. Rees, Powder Technol. 30 (1981) 255-266.

[19] E. Šupuk, C. Seiler, M. Ghadiri, Part. Part. Syst. Char., 26 (2009) 7–16.

[20] W. Kaialy, M.D. Ticehurst, A. Nokhodchi, Int. J. Pharm, 423 (2012) 184-194.

[21] W. Kaialy, H. Larhrib, M.D. Ticehurst, A. Nokhodchi, Cryst. Growth Des. 12 (2012) 3006-3017.

[22] W. Kaialy, G.P. Martin, H. Larhrib, M.D. Ticehurst, E. Kolosionek, A. Nokhodchi, Colloids and Surf. B: Biointerf, 89 (2012) 29–39.

[23] X. Mu, M.J. Tobyn, and J.N. Staniforth, J. Controlled Release 93 (2003) 309-318.

[24] K.A. Khan, J Pharm. Pharmacol. 27 (1975) 48-49.

[25] J. Siepmann, N. A. Peppas, Adv. Drug Deliv. Rev. 48 (2001) 139-157.

[26] E. Šupuk, A. Zarrebini, J.P. Reddy, H. Hughes, M.M. Leane, M.J. Tobyn, P. Timmins, M. Ghadiri, Powder Technol, 217 (2012) 427-434.

[27] F. Lai, J.A. Hersey, J.N. Staniforth, Powder Technol. 28 (1981) 17-23.

[28] A.R Rajabisiahboomi, R.W. Bowtell, P. Mansfield, A. Henderson., M.C. Davies, C.D. Melia, J. Controlled Release 31 (1994) 121-128.

[29] T.D. Reynolds, S.H. Gehrke, A.S. Hussain, and L.S. Shenouda, J. Pharm. Sci. 87 (1998) 1115-1123.

[30] P. L. Ritger, N. A. Peppas, J. Controlled Release 5 (1987) 23-36.

Table 1. The effect of agitation rate on release rates and mechanism of theophylline from from E4M and K4M tablet matrices

Tablet Formulation	Agitation (dpm)	DE_{310min} (%)	MDT (min)	MDR (%$min^{-1/2}$)	RSQ (r^2)	n
E4M	5	61.11	77.64	0.21	0.9**873**	0.40
	10	72.13	61.50	0.19	0.9913	0.28
	15	87.35	43.00	0.19	0.9803	0.24
	20	79.4	54.60	0.19	0.9888	0.24
	30	91.37	33.80	0.16	0.9835	0.22
	5-30	51.22	102.44	0.21	0.9977	0.50
	30-5	87.82	40.34	0.17	0.9834	0.20
K4M	5	31.36	119.69	0.15	0.9962	0.65
	10	40.66	119.41	0.20	0.9978	0.65
	15	45.64	120.23	0.22	0.998	0.65
	20	52.96	114.80	0.25	0.9977	0.60
	30	63.13	99.28	0.27	0.9951	0.54
	5-30	33.91	146.36	0.2	0.9959	0.80
	30-5	55.04	103.03	0.25	0.9884	0.61

Table 2. Theophylline release from E4M and K4M matrices in media with different ionic strengths

Polymer	Media (Ionic strength)	Agitation (dpm)	DE_{310min} (%)	MDT (min)	MDR (%min^{-1})	RSQ (r^2)	n
E4M	Water (0)	20	81.58	21.18	0.14	0.9935	0.27
	pH media	20	79.40	21.44	0.14	0.9888	0.24
	pH media with 0.2 M NaCl	20	91.59	16.97	0.11	0.9577	0.14
	pH media with 0.4 M NaCl	20	91.44	15.09	0.09	0.9786	0.12
K4M	Water (0)	20	55.62	25.00	0.14	0.9976	0.61
	pH media	20	52.96	26.40	0.14	0.9977	0.60
	pH media with 0.2 M NaCl	20	55.71	25.62	0.13	0.9973	0.48
	pH media with 0.4 M NaCl	20	56.41	25.34	0.13	0.9949	0.39

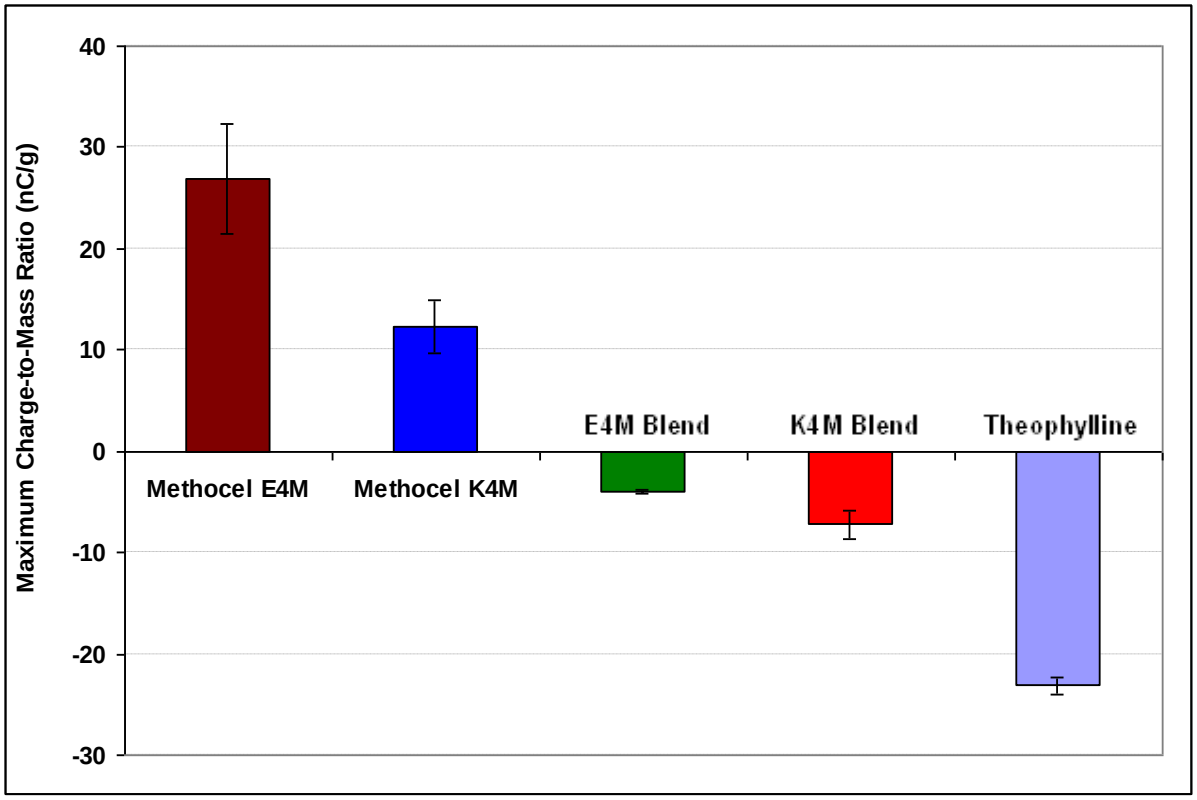

Figure 1. Charge to mass ratio for E4M and K4M HPMC polymers, theophylline drug, E4M and K4M formulation blends tested against stainless steel container (mean ± SD, *n*=3).

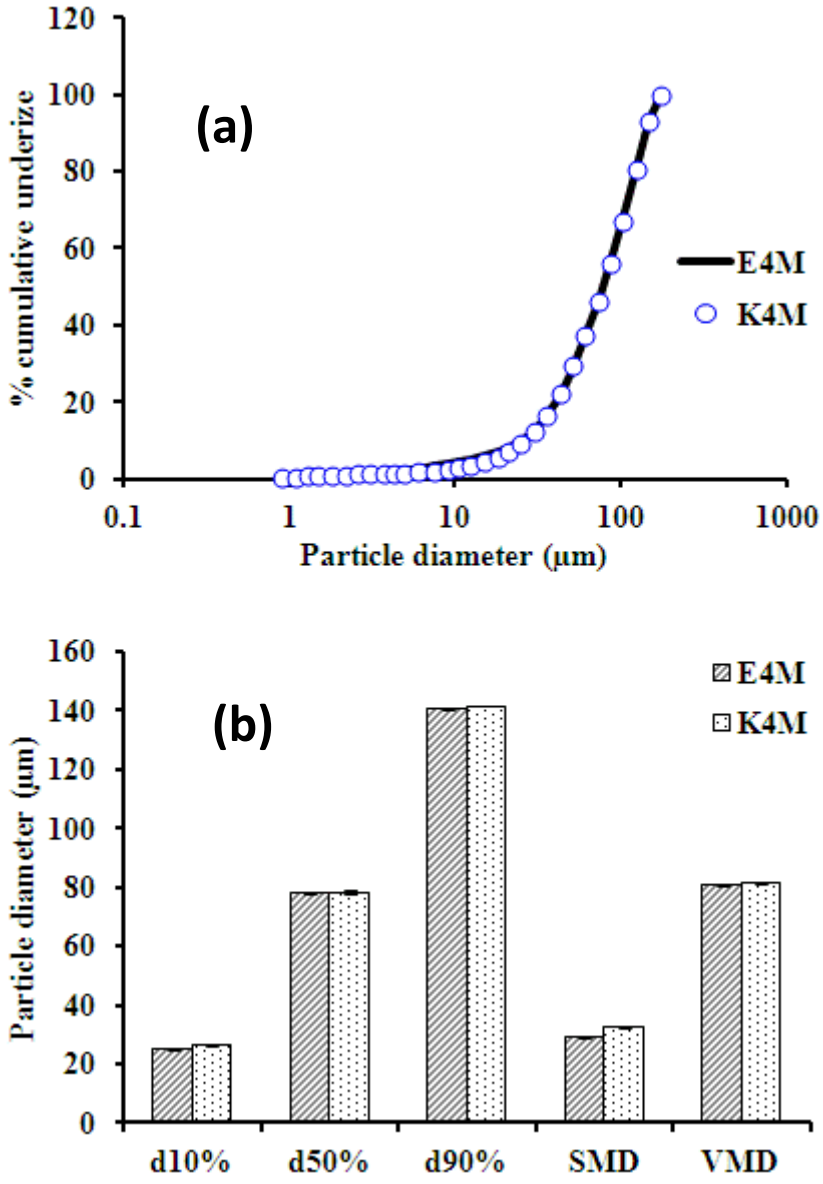

Figure 2. Cummulative undersize (%) particle size distribution (a) the mean particle size ($D_{10\%}$, $D_{50\%}$ and $D_{90\%}$), Surface mean diameter (SMD) and Volume mean diameter (VMD) of HPMC E4M and K4M polymers as measured by laser diffraction (mean ± SD, *n*=3).

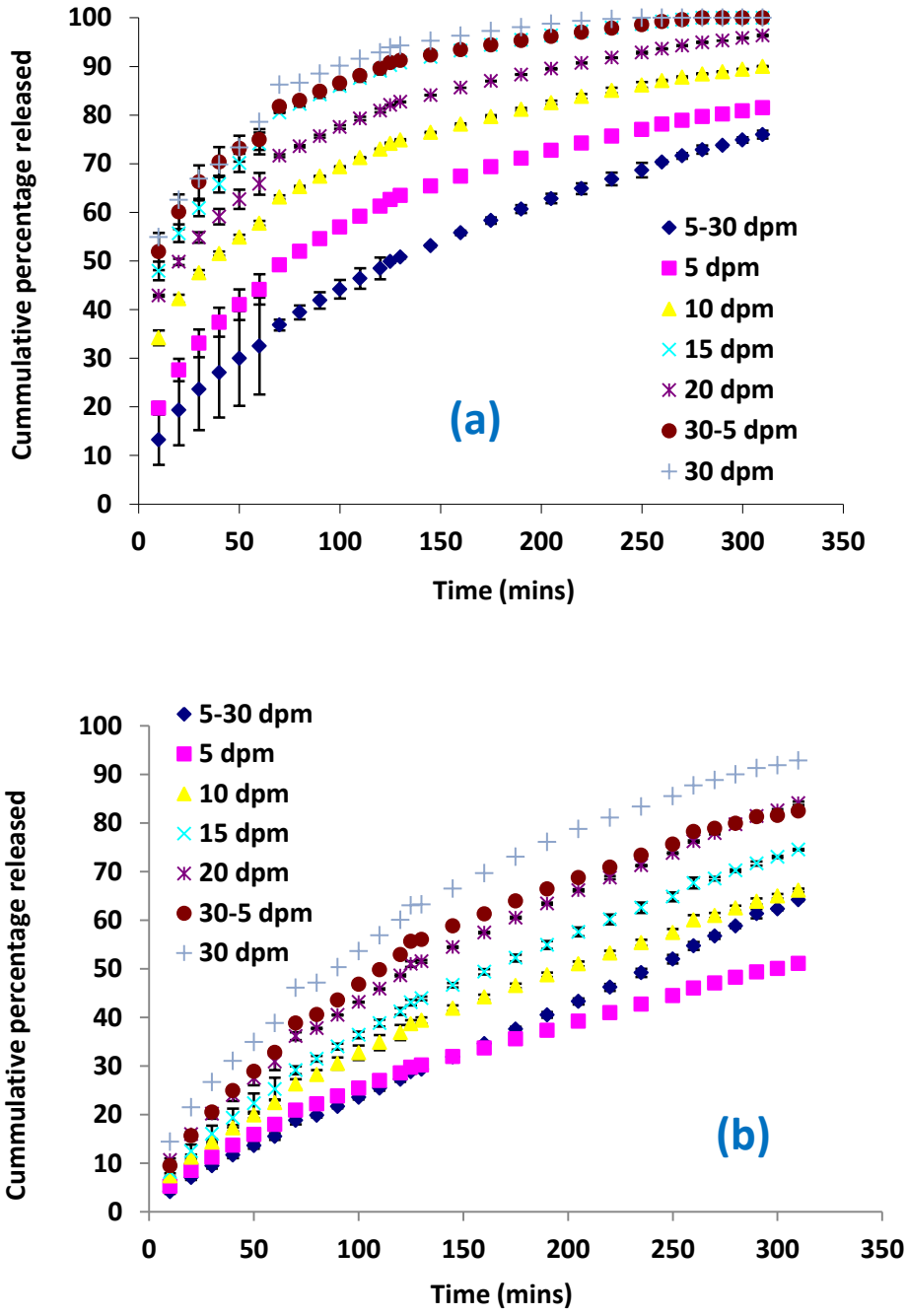

Figure 3 (a and b). The influence of agitation on theophylline release from HPMC matrices (a. E4M b. K4M) in pH 1.2 – 7.5 (mean ± SD, *n*=3).

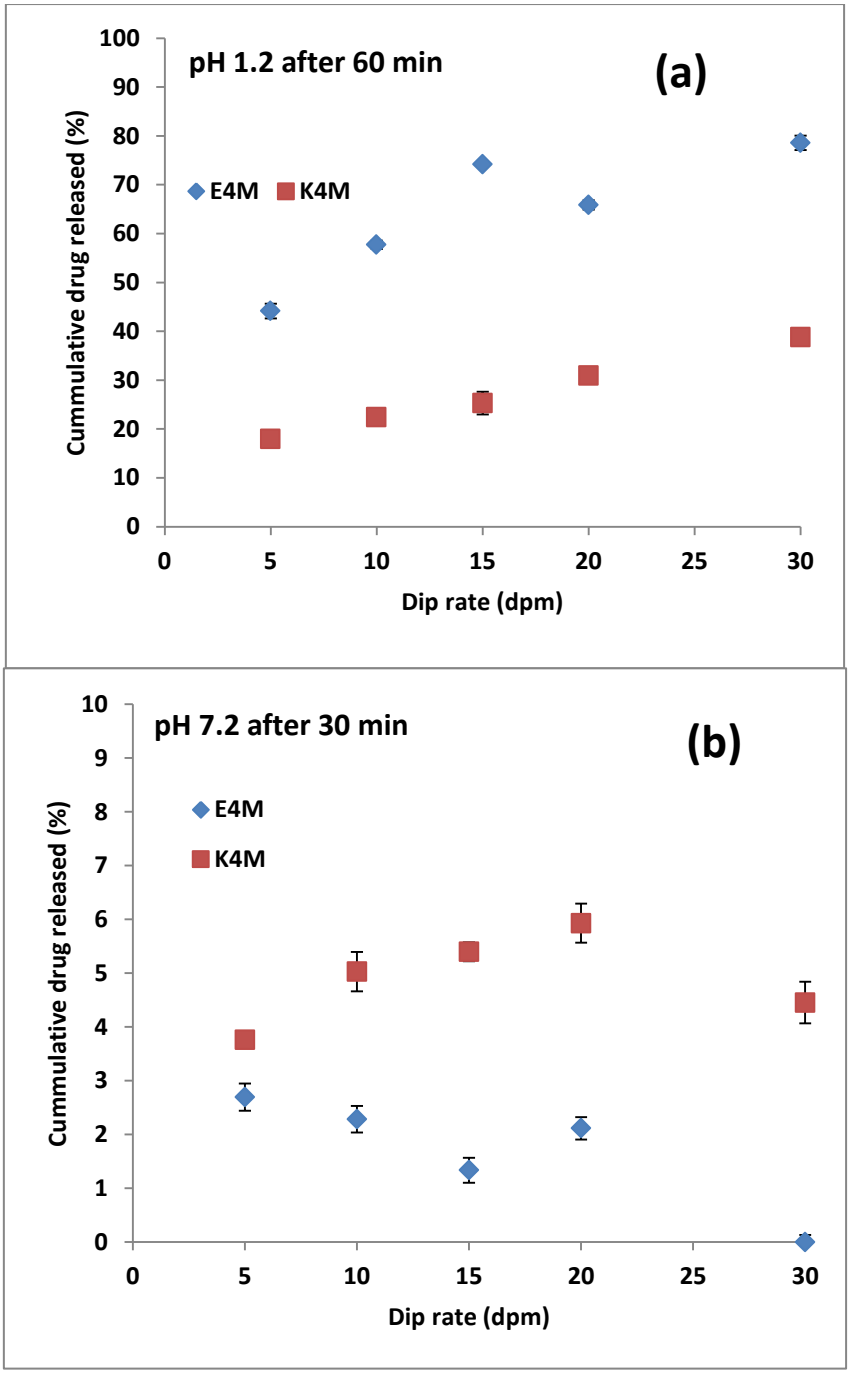

Figure 4 (a-b). The influence of agitation on theophylline release from E4M and K4M matrices in various media (mean ± SD, *n*=3).

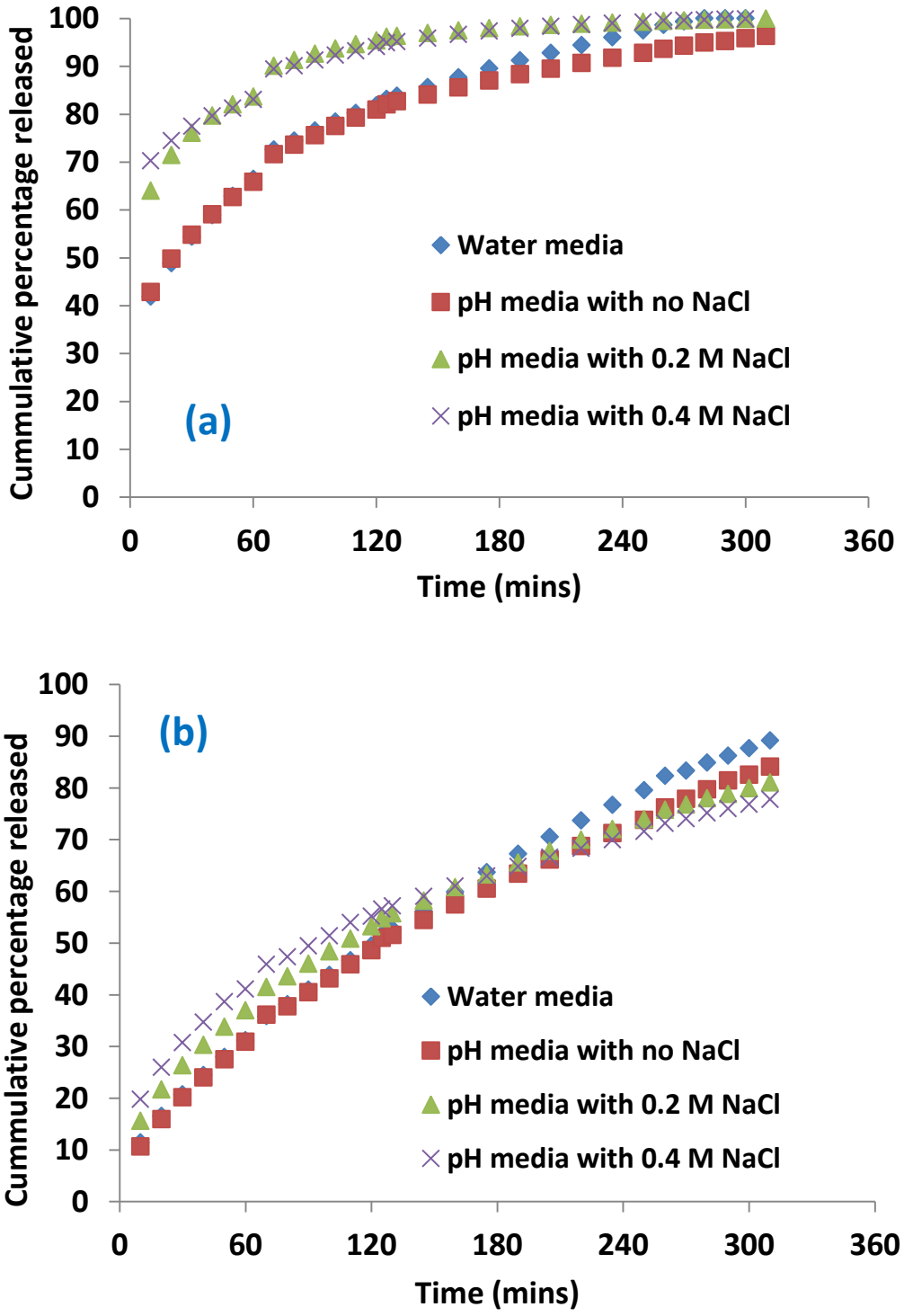

Figure 5 (a and b). The effect of ionic strength on drug release from HPMC (a. E4M b. K4M) matrices. Standard deviations not shown as smaller than symbol size (mean ± SD, *n*=3).

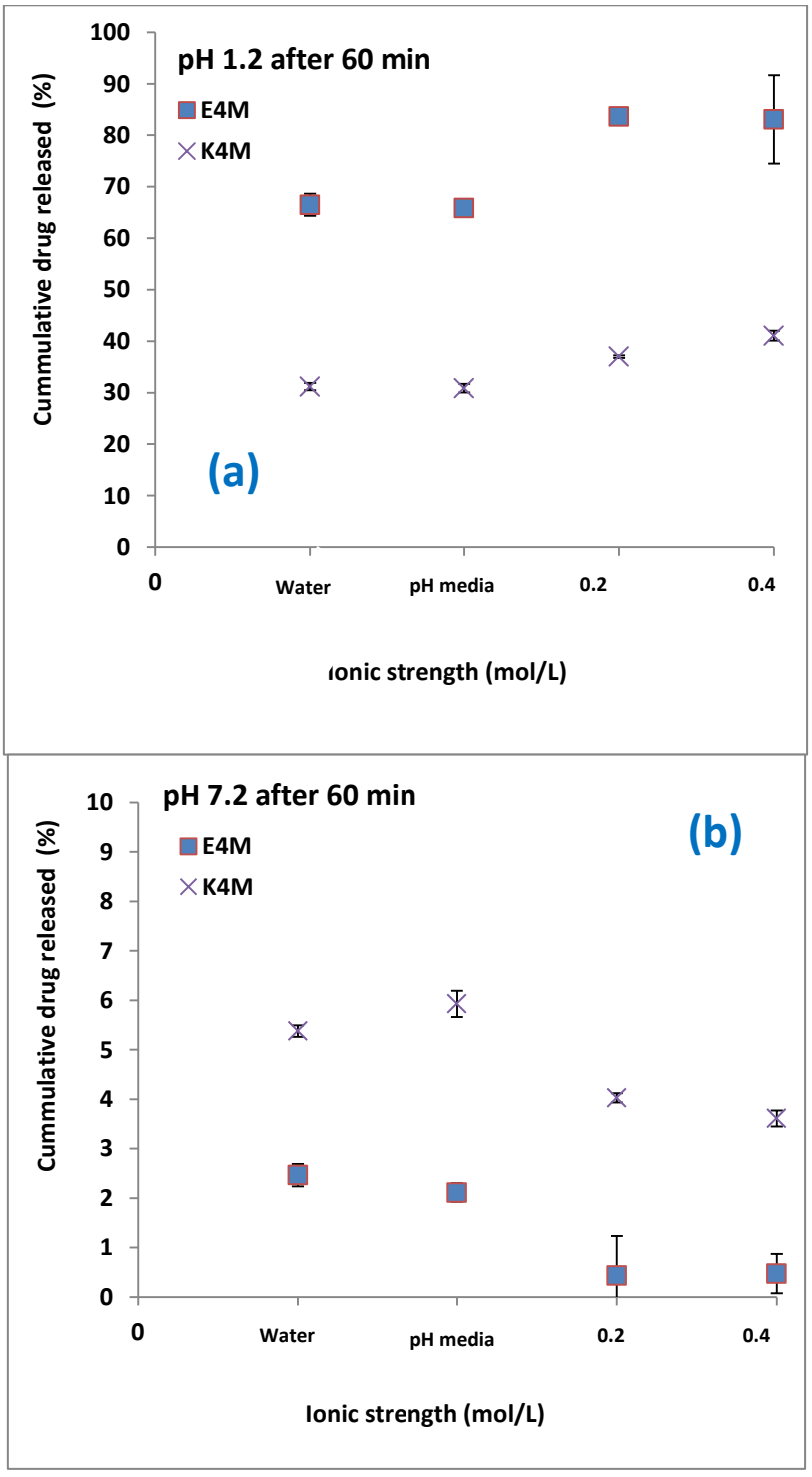

Figure 6 (a-b). Theophylline releaase from HPMC matrices at different ionic strengths in different pH (mean ± SD, *n*=3).