The effect of inorganic cations Ca^{2+} and Al^{3+} on the release rate of propranolol hydrochloride from sodium carboxymethylcellulose matrices

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ABSTRACT

Background and purpose of the study: Several methods are available for control release of propranolol hydrochloride (PLH). The aim of the present study was to develop a novel technique to sustain PLH release from matrices.

Materials and methods: Matrices of PLH containing sodium carboxymethylcellulose (Na CMC) and various amounts of the inorganic cations Ca^{2+} and Al^{3+} were prepared. Dissolution of the matrices was carried out using the USP apparatus I. Analysis of release data was performed by some model independent and dependent approaches.

Results: The release of PLH was affected by incorporation of different amounts (milliequivalents, meq) of Ca^{2+} and Al^{3+}. When the Ca^{2+}amount increased from 0- 0.375 meq, the fraction of PLH which released within 480 min was augmented from 0.74 to 1 apparently via disintegrating effect of the cation. Al^{3+}in the range 0- 0.125 meq, decreased the fractional release from 0.74 to 0.37 presumably by *in situ* cross- linking with polymer. Al^{3+} between 0.125 and 0.5 meq enhanced the release from 0.37 to 1 possibly due to the disintegrating effect. Among model independent metrics, the mean release time (MRT) failed to represent the effect of the cations on the release but the release efficiency (RE) as well as a suggested mean release rate (MRR) correlated well with the experimental release rate. Due to the complexity of the release, the only suitable kinetic model was the Weibull distribution. The minimum and maximum Weibull release rate constants for matrices containing Al^{3+} were 0.0007-0.017 1/min. The corresponding values for the matrices with Ca^{2+} were 0.0029-0.0082 1/min.

Conclusion: Through careful choice of the amount of Al^{3+}in NaCMC matrices the release of PLH can be controlled at a desired rate. The best model independent approach is MRR and the most accurate model dependent method is Weibull distribution to describe the release data.

Keywords: Propranolol hydrochloride, Sodium carboxymethylcellulose, Ca^{2+} and Al^{3+}, Matrix, Cross- linking

INTRODUCTION

Several approaches have been used to control the release of highly water-soluble drugs with short elimination half life and low therapeutic index as matrix tablets in recent years. The methods are based on incorporation of drug with water-soluble (1) as well as water- insoluble hydrophilic polymers (2) and mixture of water-soluble and water-insoluble non polymeric materials (3) into single and three layer matrices (4). Also mixture of hydrophilic polymers with the fatty excipients in single layer matrices was sometimes used for

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this purpose (5). The main advantages of sustaining the release of such drugs are reducing frequency of the daily dosage, decreasing the degree of drug plasma level fluctuations, reducing drug side effects and improving patient compliance. Propranolol hydrochloride, a beta blocker, is used in the management of several cardiovascular diseases including hypertension, angina pectoris, myocardial infarction, various cardiac arrhythmias and hypertrophic cardiomyopathy. Propranolol hydrochloride, PLH, with high water solubility and a relatively short biological half-life (3-6 hrs) is administered twice to four times daily depending on the kind of disease and patient conditions (6). For these reasons several attempts have been made to sustain and/or extend propranolol release via different delivery systems such as pellets (7), matrices prepared with various materials (8), osmotic systems (9), microspheres (10) and beads (11). In fact propranolol beads and spheroids are commercially available (11). Cross-linking of polyanionic polymers with inorganic cations Zn^{2+} (12), Ca^{2+}(13), and the organic cation chitosan (14) as well as mixture of inorganic and organic cations (14) have been used to prepare drug beads to control the drug release. The process of bead formation involved the cross-linkage in the aqueous media, separation and subsequent drying of the beads. One of the novel techniques for prolongation of drug release was the incorporation of drug with a polyanionic polymer and a polyvalent inorganic cation in the dry state into matrix tablet. The role of cations was in situ cross-linking of the anionic polymer chains in the matrix in the aqueous dissolution medium (15, 16). In the present work a novel approach was used to control the release of the highly water-soluble PLH as a model drug. The approach involved preparation of the drug matrix containing a polyanionic polymer i.e. sodium carboxymethylcellulose, Na CMC, together with calcium and aluminum chlorides as cross-linking agents. The influence of concentrations of the polyanionic polymer as well as Ca^{2+} and Al^{3+} on the drug release rate has been studied. Kinetic analysis of dissolution data was carried out using different models in order to elucidate the release mechanism. The biological half- life of PLH in human is relatively short (3-6 hrs), thus, its conventional dosage forms are administered 2-4 times daily (17). Usually the high frequency of daily dosage is related to patient compliance, greater fluctuation in drug plasma level and occurrence of side effects. For these reasons several attempts have been made to sustain PLH release (3, 4, 6-9). PLH is highly soluble in water and its solubility is higher than 150 mg/ml (9). Therefore, sustaining its release, necessitates the use of expensive ingredients and involvement of time consuming and complicated techniques. The objective of the present investigation was to formulate controlled release matrices of PLH containing sodium carboxymethylcellulose and to study the influence of Ca^{2+} and Al^{3+} on the drug release. Since ingredients and the technique i.e., direct compression which were employed were the same as those for ordinary tablets, results could be of beneficial and economical in comparison to other complicated techniques.

MATERIAL AND METHODS

Chemicals

PLH powder was from Daru Pakhsh, Tehran, Iran. Sodium carboxymethylcellulose (Tylopur C 1000 P2, viscosity of 1.8% solution at 20 ºC is 1800-3000 mPa s) was from Clariant, Muttenz, Switzerland. Aluminum chloride hexahydrate, calcium chloride dihydrate and magnesium stearate were purchased from Merck, Darmstadt, Germany.

Preparation of matrices

The required amounts of PLH, Na CMC, either aluminum or calcium chloride and magnesium stearate powders for preparation of 20 matrices were triturated using mortar and pestle for 30 minutes. The mixture was directly compressed under 29.4 MPa by means of a compressor (Riken, Hirosawa, Japan). The dwell time was 3 seconds. The diameter of the matrices was 8 mm and their thicknesses were 2-3 mm depending on the amounts of ingredients which were used. The matrices were kept in a desiccator until subsequent studies. Details of the formulations are shown in Table 1.

In vitro dissolution

The in vitro dissolution tests of PLH from the matrices were carried out using the USP 29 dissolution apparatus I (18), the rotating basket method, (Caleva, Dorset, UK) at the stirring rate of 100 rpm at 37± 0.5 ºC in 900 ml of distilled water. By using this volume of dissolution medium the sink condition was maintained because of the high solubility of PLH. The reason for the use of distillated water instead of conventional buffer solution e.g. phosphate buffer was to prevent any chemical interactions between phosphate anions and the inorganic cations which may affect the drug release.

Five ml samples were taken from the dissolution vessel at predetermined times of 15, 30, 60, 90,

Table 1. Formulation ingredients of sodium carboxymethylcellulose (Na CMC) matrices of propranolol hydrochloride (PLH) containing various milliequivalents (meq) of Al^{3+} and Ca^{2+}

Formulation	PLH (mg)	Na CMC (mg)	$AlCl_3$, $6H_2O$(mg)	$CaCl_2$, $2H_2O$(mg)	Mg Stearate (w/w%)	Matrix Weight(mg)	Al^{3+} (meq)	Ca^{2+} (meq)
F_1	80	80	-	-	2	163.2	-	-
F_2	80	120	-	-	2	204	-	-
F_3	80	80	2.5	-	2	165.8	0.03125	-
F_4	80	80	5.0	-	2	168.3	0.0625	-
F_5	80	80	10.1	-	2	170.5	0.125	-
F_6	80	80	15.1	-	2	178.6	0.1875	-
F_7	80	80	20.1	-	2	183.7	0.250	-
F_8	80	80	30.2	-	2	194.0	0.375	-
F_9	80	80	40.2	-	2	204.2	0.500	-
F_{10}	80	80	-	2.3	2	165.6	-	0.03125
F_{11}	80	80	-	4.6	2	167.9	-	0.0625
F_{12}	80	80	-	9.2	2	172.6	-	0.125
F_{13}	80	80	-	18.4	2	182.0	-	0.250
F_{14}	80	80	-	27.6	2	191.4	-	0.375

120, 180, 240, 300, 360, 420 and 480 min, filtered through 0.45 µm membrane filter. The drug concentration in the samples was determined spectrophotometrically (Shimadzu UV-160, Kyoto, Japan) at 289.6 nm using a Beers plot. The correction was made on the concentration considering the previous samples. The dissolution profile was prepared by plotting fractional drug which was dissolved against time.

Complexation study

One end of a 25 cm length of dialysis tubing (Scientific Instrument Center, Ltd., London, UK) having inflated diameter of 2.14 cm was tied off and 20 ml of a solution containing 80 mg of PLH and 120 mg Na CMC (similar to the composition of the matrix F2 which had maximum amount of the polymer) was poured into the dialysis sac. The sac was suspended vertically in the beaker containing 880 ml distillated water (the dissolution medium). A control set up with drug solution in the absence of the polymer inside the sac was also assembled. The test was carried out 3 times. After establishment of equilibrium (48 hrs) the absorbances of the solutions outside sac of test and control were measured spectrophotometrically.

Comparison of release profiles

Two classical model-independent metrics i.e. dissolution efficiency (19) denoted here as release efficiency (RE) as well as mean dissolution time(20) designated as mean release time (MRT) and a suggested simple metric named as mean release rate (MRR) have been used to compare the release profiles. The metrics were calculated by the equations 1, 2 and 3:

$$RE = 100 \times \frac{\int_0^{480'} f.dt}{1 \times 480'} \quad (1)$$

$$MRT = \frac{\sum_{i=1}^{n} \bar{t}\Delta f_i}{\sum_{i=1}^{n} \Delta f_i} \quad (2)$$

$$MRR = 100 \times \frac{\sum_{i=1}^{n} (\Delta f / \Delta t)_i}{n} \quad (3)$$

The integral $\int_0^{480'} f.dt$ is the area under fraction of drug released *versus* time curve between time zero and 480 min. $\bar{t}$ is the arithmetic mean of sampling times of t_i and t_{i-1}, Δf_i is the difference of fractions of drug released between sampling times, $(\Delta f / \Delta t)_i$ is the release rate over the mentioned times and n is the number of release data for each formulation. It is obvious that RE and MRR are directly proportional to the drug release. The higher the metrics the higher is the release rate. In contrary, MRT is inversely related to the release rate and the lower its value higher is the release rate.

Kinetic analysis of data

The available kinetic models for drug release from matrices were Higuchi, Peppas and Weibull (20) models to elucidate probable release mechanism.

Corresponding working formulae are equations 4, 5 and 6 respectively:

$$f = k_H t^{0.5} \quad (4)$$

$$\ln f = \ln k_P + \alpha \ln t \quad (5)$$

$$\ln[-\ln(1-f)] = b \ln k_W + b \ln t \quad (6)$$

K_H is Higuchi's release rate constant expressed as fraction/$\sqrt{\min}$ calculated from slope of line obtained from plotting f versus $t^{0.5}$, $k_P$is release rate constant of Peppas (fraction/$\min^{\alpha}$) obtained from ordinate intercept of the line *lnf* against *lnt*, α is slope of the line, k_w is Weibull release rate constant (1/min) and b is a shape factor of the Weibull plot and is equal to the slope of Weibull line. The models of Higuchi and Weibull are applicable for $0< f \leq 1$ and $0< f <1$, respectively. Whereas the Peppas model is applicable for $0< f \leq 0.6$. In order to evaluate the fitness of data to the models, the squared correlation coefficient (R^2) and percent absolute deviation (PD) of predicted f value ($f_{i,pred}$) relative to observed f ($f_{i,obs}$) were employed. The latter was calculated by the following equation:

$$PD = \frac{100}{n} \sum_{i=1}^{n} \left(\left| f_{i,pred} - f_{i,obs} \right| \Big/ f_{i,obs} \right) \quad (7)$$

The higher R^2 and lower PD values were indicative of accuracy of a given model.

RESULTS AND DISCUSSION

Mean fractions of PLH released versus time for various formulations are shown in Figure 1. As it is shown, increase in the concentration of Na CMC slows down the drug release appreciably due to more concentrated polymer gel in the matrix body which in turn reduces the dissolution and diffusion and as a result reduces fractional release from 0.74 to 0.54 within 8 hrs.

Al^{3+} and Ca^{2+} affect the drug release from the matrices in different ways. Al^{3+} at the concentration of 0-0.125 meq decreases the release rate (Figure 1a). This phenomenon may be due to penetration of water molecules from dissolution medium into the matrix, dissolving Al^{3+} as well as anionic polymer, cross- linking of the latter ions and subsequent rigid gel formation in the matrix body. The gel presumably entraps drug particle and subsequently delays its dissolution and diffusion from the matrix. However, Al^{3+} in concentration higher than 0.125 meq progressively enhances the release in the way that in concentration higher than 0.250 meq, it augments release considerably (Figure 1a). Apparently Al^{3+} higher than 0.125 meq exeeds its amount required for cross- linkage with polymer and some remains free in the matrix body. Since Al^{3+} is highly water soluble therefore its free uncross- linked form dissolves in the matrix causing porosities and hence disintegrates the matrix. This may account for the rapid drug release at the higher concentration.

Ca^{2+} unlike Al^{3+} only increases the drug release (Figure 1b). Ca^{2+} is a bivalent whereas Al^{3+} is a trivalent cation which means the former reacts with two negative sites and the latter reacts with three negative sites of the polymer to form two and three dimensional structures, respectively (21). Furthermore, Ca^{2+} has less positive charge per unit surface of the cation than Al^{3+}. As a result cross- linkage by Ca^{2+} must be much weaker than that of Al^{3+}. Consequently, Ca^{2+} because of high solubility, increases the drug release.

In addition to investigations cited in the introduction of this paper (12-14), several other studies for sustaining or controling drug release via cross-linkage of polyanionic macromolecules with the inorganic cations Ca^{2+} and Al^{3+} to produce the drug beads have been reported. The details of formulation of beads are given in a review article (22). In these works the beads of drugs were prepared by cross-linkage of the polyanionic polymers with the cations in the aqueous media followed by separation and drying of the beads. In this study the cross-linkage was formed *in situ* in the dissolution medium in the drug matrix prepared from dry ingredients. This is a novel technique which is reported for the first time (15).

Equilibrium dialysis study revealed that a soluble complex was formed between the cationic drug and the anionc polymer in solution. The equilibrium drug concentration outside the dialysis sac in the test set up was 56% that of control set up. It should be mentioned that when the drug solution was mixed with the polymer solution no turbidity or precipitation was formed indicating a water soluble complex. It is obvious that complexation with the macromolecule due to its bulkiness could also reduces the diffusion rate of drug from the gelled structure of the matrix and potentiate the influence of *in-situ* cross-linkage effect on decreasing the drug release.

Model independent metrics for drug release comparison

Figure 2 shows the influence of various amounts of Ca^{2+} and Al^{3+} on MRT, RE and MRR of the matrices. It is clear from the figure that MRT does not confirm the experimental realities shown in

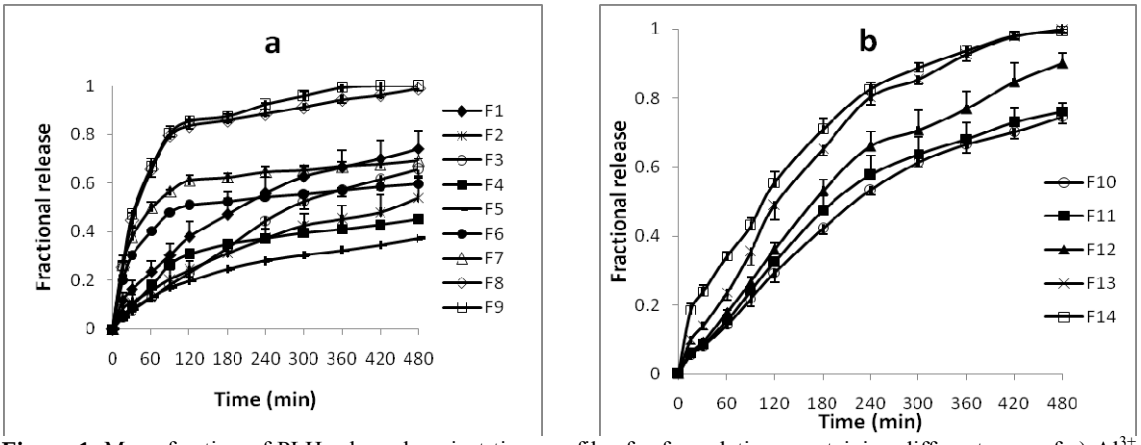
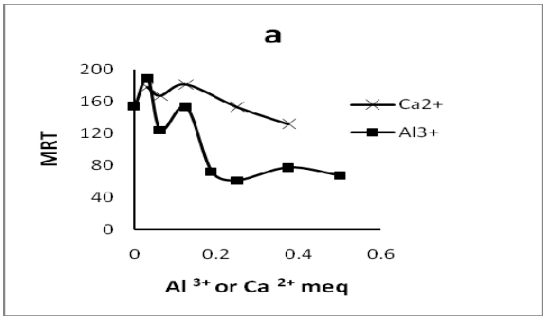
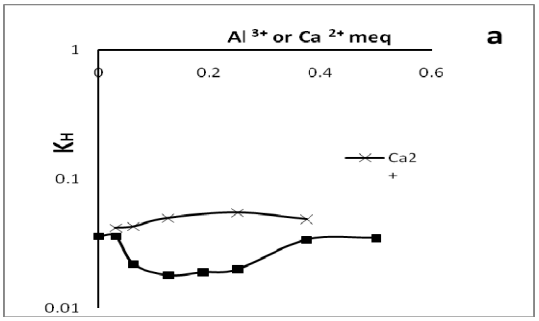
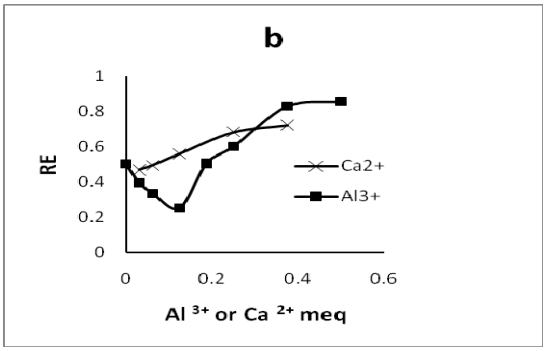
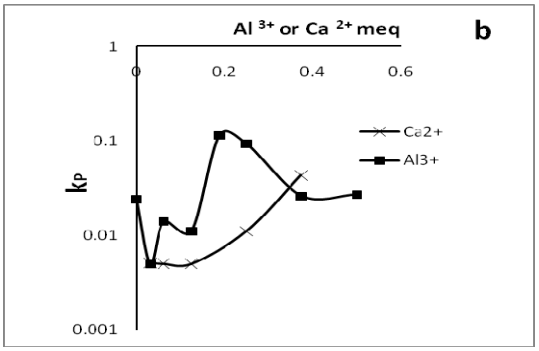


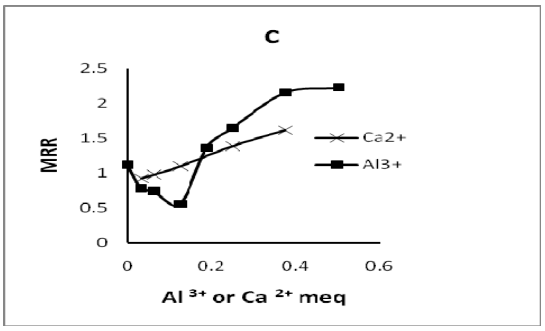
Figure 1. Mean fraction of PLH released against time profiles for formulations containing different meq of a) Al^{3+} and b) Ca^{2+}.











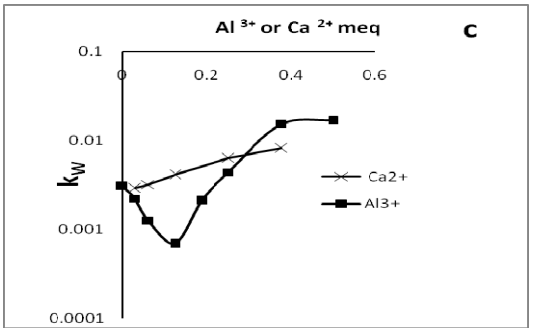


Figure 2. Effect of different meqs of Ca^{2+} and Al^{3+} on: a) MRT, b) RE and c) MRR of matrices.

Figure 3. a) Higuchi, b) Peppas and c) Weibull rate constants versus Ca^{2+} and Al^{3+} contents of various formulations.

Table 2. Parameters, squared correlation coefficients (R^2) and percent deviations (PD) of different models applied to formulations.

Formulation \ Model	Higuchi	Peppas	Weibull
F_1	k_H= 0.036, I* = - 0.028 R^2 = 0.995, PD= 3.60	k_p† = 0.024, a= 0.570, I=-3.727 R^2 = 0.996, PD = 2.94	I= -4.132, b= 0.713, k_w‡ = 0.00305 R^2 = 0.994, PD=3.745
F_2	k_H= 0.029 , I=-0.06 R^2 = 0.986, PD=7.949	k_p= 0.015, a= 0.583, I=-4.170 R^2 = 0.994, PD=4.068	I=-4.487, b=0.689, k_w=0.00149 R^2 = 0.982, PD=6.607
F_3	k_H= 0.036, I=-0.135 R^2= 0.988, PD=14.99	k_p= 0.005, a=0.804, I=-5.289 R^2 =0.997, PD=4.393	I=-5.702, b=0.933, k_w=0.00221 R^2 = 0.993, PD=5.971
F_4	k_H= 0.022, I=-0.016 R^2 = 0.928, PD=18.99	k_p=0.014, a=0.598, I=-4.303 R^2 = 0.933, PD=15.241	I=-4.506, b=0.676, k_w=0.00127 R^2 =0.948, PD=12.665
F_5	k_H=0.018, I=-0.008 R^2 =0.991, PD=6.67	k_p=0.011, a=0.580, I=-4.492 R^2 =0.985, PD=7.048	I= -4.649, b=0.639, k_w=0.00069 R^2 =0.991, PD=5.370
F_6	k_H=0.019, I=0.232 R^2 =0.830, PD=11.26	k_p=0.114, a=0.283, I=-2.167 R^2 =0.898, PD=8.484	I=-2.279, b=0.37, k_w=0.0021 R^2 =0.924, PD=6.82
F_7	k_H=0.020, I=0.308 R^2 =0.803, PD=10.68	k_p= 0.093, a= 0.401, I=-2.375 R^2 =0.987, PD=3.156	I=-1.945, b=0.358, k_w=0.00439 R^2 =0.924, PD=6.21
F_8	k_H=0.034, I=0.328 R^2 =0.799, PD=15.82	k_p=0.026, a=0.838, I=-3.656 R^2 =1, PD=0.0004	I=-2.825, b=0.674, k_w=0.01512 R^2 =0.959, PD=5.685
F_9	k_H=0.035, I=0.337 R^2 =0.811, PD=15.035	k_p= 0.027, a=0.834, I=-3.596 R^2 = 1, PD=0.0004	I=-3.035, b=0.745, k_w=0.017 R^2 =0.973, PD=5.146
F_{10}	k_H=0.042, I=-0.145 R^2 =0.989, PD=12.74	k_p=0.0051, a=0.841, I=-5.276 R^2 =0.993, PD=5.840	I=-5.687, b=0.975, k_w= 0.0029 R^2 = 0.992, PD=6.42
F_{11}	k_H=0.043, I=-0.135 R^2 = 0.986, PD=12.20	k_p=0.005, a=0.864, I=-5.292 R^2 =0.991, PD=6.32	I=-5.62, b=0.978, k_w= 0.0032 R^2 =0.992, PD=6.40
F_{12}	k_H=0.050, I=-0.170 R^2 =0.992, PD=11.82	k_p= 0.005, a=0.884, I=-5.278 R^2 =0.991, PD=6.17	I=-5.85, b= 1.07, k_w=0.0041 R^2 = 0.992, PD=6.24
F_{13}	k_H=0.055, I=-0.136 R^2 =0.981, PD=9.84	k_p=0.011, a=0.768, I=-4.492 R^2 =0.981, PD=7.40	I=-4.49, b=0.768, k_w=0.0063 R^2 =0.981, PD=7.40
F_{14}	k_H=0.049, I=-0.0048 R^2= 0.979, PD=5.76	k_p=0.043, a=0.517, I=-3.14 R^2 = 0.982, PD=5.08	I=-4.51, b=0.937, k_w= 0.0082 R^2 =0.957, PD=9.11

* I is the ordinate intercept of Higuchi and linear forms of Peppas as well as Weibull models.

† $k_p = e^I$ in which e is base of natural logarithm.

‡ $k_w = e^{(I/b)}$ where $1/k_w$ is time required for 0.632 fractional release (63.2% release). The time is usually denoted as the dissolution and /or release time for release process obeying Weibull distribution.

Figure 1 in that it does not mirror the effect of cations on the drug release. Therefore, MRT and/ or MDT does not seem to be a reliable metric for comparison of the drug release. Since, results of this metric do not differentiate properly the effect of formulation ingredients on the release. Whereas RE as well as MRR do indicate the observed impact of the cations on the release. For example Al^{3+} at 0.125 and 0.5 meq produces the slowest and quickest release rates, respectively. This reality is reflected on the RE and MRR plots (Figure 2b and 2c) but not on the MRT plot

(Figure 2a). It is worth to mention that MDT is a key parameter for establishment of the level B *in vitro-in vivo* correlation recommended in the USP XXIX. In the light of the present finding on MDT it is suggested that the use of this metric is reconsidered and replaced by an appropriate metric e.g. RE or MRR.

Model dependent kinetic results

The results of kinetic analyses are gathered in Table 2. The release data does not obey the Higuchi model due to higher PD associated with this model. Because as it was expected the model is strictly applicable to non erodible, non reactive and non-disintegrating matrices with sole diffusion release

mechanism whereas the drug release from the matrices here depends on water penetration into the matrix, polymer hydration and swelling, cross-linkage phenomenon, erosion, disintegration, diffusion and dissolution. Peppas and Weibull models seem to be better models since the majority of the corresponding PDs are single figures and the squared correlation coefficients (R^2) are high. However, only the Weibull rate constant correlate with the amount of the cations correctly (Figure 3c) which is parallel the same results as those of RE and MRR. However; Higuchi and Peppas models do not conform to the experimental realities (Figure 3a and 3b).

CONCLUSION

The inorganic cations Ca^{2+} and Al^{3+} when incorporated at various amounts into Na CMC matrices affect PLH release differently.Thus by adjustment of Al^{3+} amount the PLH release rate can be controlled at any desired level. One of the most important classical model independent metrics i.e., MRT and/or MDT failed to differentiate between the formulations although other metrics i.e. RE and a suggested MRR correlated well with the experimental release rate. Kinetic analyses revealed complicated release mechanism and the best model to describe correctly the effect of inorganic cations on the release was the Weibull distribution.

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