The effect of pH and ionic strength of dissolution media on in-vitro release of two model drugs of different solubilities from HPMC matrices

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Abstract

The evaluation of the effects of different media ionic strengths and pH on the release of hydrochlorothiazide, a poorly soluble drug, and diltiazem hydrochloride, a cationic and soluble drug, from a gel forming hydrophilic polymeric matrix were the objectives of this study. The drug to polymer ratio of formulated tablets was 4:1. Hydrochlorothiazide or diltiazem HCl extended release (ER) matrices containing hypromellose (hydroxypropyl methylcellulose (HPMC)) were evaluated in media with a pH range of 1.2-7.5, using an automated USP type III, Bio-Dis dissolution apparatus. The ionic strength of the media was varied over a range of 0-0.4 M to simulate the gastrointestinal fed and fasted states and various physiological pH conditions. Sodium chloride was used for ionic regulation due to its ability to salt out polymers in the midrange of the lyotropic series. The results showed that the ionic strength had a profound effect on the drug release from the diltiazem HCl K100LV matrices. The K4M, K15M and K100M tablets however withstood the effects of media ionic strength and showed a decrease in drug release to occur with an increase in ionic strength. For example, drug release after the 1 hr mark for the K100M matrices in water was 36 %. Drug release in pH 1.2 after 1 hr was 30 %. An increase of the pH 1.2 ionic strength to 0.4 M saw a reduction of drug release to 26 %. This was the general trend for the K4M and K15M matrices as well. The similarity factor f_2 was calculated using drug release in water as a reference. Despite similarity occurring for all the diltiazem HCl matrices in the pH 1.2 media (*f2*=64-72), increases of ionic strength at 0.2 M and 0.4 M brought about dissimilarity. The hydrochlorothiazide tablet matrices showed similarity at all the ionic strength tested for all polymers (*f2*= 56-81). The values of f2 however reduced with increasing ionic strengths. DSC hydration results explained the hydrochlorothiazide release from their HPMC matrices. There was an increase in bound water as ionic strengths increased. Texture analysis was employed to determine the gel strength and also to explain the drug release for the diltiazem

hydrochloride. This methodology can be used as a valuable tool for predicting potential ionic effects related to *in vivo* fed and fasted states on drug release from hydrophilic ER matrices.

Keywords: Ionic strength, HPMC polymeric matrix tablets, Similarity factor, Kinetics of drug release, Hydration, Diltiazem HCl, Hydrochlorothiazide.

1. Introduction

HPMC matrices swell when placed in water and the polymer is responsible for forming a gel layer around the tablet. The release of the drug from the matrix depends on the possible interactions between aqueous medium, polymer, drug and other tablet ingredients [1]. The non-ionic nature of HPMC means that when API solubility is pH-independent, the matrices produce pH-independent drug release profiles. Two major variables of the gastrointestinal (GI) fluids are pH and ionic strength. They vary greatly along the GI tract under fasting and fed conditions [2, 3] and can affect the rate at which a drug is released from hydrophilic ER matrices [4-6]. In man under both fasted and fed states and various physiological pH conditions, the ionic strength of GI fluids cover a range of 0-0.4 M [4]. In a fasted stomach, ionic strength has been estimated at approximately 0.11 M [7]. There is a variation in that value after meal consumption and is dependent on the composition of the food. The ionic strength in the intestinal tract has been estimated to be around 0.14 M [7]. Cellulose ethers are susceptible to ionic effects of the media in the following order: chloride < tartrate < phosphate and potassium < sodium. 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 [4, 8]. As oral extended release formulations are subjected to different pHs and ionic strength along the GI tract, it is important to evaluate their performance under those conditions.

There are three types of hydration water, each possessing different physical properties [9]. Type I (freezing or free, bulk-like water) melts at the normal melting point of pure water (0 ^{o}C). Type II (freezing or bound water) weakly interacts with macromolecules and displays a lower melting point than pure water (< 0 ^{o}C). Type III (bound water) strongly interacts with hydrophilic and ionic groups of the polymer and shows non freezing behaviour. According to Aoki and co workers [10] during the initial stage of dissolution, water penetrates into the matrix and usually acts as non-freezing (bound) water. In the next stage, the water content of the matrix increases and freezable water is detected at levels that are related to drug release. They also reported that the transport of solutes mainly occurs through the free water and that only little transport occurs through bound water. Yoshioka and co workers [11] studied hydrophilic polymeric gelatin gels and also claimed that bound water did not participate to any significant effect in the hydration process and that the hydrolysis/water uptake rate depended mainly on the amount of free water present in the system. Therefore, knowing the dynamics and state of water molecules in hydrogels enables a better understanding of the swelling process of the hydrophilic matrices and the release of drugs from these systems [12].

In a recent study, the influence of changing the agitation sequence on drug release from HPMC matrices were studied in a USP III dissolution apparatus modeling fed and fasted conditions [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 [14]. The same authors then investigated agitation and ionic strength effects using theophylline as a model drug from HPMC E4M and K4M tablet matrices 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 [15]. The present work employs these methodologies to determine the effect of ionic strength and

media pH on a cationic drug and a poorly soluble drug using the USP III Apparatus. This study also explores a differential scanning calorimetry (DSC) methodology as reported by the same authors to determine free and bound water to explain drug release in the different media. This study also explores a Texture analysis (TA) methodology in order to understand ionic strength and its impact on the gel layer strength and drug release. This study gives a greater insight into potential fed and fasted effects on drug release from hydrophilic extended release matrices.

2. Materials and methods

2.1. Materials

Hydrophilic matrix tablets were prepared using Diltiazem hydrochloride (Sigma) or Hydrochlorothiazide (Spectrum) as the model drug and HPMC (METHOCEL™ Premium K100LV, K4M, K15M and K100M (Colorcon Ltd, UK) polymers as the hydrophilic matrix former. 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 (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 either hydrochlorothiazide or diltiazem HCl with HPMC in the ratio of 4:1 for 10 min in a Turbula® blender (Type T2 C, Switzerland). Tablet compression, true density measurements of the powder mixtures and porosity calculations are detailed elsewhere [14].

2.3. Dissolution testing and influence of ionic strength

An automated USP type III Bio-Dis (Varian, US) was used to carry out the dissolution studies. The dip rate used for the ionic strength studies was 20 dpm. The absorbance of the released diltiazem hydrochloride and hydrochlorothiazide was measured at 240 nm and 272 nm respectively, using a UV/Visible spectrophotometer (Varian, Cary 50). Drug-release behaviour of all the above formulations was investigated in deionised water and in six dissolution media to determine sensitivity of different grades of HPMC to pH and ionic strength. The dissolution testing was conducted for 310 minutes for all formulations. The influence of media ionic strengths on diltiazem hydrochloride and hydrochlorothiazide release from the METHOCEL K100LV, K4M, K15M and the K100M tablet matrices was studied. 0.2 M and 0.4 M sodium chloride was added to regulate the ionic strength in buffers with pH of 1.2, 2.2, 5.8, 6.8, 7.2 and 7.5. All four HPMC (K100LV, K4M, K15M and K100M) formulations for each model drug were tested using this methodology. This allowed discrimination of the effect of the ionic strength on the formulations where different grades of HPMC were used [14, 15].

2.4. Similarity factor

To determine the similarity between the obtained drug release profiles, *f2* factor [16, 17] was calculated as detailed in [14]. Drug release in deionised water was used as the reference in the determination of *f2*.

2.5. Differential Scanning Calorimetry

DSC (Mettler-Toledo) was performed on samples of physical mixtures of drug and polymer after blending described in Section 2.2 were placed in standard 40 µm aluminium crucibles and sealed. The aluminum crucibles were heated from 25 to 300 ^{o}C at 10 ^{o}C/min rate under nitrogen gas to identify any potential material interactions. The methodology for DSC hydration was taken from [14].

2.6. Texture Analysis of Hydrated HPMC Tablet Matrices

Tablets, prepared as described in section 2.2, were hydrated in either deionised water (0 ionic strength), pH 1.2, pH 1.2 (+ 0.2 M NaCl) and pH 1.2 (+ 0.4 M NaCl) for 10 and 30 minutes using a USP Apparatus II (Paddle) (Varian) at 100 rpm (to mimic dissolution conditions). To avoid the adhesion of the hydrated tablets to the bottom of the dissolution vessel, the dissolution test was modified using a mesh device similar to that described in Durig *et al.*, [18]. After the tablets were placed onto the device, the distance between rotating dissolution paddle and the device was adjusted back to 2.5 cm (the distance between the paddle and the lower part of the dissolution vessel in the absence of the devise used). After hydration, tablets were removed from the dissolution vessels and placed directly on the platform of texture analyzer (Stable Micro System) equipped with an interchangeable load cell of 5 kg. The 2 mm SMS P/2 was used as the penetration probe. A pre-test, test and post-test speed of 0.05 mms^{-1}, 0.05 mms^{-1} and 0.20 mms^{-1} were used respectively. Gel strength was determined as the work of penetration integrated to the first peak normalised by the tablet thickness to the first peak (distance travelled by the probe). The extremes of HPMC K chemistry viscosities (i.e., K100LV and K100M) for both drugs were studied. All experiments were analysed in controlled environment at room temperature and done in triplicate.

3. Results and Discussion

Compacts containing diltiazem HCl had similar volumes (0.282-0.283 cm^3) and tablet porosities (35 %). All hydrochlorothiazide tablets also had similar volumes (0.252-0.254 cm^3) and similar tablet porosities (27 %) (For full details please refer to supplementary materials Table S1). Figures 1 and 2 show the influence of ionic strength on drug release from tablets containing HPMC K100LV and K100M (for K4M and K15M, please refer to supplementary materials Figures S1 and S2). USP buffers used in this study have different ionic strength levels, ranging from 0.05-0.14 M. Addition of sodium chloride at 0.2 and 0.4 M to these results in actual ionic strengths from 0.45 and 0.54 M so are referred to in terms of amount of added sodium chloride for clarity. The ionic strength of the media had a significant effect on diltiazem HCl release from K100LV matrices (Figure 1a). It is important that the formation of a gel layer occurs quickly enough to prevent fast water penetration inside the tablet core and potential matrix disintegration [19, 20]. It was however observed that for matrices that contain**ed** HPMC K100LV, once placed in media with agitation, there was visible surface erosion prior to formation of the gelatinous layer. Drug release was in the order of K100LV > K4M > K15M > K100M (See supplementary materials Table S2**).** The K4M, K15M and K100M in the water and "pH media" for the diltiazem hydrochloride matrices showed that the difference in their release profiles which in this case is more evident after the 120 minutes time point is also due to the effect of the phosphate ionic species and the cationic nature of the drug. The pH media had ionic strengths from 0.05-0.14 M indicating that the decrease observed here can be attributed to the effect of the ion species present. Drug release is decreased further as the ionic strength is increased. The cationic nature of the drug and the increase in pH as matrix moves from vial to vial cause a change in the hydration properties of the gel and thus a difference in the total solubility of the ionized and the non-ionized forms of the drug. Due to the drugs pKa being 7.7, it is important to note that that drug will be in its ionised form below this pH [21]. The additional salt and those in the buffers exert a strong

ionic effect decreasing the diltiazem HCl dissolution. Mitchell and co workers [22] found that some drug substances such as propananol HCl increased the hydration of HPMC; and that many electrolytes have the ability to depress gel points of polymers by affecting dehydration. It was noted with regards to the poorly soluble drug hydrochlorothiazide that there was a general increase in drug release as the ionic strength of the media was increased. This however was very minimal and not significant. Hydrochlorothiazide is a bivalent acid, with pKa of 8.6 and 9.9 so mostly unionized at pHs studied [23].

The model drugs used showed that despite HPMC being a non-ionic polymer, the medium ionic composition can influence its behaviour. This was in agreement with work done by Kavangh and co workers [24]. They showed that an increase in ionic strength brought about a decrease in matrix erosion rate. They found this phenomenon was more apparent for K100LV tablets as this relatively low viscosity HPMC polymer is more susceptible to erosion. They showed that this effect was less significant for the higher molecular HPMC polymers. Asare-Addo and co workers [14] also showed the drug release rates for all the K chemistry HPMC polymers to decrease with increasing ionic strengths for theophylline matrices. The decrease in erosion rates as the ionic strength increased was attributed to the "salting out" of the polymer by the organic ions present in the dissolution media. Alderman [25] also noted that as the ionic strength of the medium increases, the polymer molecular chains lose water of hydration due to ions competing for the available water. This could explain the quick release from the K100LV matrices for diltiazem hydrochloride meaning that *f2* values could not be calculated. Diltiazem HCl release from K4M, K15M and K100M matrices in the "pH media" using the deionised water as a reference were similar (*f2* = 64-72) (See supplementary materials Table S3). Similarity values however fell as ionic strength was increased with 0.2 M and 0.4 M NaCl for all K4M, K15M and K100M formulations (*f2* = 41-49). Release of

hydrochlorothiazide was similar at all ionic strengths studied (*f2* = 56-81). Also *f2* values in "pH media" were the highest (72-81). The K100M tablets were the most robust of all the matrices studied (see supplementary materials Table S3). For the purposes of this study, the similarity values obtained give an indication of the ability of the HPMC matrices to withstand the impact of increases in ionic strength that could occur in the body. This can help to decide which formulations could be excellent candidates for producing drug dissolution profiles affected to a lesser degree by foods rich in ion content. The results of this study show that with hydrochlorothiazide as a model drug, all polymers used could be excellent candidates for producing drug dissolution profiles not significantly affected by foods rich in ionic content. Care must however be taken with regards to the nature of drug used as in the case of diltiazem hydrochloride.

The diltiazem hydrochloride HPMC matrices showed a general decrease with increasing ionic strength (See supplementary materials Figure S3a). This general negative slope in Figure S3a for the diltiazem hydrochloride tablet matrices indicates a reduction in drug release taking place as the ionic strength of the medium was increased due to the cationic nature of the drug. This phenomenon was however not evident for K100LV matrices and became more apparent as the viscosity of the polymer grades used increased. For example, diltiazem HCl release from K4M tablets decreased from 38 % in deionised water to 36 % in the medium with 0.4 M NaCl after 60 minutes whereas the corresponding decrease was from 36% to 26 % for K100M matrices. After 310 min drug release from K4M matrices decreased from 97 % in the water media to 79 % in the medium containing additional 0.4 M NaCl with a corresponding change from 91 % for K100M matrices. Hydrochlorothiazide release from HPMC matrices increased with an increase in the ionic strength of the medium. This general positive slope in Figure S3b for the hydrochlorothiazide tablets also indicates that there was

an increased erosion taking place as the ionic strength of the medium increased. These hydrochlorothiazide results were similar to the data obtained for the theopylline matrices as reported by Asare-Addo and co workers [14]. Hydrochlorothiazide release from K100LV matrices increases from 35 % in deionised water to 42 % in the medium with 0.4 M NaCl after 60 minutes. This less significant increase could also be attributed to the poorly soluble nature of hydrochlorothiazide. There was a minimal increase in drug release as compared to the K100LV matrices with increasing ionic strength. For example, 18 %, 15 % and 10 % of drug was released in water and when the ionic strength was increased with the addition of 0.2 M NaCl, the amount of the active released increased to 21 %, 21 % and 14 % for the K4M, K15M and K100M tablets respectively (see supplementary materials Figure S4 and S5). A closer look at the slopes obtained from plotting % release vs. square root of time for different ionic strenths (see supplementary materials Table S4) show that for the HPMC polymers, values were in the order of K100LV > K4M > K15M > K100M. This could be due to a number of reasons, i.e. the gel formed on the surface of the tablet upon its introduction into the medium limiting the amount of drug being transported into the solution as the apparatus moved the matrix from one medium to another. The change in the tablets geometry as a result of agitation in previous medium/media also meant the remaining tablet matrix had a decreased surface area making the little drug remaining in the gel layer to have a relatively lower slope upon its introduction into the ensuing fresh volume of the medium. The K100M tablets however had lower slope values as compared to the K4M and K15M matrices for the model drugs thus demonstrating the resilience of K100M polymer to the effects of agitation.

DSC thermograms for the physical mixtures of the polymers and model drugs showed no material interactions (Figure not included). Figures 3 and 4 show the results obtained for the K100LV and K100M tablet formulations of 4:1 drug: polymer hydrated in the different

media used to obtain the values of bound and free water. Table 1 shows the amount (%) of bound water for different grades of HPMC after 10 minutes hydration for all matrices containing the studied model drugs. There was a general increase water uptake for all HPMC polymers tested over the 30 minute period (results not included). This increase was slightly higher for the higher molecular HPMC grades consistent with the results reported by Wan and co workers [19]. They attributed this phenomenon to the larger hydrodynamic volume occupied by the chains of the hydrated polymers with higher molecular weight. To coincide with the first sample time in the dissolution studies being at 10 minutes, water uptake was also studied at 10 minutes. It is generally known that as the ionic is increased, the solubility of the polymer decreases thus reducing the amount of water available for polymer hydration [4]. The hydration curves for all the polymers containing diltiazem hydrochloride in deionised water were different from those of the other media used (Figure 3) highlighted on the thermograms by a black arrow. What is noticed here is that, as the ion content in the media is increased, there is a smoothing effect of the curve occurring. This however was not the case for hydrochlorothiazide. Instead there was a slight decrease in peak temperature as the ionic strength of the media was increased (also indicated by a black arrow, Figure 4). Katzhendler and co workers [26] hydrated naproxen sodium incorporated into HPMC K4M matrices and showed a similar behaviour to that of diltiazem hydrochloride. They suggested this was due to the drug participating in the crystallization of water leading to a three dimensional network structure formation that decreased the freedom of water. Other theories include part of the water solidifying in an amorphous form during the cooling process and the water crystallising during the heating process. The faint endothermic peak is attributed to the melting of imperfect water and possible interaction between the drug, HPMC and water [10, 26, 27].

According to Aoki and co workers [10] during the initial stage of dissolution, water penetrates into the matrix and usually acts as non-freezing (bound) water. In the next stage, the water content of the matrix increases and freezable water is detected at levels that are related to drug release. Before hydration of the whole matrix, water penetrates into the dry portion of the matrix, hydrates and swells the polymer. Further penetration of water does not increase the water content of the hydrated portion but newly hydrates a dry portion of the matrix. After hydrating the whole matrix, the amount of water at the surface gradually increases with time. Aoki and co workers [10] also reported that the transport of solutes mainly occurs through the free water and that only little transport occurs through bound water. The K100LV diltiazem hydrochloride formulation, after 10 minutes hydration in the relevant media showed approximately 19 %, 19 %, 31 % and 39 % uptake of bound water in water media, pH 1.2, pH 1.2 + 0.2 M NaCl, and pH 1.2 + 0.4 M NaCl respectively. For hydrochlorothiazide K100LV matrices, 25 %, 26 %, 30 % and 34 % uptake of bound water had occurred in the media as outlined above. This increase in the amount of bound water with increasing ionic strength of the media was evident for all the polymers in the study (Table 1). This increase in bound water suggested that there was less free water available for polymer hydration to form the gel layer necessary for controlling drug release.

The result for hydrochlorothiazide was in agreement with work done by Aoki and co-workers [10] who found that transport of solutes mainly occurred through free water and that only little transport took place through bound water. Studies conducted by Yoshioka and co workers [11] also established, after studying hydrophilic polymeric gelatin gels, that bound water did not contribute significantly to the hydration process and that the water uptake rate was dependent mainly on the amount of the free water present in the system. This drug result was also similar to the work done on theophylline matrices by the same authors [14, 28].

Hydrochlorothiazide released after 10 minutes also correlated with the DSC hydration experiments. It was observed that as the ionic strength increased, the hydrochlorothiazide release also increased. In the highest ionic strength medium, the amount of bound water was similar for all the formulations suggesting that the strength of the gel played an important role in the drug release pattern. The results show that the first few minutes of hydration are the most important because this period corresponds to the time when the protective gel layer is formed around the matrix [29].

Table 2 shows the mean peak values and areas (obtained by the integration of the area under the force-distance profiles) for texture analysis results used to compare textural strength of the HPMC tablet matrices under investigation. Agitation at 100 rpm resulted in the formation of constantly eroding thin gel of the K100LV polymer as it was only in a low level of 20 % below the polymer percolation threshold. Due to the relatively fast drug release from the diltiazem HCl K100LV matrices, it was hard to establish any real trends although there was a significant difference in the areas under the curves (ANOVA-test, $P < 0.05$) for the diltiazem HCl and hydrochlorothiazide K100LV tablet matrices. The addition of diltiazem HCl to the HPMC K100M polymer caused a decrease in the mean peak values from 0.69 N in water to 0.35 N when 0.4 M NaCl was added. This process is also evident in the values of the area under the curves obtained. Diltiazem hydrochloride matrices in the water media after analysis after the 10 min time point (chosen to correspond to the first time point in the dissolution process) produced an area of 1.46 gs. The increased ionic strength caused this value to decrease to 0.56 gs in the highest ionic strength media ($p=0.0031$). Statistical analysis also showed significant differences in the gel strengths for the tablet matrices of hydrochlorothiazide K100M matrices (ANOVA-test, $P < 0.05$). As a general trend it was found that the freely water-soluble diltiazem HCl increased the drug release rate from the

hydrophilic matrices in deionised water, possibly due to its high aqueous solubility. However when ionic strength was increased, drug release rate was reduced. This phenomenon may be due to interactions between the drug, the polymer and the salt contents in the other media (pH 1.2 (no salt), pH 1.2 (+ 0.2 M NaCl) and pH 1.2 (+ 0.4 M NaCl)). Kavanagh and Corrigan [24] showed the time to attainment of maximum wet weight of K100LV discs to increase with increasing ionic strength with this effect being much less for the higher molecular weight polymer K15M. They showed that dissolution uptake rate decreased linearly with increasing ionic strength and also that the decrease in erosion rate occurring with the increase in ionic strength could be attributed to salting out and loss of water of hydration.

The statistical analysis of the drug release profiles (Tables 3 and 4) indicate that a decrease in the viscosity grade of the K chemistry HPMC polymers resulted in an increase in the Dissolution efficiency (DE) value. 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 of a pharmaceutical dosage form. Thus, DE was in the K100LV > K4M > K15M > K100M order depicting that the lower viscosity grade of HPMC K100LV had the highest DE values. Diltiazem HCl had anomalous transport dominating its kinetics of release. The only exceptions were K100LV matrices in deionised water and when the ionic was increased by the addition of 0.2 M NaCl. n values of 0.9862 and 0.8960 respectively, suggested that Case-II transport was the dominant mechanism of drug release for the matrices as these specified agitations (Table 3). It was noticed with the K4M, K15M and K100M tablets that DE decreased with an increase in the ionic strength (Table 3). Hydrochlorothiazide showed Fickian diffusion for K100LV matrices in the media containing the addition of 0.4 M NaCl with an n value of 0.3863. All other hydrochlorothiazide formulations showed anomalous transport with n values ranging from 0.4602-0.7668 (Table 4) for all ionic strengths. It was

also observed that there was a general decrease in the value of n with an increase in the ionic of the media for all hydrochlorothiazide matrices. The poorly soluble nature of this drug however meant that all DE, MDT and MDR values were low compared to diltiazem HCl matrices.

4. Conclusion

Ionic strength of dissolution media had a significant effect on diltiazem release from K100LV matrices. K4M, K15M and K100M were however resilient to the influence of media ionic strength. The poorly soluble nature of hydrochlorothiazide meant that, despite the low amount of HPMC used in this study (20 %), ioinc strength did not impact release rates. The DSC hydration method proved to be useful in explaining the mechanism of hydrochlorothiazide release from HPMC matrices. As a general trend it was found that freely water-soluble diltiazem hydrochloride seemed to increase the drug release rate from the hydrophilic matrices in the presence of deionised water only. However, when ionic strength was increased, drug release rates were reduced. Texture analysis proved useful in explaining these results. Changing dissolution medium ionic strength in this research has shown that this method could be an additional tool in allowing for foods with differing salt contents to be screened, and that both the matrix former and the drug will impact results.

5. References

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Table 1. Amount (%) of bound water for different grades of HPMC resulting after 10 min hydration with the relevant media of different ionic strength **(n=3)**

Dissolution medium (ionic strength)	**Diltiazem hydrochloride formulation**				**Hydrochlorothiazide formulation**			
	K100LV	**K4M**	**K15M**	**K100M**	**K100LV**	**K4M**	**K15M**	**K100M**
Water (0)	18.68 ± 1.09	15.37 ± 2.25	17.57 ± 2.69	10.86 ± 1.63	25.01 ± 1.7	23.16 ± 3.25	23.87 ± 1.12	21.28 ± 1.11
pH 1.2 (no NaCl)*	18.53 ± 1.67	20.28 ± 1.89	23.23 ± 0.96	23.23 ± 1.75	26.25 ± 1.15	28.24 ± 2.32	25.72 ± 0.81	24.06 ± 2.32
pH 1.2 (+0.2 M NaCl)$	31.42 ± 1.59	33.29 ± 2.57	32.8 ± 3.12	33.71 ± 3.10	30.29 ± 2.34	32.9 ± 0.86	31.05 ± 1.73	29.97 ± 1.41
pH 1.2 (+0.4 M NaCl)#	39.13 ± 1.27	38.54 ± 2.61	41.31 ± 0.61	37.39 ± 1.81	34.28 ± 1.33	34.55 ± 0.08	33.39 ± 1.82	32.28 ± 1.21

* Actual ionic strength = 0.14 M, $ actual ionic strength = 0.34 M, # actual ionic strength = 0.54 M.

Table 2. Peak force values and integrated areas of curves obtained from texture analysis for three model drugs **(n=3)**

Formulation	Media	Mean peak force (N)	Distance (mm)	Time (sec)	Area (gsec)
K100LV Diltiazem HCl matrices	water	0.10 ± 0.00	0.18 ± 0.00	3.93 ± 0.01	0.24 ± 0.00
	pH 1.2 (no NaCl)	1.55 ± 0.35	0.19 ± 0.00	4.05 ± 0.01	2.33 ± 0.00
	pH1.2 (+0.2 M NaCl)	0.80 ± 0.00	0.19 ± 0.00	4.04 ± 0.00	2.02 ± 0.00
	pH1.2 (+0.4 M NaCl)	0.10 ± 0.00	0.19± 0.00	4.02 ±0.04	0.25 ± 0.05
K100M Diltiazem HCl matrices	water	0.69 ± 0.01	0.19± 0.00	3.99 ± 0.07	1.46 ± 0.17
	pH 1.2 (no NaCl)	0.50 ± 0.14	0.19± 0.00	4.05 ± 0.01	1.40 ± 0.14
	pH1.2 (+0.2 M NaCl)	0.50 ± 0.00	0.19± 0.00	4.05 ± 0.01	1.39 ± 0.02
	pH1.2 (+0.4 M NaCl)	0.35 ± 0.07	0.19± 0.00	4.05 ± 0.01	0.56 ± 0.02
K100LV Hydrochlorothiazide matrices	water	0.20 ± 0.00	0.18 ± 0.00	3.91 ± 0.00	0.42 ± 0.00
	pH 1.2 (no NaCl)	1.30 ± 0.14	0.19± 0.00	4.04 ± 0.01	2.66 ± 0.26
	pH1.2 (+0.2 M NaCl)	0.85 ± 0.07	0.19± 0.00	4.06 ± 0.00	2.09 ± 0.16
	pH1.2 (+0.4 M NaCl)	0.80 ± 0.14	0.19± 0.00	4.04 ± 0.00	1.87 ± 0.21
K100M Hydrochlorothiazide matrices	water	0.40 ± 0.14	0.19± 0.00	4.03 ± 0.03	0.85 ± 0.21
	pH 1.2 (no NaCl)	0.45 ± 0.07	0.19± 0.00	4.04 ± 0.01	1.25 ± 0.16
	pH1.2 (+0.2 M NaCl)	0.35 ± 0.07	0.19± 0.00	4.04 ± 0.00	1.03 ± 0.12
	pH1.2 (+0.4 M NaCl)	0.75 ± 0.07	0.19± 0.00	4.03 ± 0.00	1.97 ± 0.09

Table 3. The influence of varying ionic strength of the dissolution medium on mechanism of diltiazem HCl release

			Drug-release characteristics				
Tablet Formulation	Ionic strengths	Agitation (dpm)	$DE_{310mins}$ (%)	MDT (min)	MDR (%min^{-1})	RSQ (r^2)	n
K100LV	Water (0)	20	92.34	23.74	0.27	0.9869	0.9862
K100LV	(no NaCl)	20	91.12	27.52	0.26	0.9372	0.6238
K100LV	(+0.2 M NaCl)	20	91.87	25.21	0.27	0.9459	0.8960
K100LV	(+0.4 M NaCl)	20	92.75	22.49	0.23	0.9941	0.5598
K4M	Water (0)	20	69.27	87.52	0.31	0.9688	0.6599
K4M	(no NaCl)	20	67.87	99.60	0.31	0.9922	0.7571
K4M	(+0.2 M NaCl)	20	54.93	111.57	0.26	0.9924	0.6685
K4M	(+0.4 M NaCl)	20	54.65	94.93	0.23	0.9864	0.5262
K15M	Water (0)	20	62.26	27.45	0.17	0.9942	0.6410
K15M	(no NaCl)	20	58.62	26.83	0.16	0.9944	0.6719
K15M	(+0.2 M NaCl)	20	46.64	27.70	0.13	0.9895	0.6325
K15M	(+0.4 M NaCl)	20	42.04	27.70	0.12	0.9852	0.5832
K100M	Water (0)	20	58.74	26.72	0.16	0.9897	0.6235
K100M	(no NaCl)	20	51.64	27.66	0.14	0.9906	0.6324
K100M	(+0.2 M NaCl)	20	42.43	27.44	0.12	0.9896	0.6290
K100M	(+0.4 M NaCl)	20	37.27	27.74	0.10	0.9884	0.6367

Table 4. The influence of varying ionic strength of the dissolution medium on mechanism of hydrochlorothiazide release

			Drug-release characteristics				
Tablet Formulation	Ionic strengths	Agitation (dpm)	$DE_{310mins}$ (%)	MDT (min)	MDR (%min^{-1})	RSQ (r^2)	n
K100LV	Water (0)	20	58.45	92.77	0.26	0.9828	0.5770
K100LV	(no NaCl)	20	60.89	81.05	0.24	0.9788	0.5156
K100LV	(+0.2 M NaCl)	20	60.32	78.82	0.22	0.9893	0.4602
K100LV	(+0.4 M NaCl)	20	62.57	61.59	0.20	0.9633	0.3863
K4M	Water (0)	20	36.33	135.00	0.20	0.9967	0.7668
K4M	(no NaCl)	20	37.97	124.64	0.19	0.9975	0.6916
K4M	(+0.2 M NaCl)	20	36.09	113.36	0.17	0.9975	0.5972
K4M	(+0.4 M NaCl)	20	40.08	107.74	0.19	0.9709	0.5855
K15M	Water (0)	20	29.34	134.75	0.16	0.9959	0.7137
K15M	(no NaCl)	20	30.60	118.75	0.14	0.9972	0.6191
K15M	(+0.2 M NaCl)	20	33.28	109.69	0.15	0.9928	0.5630
K15M	(+0.4 M NaCl)	20	35.01	115.50	0.17	0.9694	0.5599
K100M	Water (0)	20	19.88	135.86	0.11	0.9946	0.6861
K100M	(no NaCl)	20	21.98	127.78	0.11	0.9959	0.6422
K100M	(+0.2 M NaCl)	20	23.22	116.60	0.11	0.9966	0.5667
K100M	(+0.4 M NaCl)	20	24.18	109.83	0.10	0.9943	0.4758

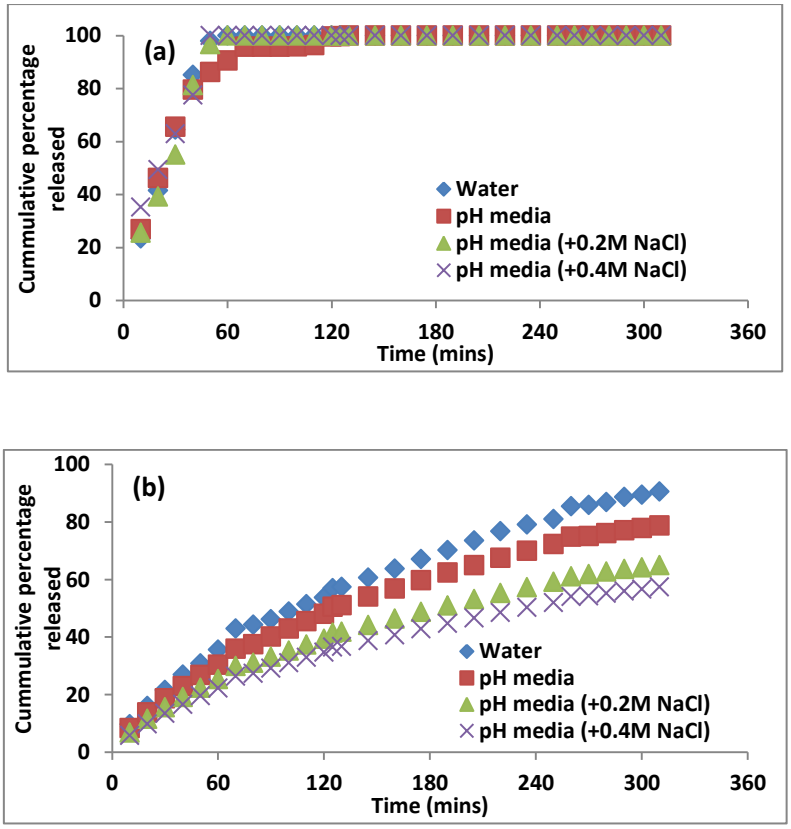

Figure 1. The influence of ionic strength on diltiazem HCl release from HPMC matrices over pH 1.2 – 7.5. a. K100LV b. K100M. Standard deviations smaller than the symbol size were not shown on the graphs.

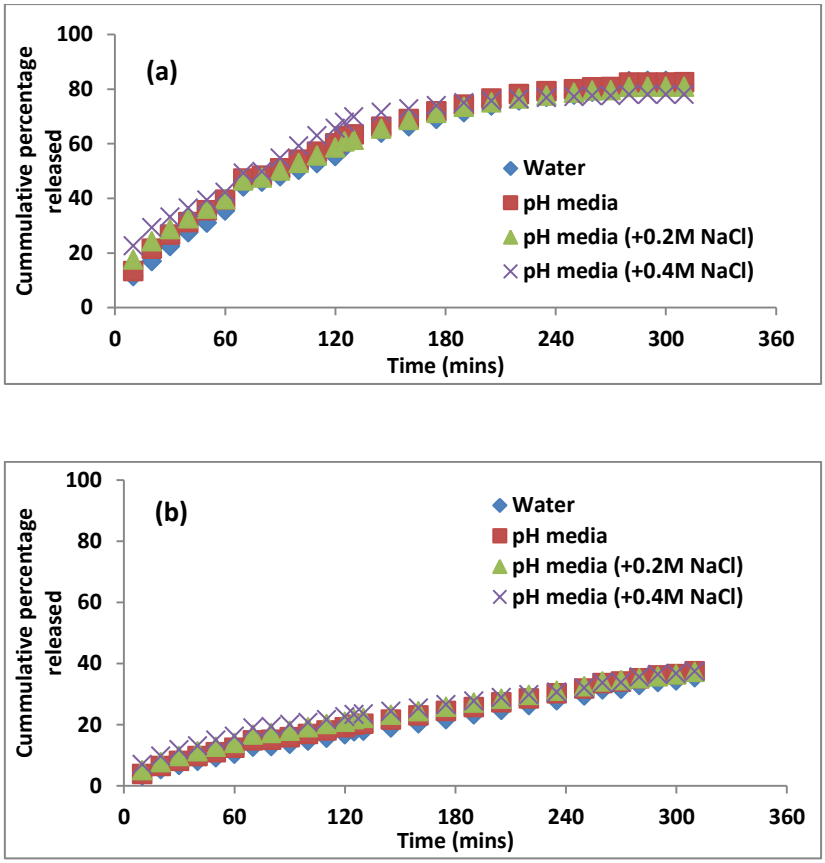

Figure 2. The influence of media ionic strength on hydrochlorothiazide release from HPMC matrices from pH 1.2-7.5 a. K100LV, b. K100M. Standard deviations smaller than the symbol size were not shown on the graphs.

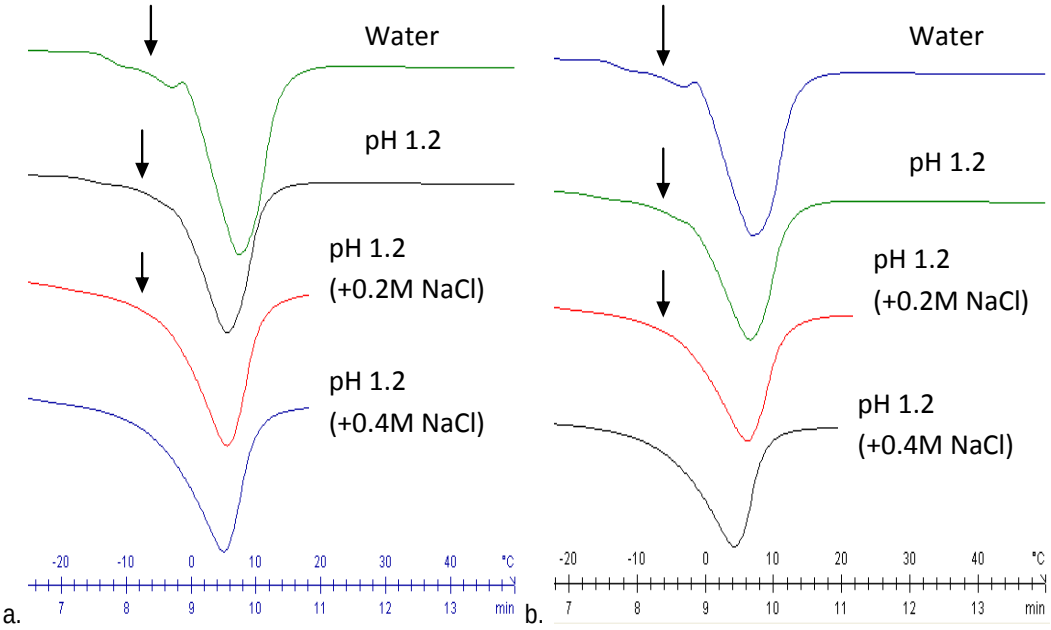

Figure 3. DSC thermograms of diltiazem HCl taken after 10 minutes hydration in relevant media of 4:1 drug:HPMC matrices a. K100LV, b. K100M

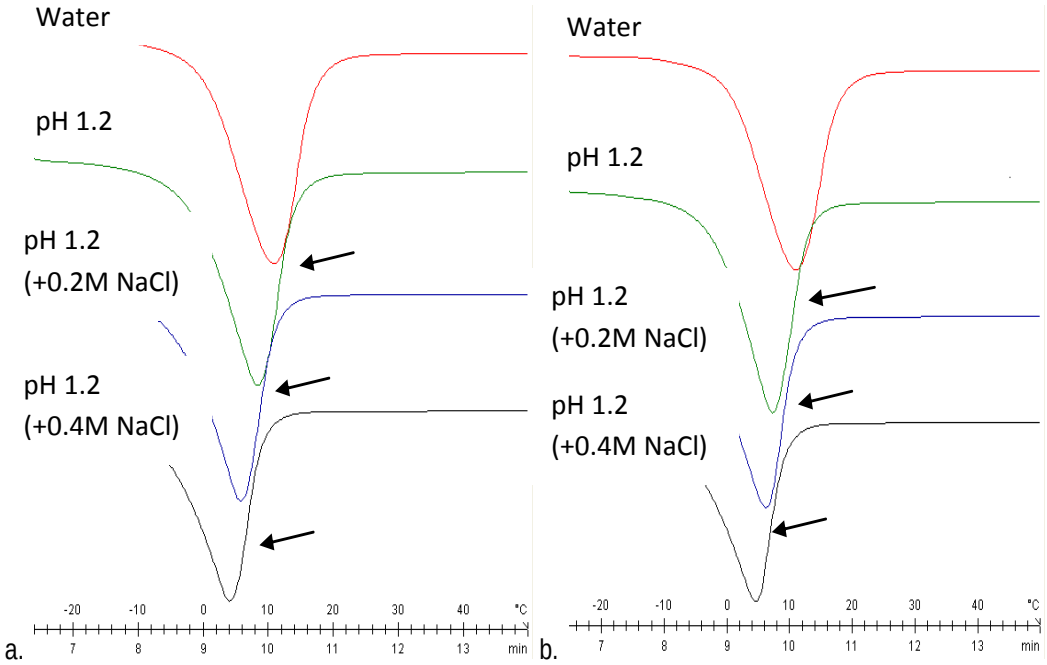

Figure 4. DSC thermographs of hydrochlorothiazide taken after 10 minutes hydration in relevant media of 4:1 drug:HPMC matrices a. K100LV, b. K100M