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Agitation Sequence and Ionic Strength on *In-Vitro* Drug Release from Hypromellose –The Influence of Compaction Force

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Abstract – The evaluations of the systematic effects of agitation and ionic strength and its impact on tablet compression force on the drug release from a gel forming matrix were the objectives of this study. To achieve this, two model drugs namely, theophylline and diltiazem HCl were formulated with hydroxypropyl methyl cellulose into matrix tablets and the drug release in a range of pHs 1.2-7.5 was evaluated using the automated USP type III Bio-Dis Varian. The effects of agitation were investigated at 10, 20 and in an ascending and descending order in the vials. Agitation had a profound effect on the drug release from the K100LV tablet matrices. Ionic strength was investigated using NaCl as the ionic strength regulator. A range of 0-0.4 M ionic strengths were studied. It was noticed that an increase in the compression of the tablet matrices for the K100LV theophylline and diltiazem HCl tablet matrices resulted in a significant difference in their drug release profiles both in the agitation sequence and with the influence of ionic concentration strength. The K100M tablet matrices for the theophylline and diltiazem HCl on the other hand were generally unaffected. This investigation also highlights the importance of controlling drug release in the desired dissolution medium as agitation could significantly influence the drug release resulting in a possible toxicity or making drug not available at the required site.

Keywords – HPMC, theophylline, diltiazem hydrochloride, ionic strength, agitation, compression, USP III Bio-Dis

1. Introduction

Hydroxypropylmethylcellulose (HPMC) or hypromellose are water-soluble polymers and are commonly known for their binding, water retention, thickening and film forming abilities. A gel layer results upon contact of the hydrophilic polymer on or near the surface due to hydration. This hydration and gel layer thus controls water ingress into the matrix and as such controls or has an influence on the mechanism by which a drug is released. Erosion is the dominant release mechanism as far as poorly soluble drugs are concerned. The other mechanistic approach by which drugs are released is through the process of diffusion. This is the dominant release mechanism as far as soluble drugs are concerned [1]-[5]. HPMC is also the most widely used polymers regarding extended release (ER) matrix formulations and comes in various grades and chemistries. For the purposes of this study, METHOCEL Premium K (hypromellose 2208, USP) polymers were used. It is known that a polymers viscosity is one of the better known factors that affect drug release from hydrophilic matrices. This therefore means an increase in the viscosity level of the polymer will result in a decreased diffusion rate. This in turn affects the water uptake and drug transport with a decrease in the release rate ensuing. As such two polymers with different viscosities (K100LV and K100M) are investigated. Dissolution testing is a quality control procedure employed in pharmaceutical product development to assist in the selection of a candidate formulation. In research the dissolution testing method helps to detect the influence of critical manufacturing variables such as the effect of binders, mixing, granulation, coating, excipients, and comparative studies of different formulations, *in vitro-in vivo* correlations and possibly as an *in vivo* surrogate under strictly defined conditions. It is therefore apparent that sensitive and reproducible dissolution data derived from physicochemical and hydrodynamical defined conditions are necessary in order to compare various *in vitro* dissolution data and be able to use such results as asurrogate for possible *in vivo* bioavailability, bioequivalence testing, and *in vitro-in vivo* correlations (IVIVC) [6] - [19]. Several studies have investigated the flow pattern of the dissolution Apparatus USP I (basket) and USP II (paddle) at various speeds by using computational fluid dynamics [20]. However, the hydrodynamics of these systems are far from that calculated for the human stomach [21]. In fact, the drug dissolution from a solid formulation is greatly influenced by fluid flow and mechanical forces, and this must be taken into account when designing an *in vitro* method which aims to predict the *in vivo* behaviour of a formulation. Various researchers have used Apparatus III, different dips per minute (dpm) with physiological and biorelevant dissolution media in their work to evaluate fasted and fed states to mimic the *in vivo* environment [22] - [27]. Recently, Asare-Addo and coworkers have been evaluating the performance of hypromellose under agitation and ionic strength conditions using the USP III Bio-Dis machine and found that the higher viscosity polymers withstand agitation and ionic strength effects and further compared agitation effect as experienced

on the machine to possible food effects [26],[27]. This present work explores the impact of tablet compaction force on the influence of agitation sequence and pH of the media on theophylline and diltiazem hydrochloride HPMC matrices using a USP III Apparatus. This study particularly focuses on these two drugs with different solubilities to see if compaction force.

2. Material and methods

2.1. Materials

HPMC grades METHOCEL™, K100LV and K100M supplied by Colorcon UK were used as the hydrophilic matrix former. Anhydrous theophylline (Sigma) and Diltiazem HCl (Sigma) was used as the model drug. Dissolution buffers were prepared according to the United States Pharmacopoeia 26 (2003) using the following materials: Potassium chloride (Acros Organics) and laboratory reagent grade hydrochloric acid (Fisher Scientific) were used in the preparation of pH 1.2 and pH 2.2 dissolution media. Potassium phosphate monobasic-white crystals (Fisher BioReagents) and sodium hydroxide (Fisher Scientific) were used in the preparations of pH 5.8, 6.8, 7.2 and 7.5 media.

2.2. Tablet preparation

Round cylindrical tablets of diameter 9.56 mm with a target weight of 250 mg were prepared by mixing either theophylline or diltiazem hydrochloride with HPMC in the 4:1 ratio respectively for ten minutes in a Turbula blender (Type 2 C, Switzerland). There was thus 200 mg of the active drug present in the 250 mg tablets prepared. The tablets however were compressed at different compactions forces this time to evaluate its effect on drug release. The compaction forces used for both the theophylline and diltiazem HCl matrices were 1000 psi (3.5 kN), 1500 psi (5.5 kN), 2000 psi (7.65 kN) and 2500 psi (9.87 kN) using the single punch tableting machine from Globe Pharma (Model MTCM-1). Prior to tablet compression, the die wall was lubricated each time with a 1 % w/v suspension of magnesium stearate in acetone.

2.2.1. Tablet breaking force and porosity determination

The Dr. SCHLEUNIGER tablet tester 8M (Serial No. 02209) was used in the determination of the tablets breaking force. Ten readings were taken in order to determine the mean and standard deviation values. Tablet dimensions were also obtained using the electronic digital calliper from Fisher Scientific to obtain the diameter and width measurements and was used in calculating tablet volume. The Ultrapycnometer 100 (Quantachrome Instruments) was used in the determination of the true density of powder mixtures used for the tableting. Tablet porosity was then calculated using (1).

$$\text{Tablet Porosity} = \left[1 - \left[\frac{\left(\frac{\text{tablet weight}}{\text{tablet volume}}\right)}{\text{True density of powder}}\right]\right] \times 100 \quad (1)$$

2.3. Dissolution Test (Effect of agitation and ionic strength)

The automated USP type III Bio-Dis Varian (DL0811C326) was used to carry out the dissolution tests. Drug-release behaviour of the above formulations was investigated in six dissolution media to determine sensitivity of different grades of HPMC to medium pH and ionic strength. The dissolution testing was conducted for 310 minutes for all formulations. Sodium chloride was used to regulate the ionic concentration strength from 0 to 0.4 M in buffers with pH of 1.2, 2.2, 5.8, 6.8, 7.2 and 7.5. As the tablet matrix starts at pH 1.2, it keeps dipping there for a period of 60 minutes before the same matrix transfers to pH 2.2 and dips for another 60 minutes, it then transfers to pH 5.8 and dips for 10 minutes and so forth. The period of time the tablet matrix stays in a particular vial before transferring is what the author has referred to as the transit time. The vessels contained 250 ml of the appropriate media and the mesh on the top and bottom screens of the cylinder (the tablet holder) was fixed at 864 microns. The temperatures were kept constant at 37 ^{o}C. The absorbance of the released theophylline and diltiazem hydrochloride released was measured at 271 nm and 240 nm respectively using a UV/Visible spectrophotometer (Varian, Cary 50). The experiments were carried out in triplicate. For the influence of agitation sequence, agitation was studied at 10 dpm, 20 dpm, the ascending order of agitation at 5-30 dpm and the descending order of agitation at 30-5 dpm. Ionic strength was studied at 20 dpm only [28], [29].

2.4. Kinetics of drug release

Several mathematical models have been used to try and explain the mechanism and kinetics of drug release from hydrophilic matrices [30]. The mathematical model which has been adopted for describing the release kinetics of drugs from the HPMC tablet matrices in this experimentation is the Power Law. The Power law as in (2) was firstly introduced by Peppas and his fellow workers [31], [32]. It is a simple yet more comprehensive way of describing drug release.

$$\frac{M_t}{M_\infty} = kt^n \quad (2)$$

Where; Mt = cumulative absolute drug amount at time t, M∞ = cumulative absolute drug amount at infinite time, k = constant (incorporates the structure and geometrical characteristics of the device) n = release exponent which determines the mechanism of drug release. For cylinders, which were the shape of the tablet matrices made in this experimentation, the n values are slightly different as derived by [33], [34]. *n* values below 0.45 are an indication of Fickian diffusion and n values above 0.89 depict Case II transport. Anomalous transport is when the n values are between 0.45 and 0.89 [35].

2.5. Similarity factor

To determine the similarity between the obtained drug release profiles f_2 factor [36], [37] was calculated according to (3).

$$f_2 = 50 \log\left\{\left[\left[1 + \frac{1}{n}\sum_{t=1}^{n} w_t (R_t - T_t)^2\right]^{-0.5} \times 100\right\}\right. \quad (3)$$

This being a mathematical treatment of the dissolution data where; n = number of pull points for tested samples, wt = optional weight factor, Rt = reference assay at time point t and Tt = test assay at time point t.
Similarity factor was calculated using the drug release profile of the compacts compressed at 1500 psi as the reference. An f_2 value ranging from 50-100 suggests a similarity between two profiles. The closer the f_2 value is to 100, the more similar or identical the release profiles are. Also dissimilarity occurs with a decrease of the f_2 value [38], [39].

3. Results and discussion

Theophylline K100LV and K100M tablet matrices had similar porosities of 40 %, 36 %, 35 % and 34 % at the increasing compaction forces of 1000 psi (3.5 kN), 1500 psi (5.55 kN), 2000 psi (7.65 kN) and 2500 psi (9.87 kN) respectively. Diltiazem HCl K100LV and K100M compacts also had tablet porosities of 38 %, 35 %, 32 % and 33 % at the increasing compaction forces of 1000 psi (3.5 kN), 1500 psi (5.5 kN), 2000 psi (7.65 kN) and 2500 psi (9.87 kN) respectively (Table 1 and 2). This showed that there was a decrease in the porosity levels of the compact made as compaction/compression forces of the tablets were increased. The decreasing porosities of the tablet matrices as the compression force was increased is also evident in the general decreasing tablet thickness values as expressed in the tables as compression was increased. The increase in tablet compression force also brought about an increase in the tablets breaking forces for both the theophylline and diltiazem HCl tablet matrices (Table 1 and 2). This was in agreement with work done by Dabbagh and coworkers (1996) who went on to further suggest the decrease that occurred in porosity values as compaction pressures increase can affect drug release and mechanism [40].

3.1. The effect of compaction force on agitation sequence

Figures 1-4 shows the influence of compaction force on drug release from the theophylline and diltiazem tablets made using the different viscosity HPMC (K100LV and K100M) in the drug: polymer ratio of 4:1 at the different agitations tested. The K100LV tablet matrices for both drugs released quicker than the K100M tablets matrices. Drug release for both HPMC polymers incorporated with the model drugs were generally in the order of 1000 psi > 1500 psi > 2000 psi > 2500 psi. This meant a decrease in drug release occurred as the compression force for the tablet making process was increased. Just a little increase in compression force from 1000 psi to 1500 psi was able to suppress the burst effect from the diltiazem HCl K100LV matrices (Figure 3). The ability for the increase in compression force to do this was very evident at high dip-rates. At 10 dpm, compacts compressed at 1000 psi had around 50 % of its drug released after the 10 min time point. The drug released at the 10 min time point reduced significantly to 15 % when compression was done at 1500 psi. At 20 dpm, at 1000 psi, 96 % of drug was released after the 10 min time point. The same amount of drug was released when agitation was in the descending order of 30 -5 dpm at the same psi. Again an increase in compression force by 500 psi to 1500 psi reduced the burst effect substantially to 27 % and 42 % respectively. A further increase in the compression force however did not seem to have any significant effect on the drug release. The diltiazem HCl K100M tablet matrices compressed at 1000 psi and subjected to an aggressive dip-rate in the form of the descending order of agitation showed burst release to occur. After 10 minutes, there was about 85 % of drug released. Again an increase in compression force to 1500 psi showed a significant decrease in drug release to 9 % at the 10 min time point. The similarity factor analysis was carried out using drug release at 1500 psi (5.5 kN) to determine if release rates at the different compression forces were similar. Or in other words, the similarity factor was used to determine if the tablet compression force had a significant effect on drug release. Due to the fast drug release for the theophylline tablet matrices at the increased agitations of 20 dpm and the descending order of agitation at 30-5 dpm, it was not possible to obtain f2 values for these release profiles. Drug release at 20 dpm showed dissimilarity occurring for the K100M tablet matrices (f2=39-44). All the other agitations tested against the theophylline drug at the various compression forces showed similarity in their drug release profiles (f2=53-87) (Table 3). This suggested that compression force did not have a significant effect on theophylline release from these matrices thus depicting the resilience of the polymers to form strong gels controlling drug release even at such low compression forces. The freely soluble nature of diltiazem HCl meant it was not possible to obtain f2 values for their K100LVdrug release profiles. With regards to their K100M drug release profiles, with the exception of when the tablet matrix was compressed at 1000 psi and subjected to agitation in the descending order of 30-5 dpm, all drug release profiles from the various compression forces showed their robustness to agitation by producing similarity values (f2=53-94) (Table 4). This shows how the mechanical properties of high molecular weight HPMC are important in the manufacture of robust hydrophilic matrices by compression [41].

The kinetics of drug release showed that there was an increase in the n value as compression force was increased for the theophylline tablet matrices. For example, at the ascending order of agitation at 5-30 dpm, the K100LV theophylline tablet matrices n values were 0.61, 0.68, 0.69, and 0.91. This indicates that an increase in compression force can affect the release mechanism. With the exception of where Fickian diffusion was occurring for K100LV tablet matrices compressed at 1000 psi and 1500 psi and undergoing agitation at 20 dpm and the descending order of agitation respectively, with respective n values of 0.38 and 0.44, all the formulated theophylline matrices (K100LV and K100M) compacted at the different pressures were dominated by anomalous transport. It was also observed when comparing the ascending and descending order of agitation that there was more of a drive towards Case-II transport when agitation was in the ascending order for both K100LV and K100M tablet matrices. This is evident in the values of n obtained (Table 5). The diltiazem HCl displayed similar trends to the theophylline matrices. Fast drug release from its K100LV polymer at the high agitation of 20 dpm and the descending order of agitation at 30-5 dpm for compacts compressed at the low pressure of 1000 psi meant that it was not possible to obtain n values for the drug release profiles here. An increase in compression force to 1500 psi, 2000 psi and 2500 psi made it possible for n values to be obtained(Table6).

Table 1: Physical characterization of theophylline compacts used in the study (*n=10*)

	Theophylline formulation							
	1000 psi		1500 psi		2000 psi		2500 psi	
Parameter	**K100LV**	**K100M**	**K100LV**	**K100M**	**K100LV**	**K100M**	**K100LV**	**K100M**
Tablet weight (mg)	252.24 ± 0.58	252.02 ± 0.75	250.47 ± 0.84	251.03 ± 0.88	251.17 ± 0.90	252.45 ± 1.01	250.74 ± 0.96	252.12 ± 1.54
Tablet thickness (mm)	3.93 ± 0.02	3.90 ± 0.01	3.73 ± 0.03	3.73 ± 0.03	3.63 ± 0.02	3.63 ± 0.01	3.58 + 0.02	3.58 ± 0.01
Tablet volume (cm^3)	0.282	0.281	0.267	0.270	0.261	0.260	0.256	0.256
Tablet breaking force (kp)	37 ± 0.32	36 ± 0.29	62 ± 0.45	63 ± 0.53	74 ± 0.63	81 ± 0.73	97 ± 0.13	97 ± 0.58
Tablet porosity (%)	40 ± 0.83	39 ± 0.75	37 ± 0.41	37 ± 0.45	35 ± 0.85	34 ± 0.27	34 ± 0.94	33 ± 0.11

Table 2: Physical *c*haracterization of diltiazem HCl compacts used in the study (*n=10*)

	Diltiazem HCl formulation							
	1000 psi		1500 psi		2000 psi		2500 psi	
Parameter	**K100LV**	**K100M**	**K100LV**	**K100M**	**K100LV**	**K100M**	**K100LV**	**K100M**
Tablet weight (mg)	254.10 ± 0.57	253.01 ± 0.79	250.39 ± 0.27	250.26 ± 0.45	252.32 + 0.55	251.63 + 0.34	252.99 ± 1.28	252.25 ± 0.33
Tablet thickness (mm)	4.20 ± 0.02	4.17 ± 0.08	3.93 ± 0.00	3.94 ± 0.00	3.71 ± 0.17	3.86 ± 0.02	3.84 ± 0.01	3.86 ± 0.02
Tablet volume (cm^3)	0.303	0.300	0.282	0.283	0.267	0.278	0.276	0.278
Tablet breaking force (kp)	37 ± 0.65	43 ± 0.73	47 ± 0.48	50 ± 0.38	84 ± 0.23	60 ± 0.58	100 ± 0.53	98 ± 0.79
Tablet porosity (%)	39 ± 0.32	37 ± 0.19	35 ± 0.25	34 ± 0.87	31 ± 0.56	33 ± 0.75	33 ± 0.31	33 ± 0.71

Table 3: f_2 similarity factor for the drug release profiles from theophylline HPMC matrices at the different compression forces subjected to different agitation rates using drug release from tablets compressed at 1500 psi as a reference standard

Compression force (psi)	10 dpm		20 dpm		5-30 dpm		30-5 dpm	
	K100LV	K100M	K100LV	K100M	K100LV	K100M	K100LV	K100M
1000	71	65	-	44	60	77	-	53
2000	71	57	-	43	87	66	-	63
2500	54	60	-	39	52	84	-	84

Table 4: $f_2$similarity factor for the drug release profiles from diltiazem HCl HPMC matrices at the different compression forces subjected to different agitation rates using drug release from tablets compressed at 1500 psi as a reference standard

Compression force (psi)	10 dpm		20 dpm		5-30 dpm		30-5 dpm	
	K100LV	K100M	K100LV	K100M	K100LV	K100M	K100LV	K100M
1000	-	94	-	53	-	81	-	-
2000	-	80	-	91	-	85	-	62
2500	-	79	-	59	-	71	-	94

Table 5: The influence of agitation rate on mechanism of theophylline release from compacts at the different compressions

Tablet Formulation	Compression (psi)	Agitation (dpm)	*RSQ* (r^2)	*n*
K100LV	1000	10	0.9934	0.5958
		20	0.9935	0.3818
		5-30	0.9956	0.6059
		30-5	0.9916	0.5341
K100LV	1500	10	0.9914	0.5471
		20	0.9932	0.4721
		5-30	0.9953	0.6771
		30-5	0.9902	0.4410
K100LV	2000	10	0.9935	0.6380
		20	0.9896	0.6340
		5-30	0.9932	0.6893
		30-5	0.9874	0.4809
K100LV	2500	10	0.9921	0.7761
		20	0.9900	0.6138
		5-30	0.9873	0.9062
		30-5	0.9905	0.5252
K100M	1000	10	0.9961	0.5524
		20	0.9920	0.4780
		5-30	0.9956	0.6059
		30-5	0.9916	0.5341
K100M	1500	10	0.9940	0.5826
		20	0.9916	0.5264
		5-30	0.9965	0.6616
		30-5	0.9854	0.5116
K100M	2000	10	0.9967	0.5737
		20	0.9630	0.6377
		5-30	0.9903	0.6599
		305	0.9870	0.5592
K100M	2500	10	0.9963	0.5947
		20	0.9703	0.6606
		5-30	0.9901	0.6524
		30-5	0.9955	0.4793

Table 6: The influence of agitation rate on mechanism of ofdiltiazem HCl release from compacts at the different compressions

Tablet Formuation	Compression (psi)	Agitation (dpm)	*RSQ (r^2)*	*n*
K100LV	1000	10	0.9052	0.3794
		20	-	-
		530	0.9736	0.9051
		305	-	-
K100LV	1500	10	0.9840	0.8662
		20	0.8561	0.4531
		530	0.9914	0.9409
		305	0.6827	0.2459
K100LV	2000	10	0.9832	0.8884
		20	0.9591	0.7376
		530	0.9570	0.9789
		305	0.8311	0.4080
K100LV	2500	10	0.9858	0.8843
		20	0.9583	0.7012
		530	0.9890	0.8714
		305	0.7742	0.3217
K100M	1000	10	0.9898	0.6983
		20	0.9910	0.6786
		530	0.9937	0.7880
		305	-	-
K100M	1500	10	0.9915	0.6662
		20	0.9906	0.6324
		530	0.9951	0.7023
		305	0.9877	0.6077
K100M	2000	10	0.9964	0.6386
		20	0.9958	0.6493
		530	0.9778	0.7897
		305	0.9941	0.6101
K100M	2500	10	0.9966	0.6508
		20	0.9958	0.5993
		530	0.9981	0.6694
		305	0.9894	0.5955

Table 7: $f_2$similarity factor for the drug release profiles from theophylline HPMC matrices at the different compression forces subjected to different ionic concentration strengths using drug release from tablets compressed at 1500 psi as a reference standard

Compression force (psi)	Water media		pH media		Ionic strength 0.2		Ionic strength 0.4	
	K100LV	K100M	K100LV	K100M	K100LV	K100M	K100LV	K100M
1000	-	77.1	-	43.6	-	54.7	-	75
2000	-	42.3	-	43.2	-	49.7	-	52.7
2500	-	34	-	39.4	-	36.7	-	39.8

Table 8: $f_2$similarity factor for the drug release profiles from diltiazem HCl HPMC matrices at the different compression forces subjected to different ionic concentration strengths using drug release from tablets compressed at 1500 psi as a reference standard

Compression force (psi)	Water media		pH media		Ionic strength 0.2		Ionic strength 0.4	
	K100LV	K100M	K100LV	K100M	K100LV	K100M	K100LV	K100M
1000 psi	-	86	-	50	-	77	-	60
2000 psi	-	67	-	91	-	91	-	84
2500 psi	-	78	-	59	-	76	-	90

Table 9: The influence of ionic strength on mechanism of theophylline release from compacts at the different compressions

Tablet Formulation	Media	Compression (psi)	Agitation (dpm)	RSQ (r^2)	n
K100LV	water	1000	20	0.9941	0.4656
	pH media			0.9935	0.3818
	0.2 M			0.9920	0.3912
	0.4 M			0.9914	0.3101
K100LV	water	1500	20	0.9933	0.5149
	pH media			0.9932	0.4721
	0.2 M			0.9933	0.2785
	0.4 M			0.9855	0.1764
K100LV	water	2000	20	0.9933	0.6396
	pH media			0.9896	0.6340
	0.2 M			0.9809	0.5380
	0.4 M			0.9956	0.6550
K100LV	water	2500	20	0.9937	0.7406
	pH media			0.9900	0.6138
	0.2 M			0.9920	0.7426
	0.4 M			0.9910	0.3342
K100M	water	1000	20	0.9976	0.5548
	pH media			0.9920	0.4780
	0.2 M			0.9929	0.4820
	0.4 M			0.9959	0.5420
K100M	water	1500	20	0.9978	0.5660
	pH media			0.9916	0.5264
	0.2 M			0.9943	0.4699
	0.4 M			0.9943	0.4143
K100M	water	2000	20	0.9947	0.6325
	pH media			0.9630	0.6377
	0.2 M			0.9949	0.6207
	0.4 M			0.9960	0.5728
K100M	water	2500	20	0.9920	0.6083
	pH media			0.9703	0.6606
	0.2 M			0.9935	0.6509
	0.4 M			0.9980	0.5293

Table 10: The influence of ionic strength on mechanism of diltiazem HCl release from compacts at the different compressions

Tablet Formulation	Media	Compression (psi)	Agitation (dpm)	*RSQ* (r^2)	*n*
K100LV	water	1000	20	-	-
	pH media			-	-
	0.2 M			-	-
	0.4 M			-	-
K100LV	water	1500	20	0.9627	0.8858
	pH media			0.8561	0.4531
	0.2 M			0.9480	0.8379
	0.4 M			0.9192	0.6578
K100LV	water	2000	20	0.8770	0.4690
	pH media			0.8640	0.5062
	0.2 M			0.9441	0.5625
	0.4 M			0.7354	0.1945
K100LV	water	2500	20	0.9922	0.8259
	pH media			0.9583	0.7012
	0.2 M			0.9719	0.6634
	0.4 M			0.9730	0.6775
K100M	water	1000	20	0.9876	0.6402
	pH media			0.7879	0.1631
	0.2 M			0.9763	0.6038
	0.4 M			0.9933	0.6058
K100M	water	1500	20	0.9897	0.6235
	pH media			0.9906	0.6324
	0.2 M			0.9896	0.6290
	0.4 M			0.9884	0.6367
K100M	water	2000	20	0.9956	0.6494
	pH media			0.9958	0.6493
	0.2 M			0.9931	0.6150
	0.4 M			0.9936	0.6478
K100M	water	2500	20	0.9963	0.6054
	pH media			0.9958	0.5993
	0.2 M			0.9929	0.5925
	0.4 M			0.9914	0.6159

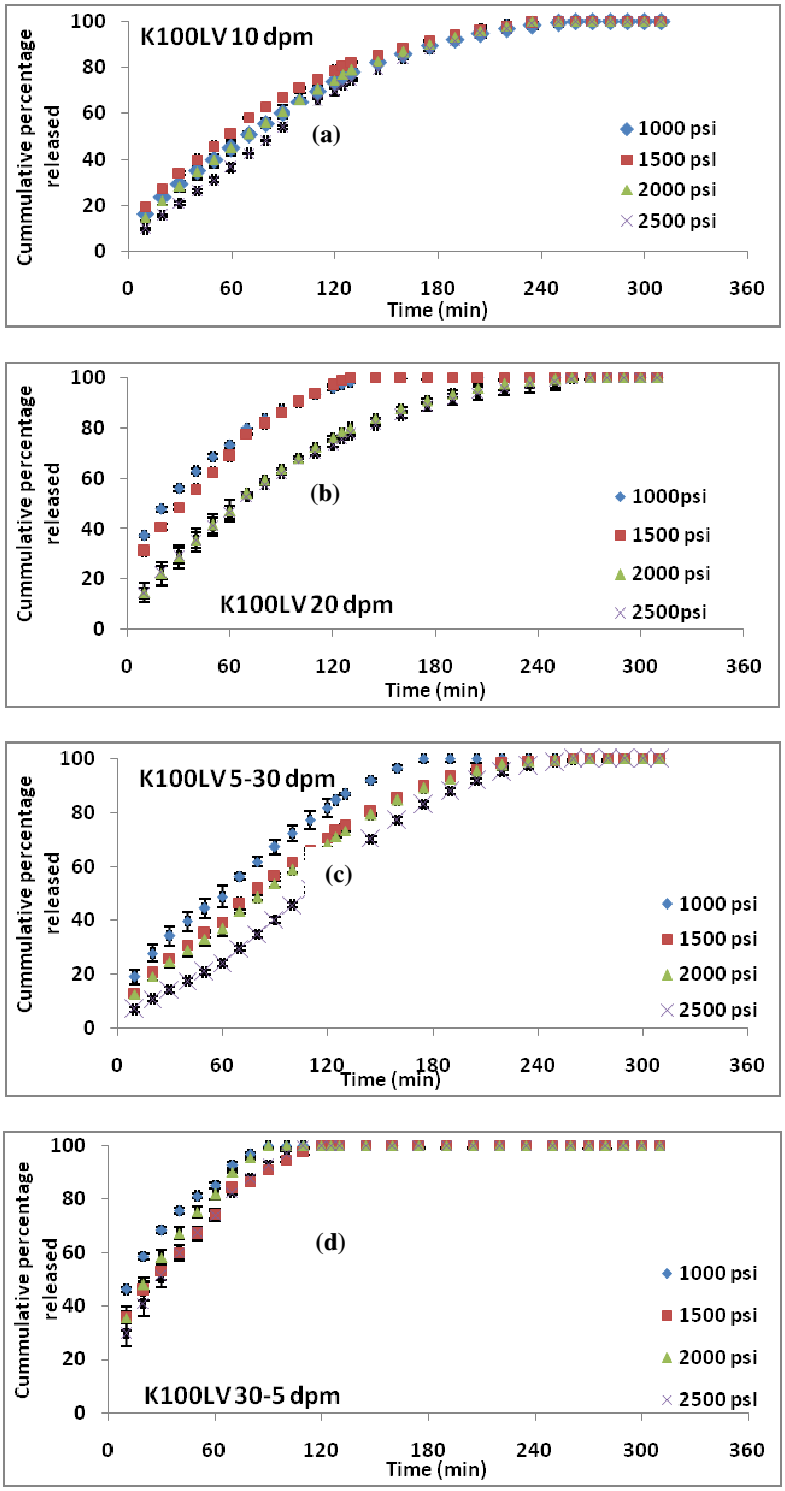

Figure 1: The effect of compaction force on the various levels of agitation on theophylline release from HPMC K100LV matrices in pH 1.2-7.5 a. 10 dpm b. 20 dpm c. 5-30 dpm d. 30-5 dpm. Standard deviations smaller than the symbol size were not shown on the graphs.

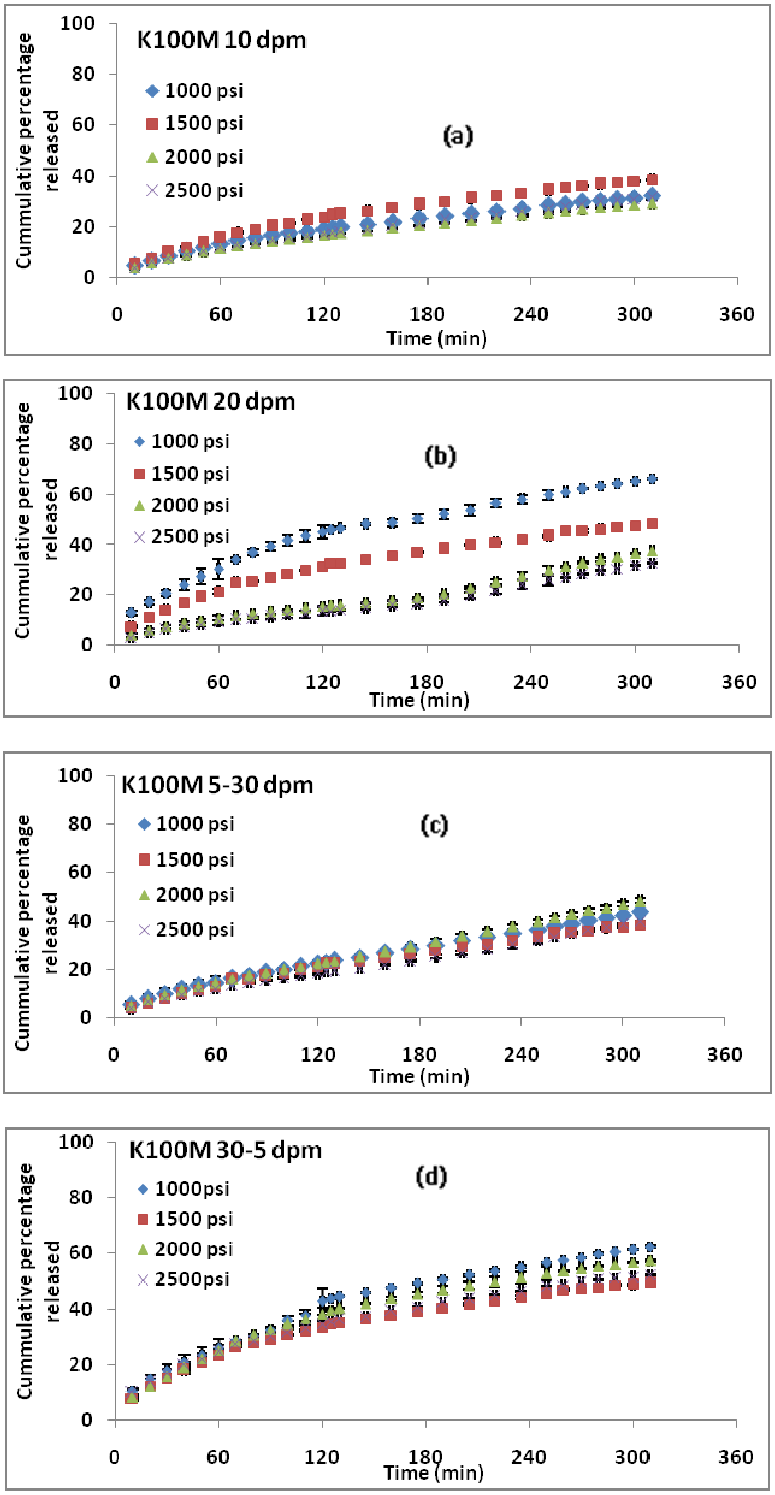

Figure 2: The effect of compaction force on the various levels of agitation on theophylline release from HPMC K100M matrices in pH 1.2-7.5 a. 10 dpm b. 20 dpm c. 5-30 dpm d. 30-5 dpm. Standard deviations smaller than the symbol size were not shown on the graphs.

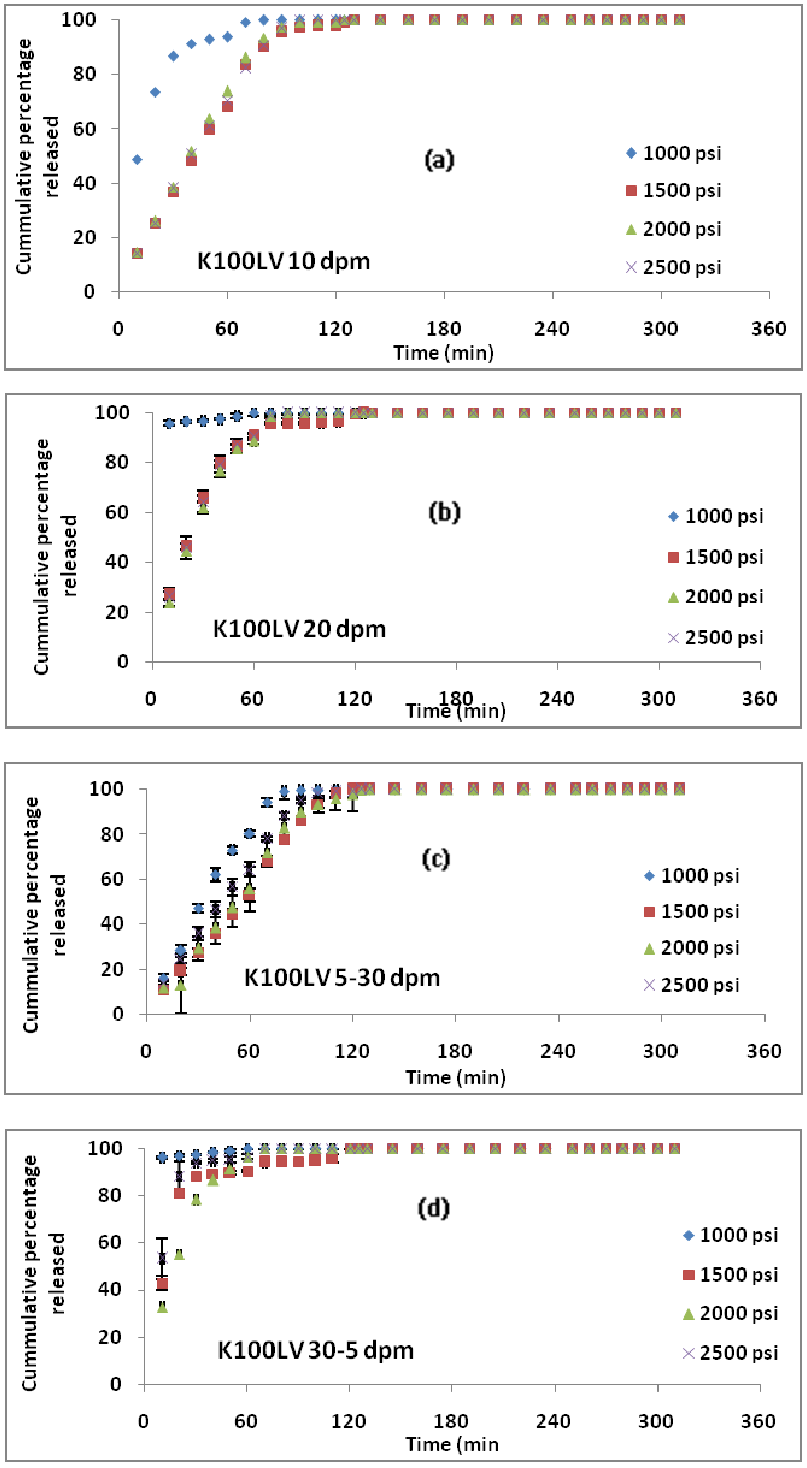

Figure 3: The effect of compaction force on the various levels of agitation on diltiazem HCl release from HPMC K100LV matrices in pH 1.2-7.5 a. 10 dpm b. 20 dpm c. 5-30 dpm d. 30-5 dpm. Standard deviations smaller than the symbol size were not shown on the graphs

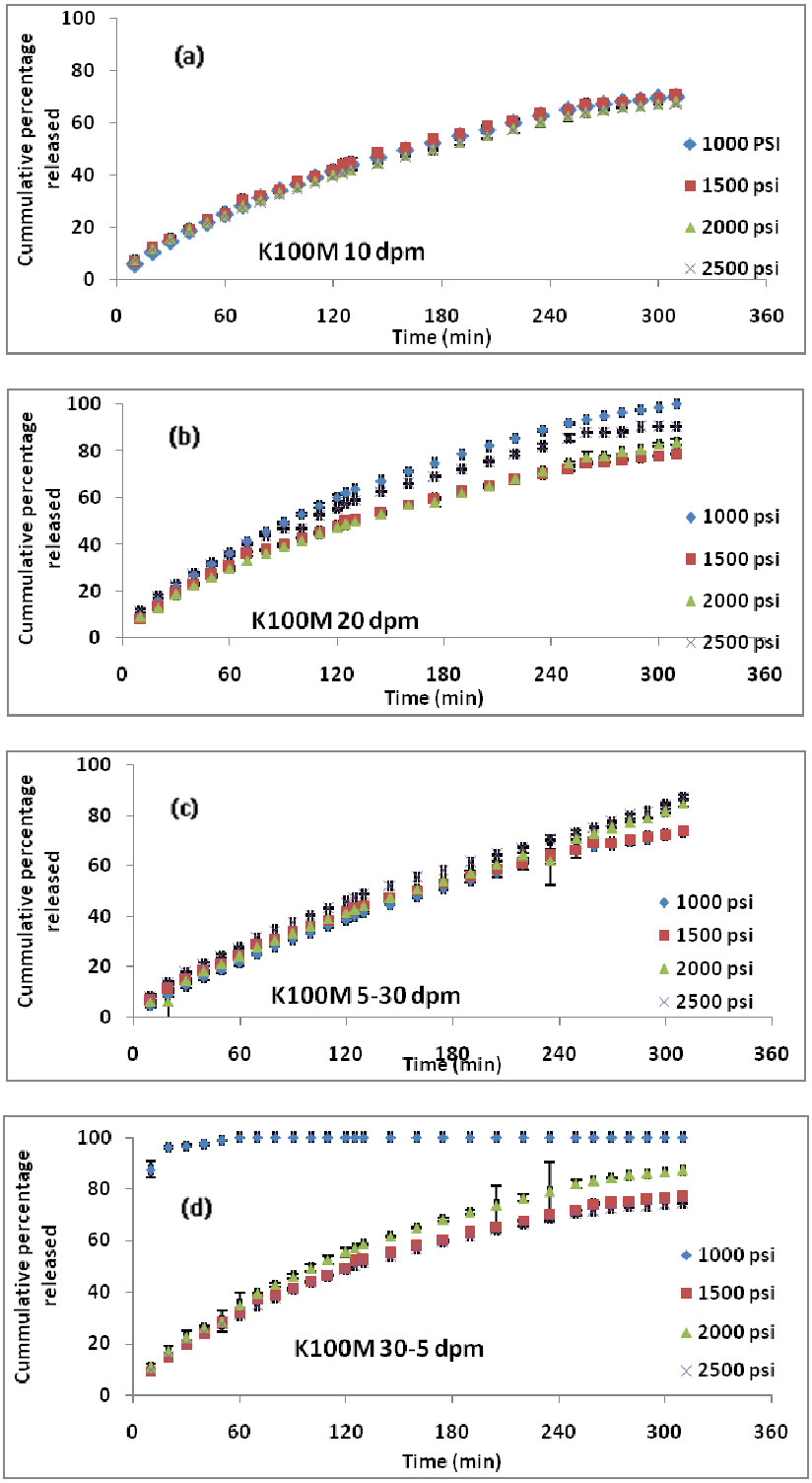

Figure 4: The effect of compaction force on the various levels of agitation on diltiazem HCl release from HPMC K100M matrices in pH 1.2-7.5 a. 10 dpm b. 20 dpm c. 5-30 dpm d. 30-5 dpm. Standard deviations smaller than the symbol size were not shown on the graphs

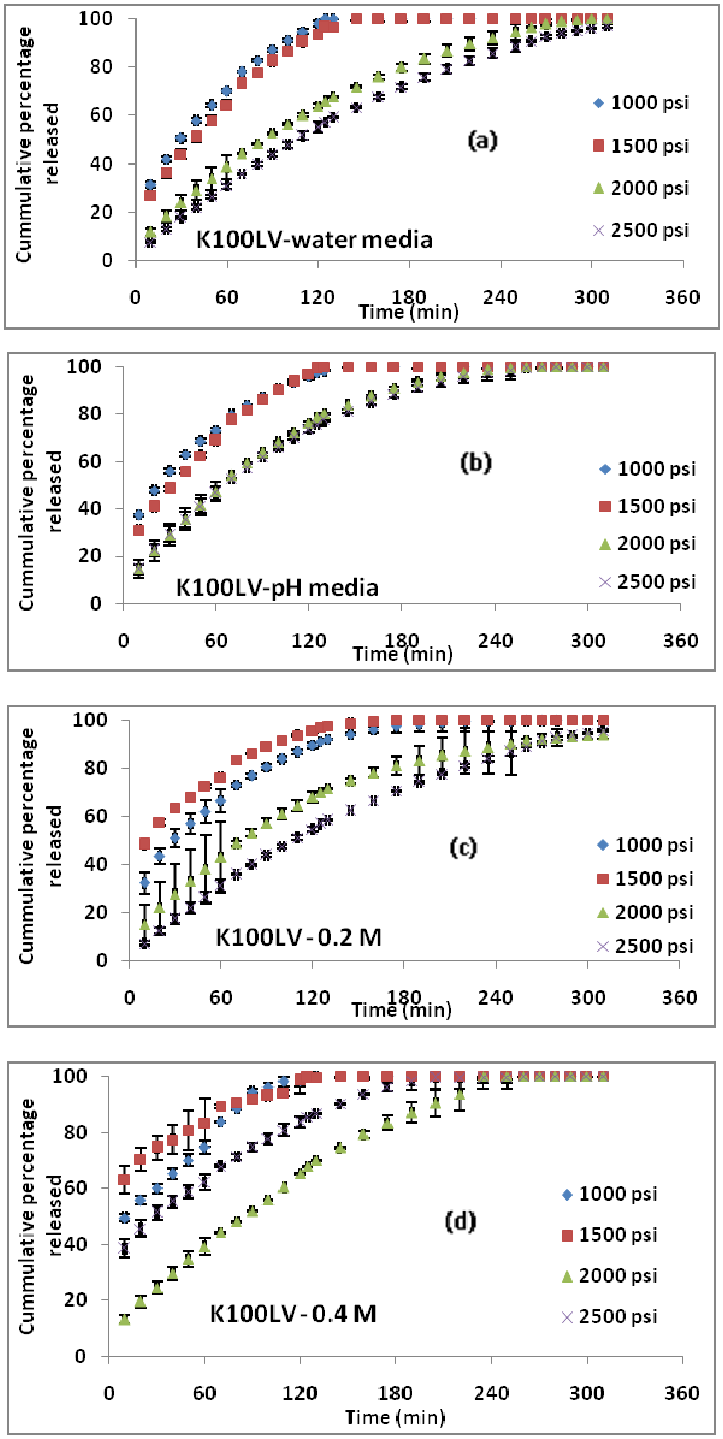

Figure 5: The effect of compaction force on the influence of media ionic strength on theophylline release HPMC K100LV matrices in pH 1.2-7.5 a. water media b. pH media c. pH media of ionic strength 0.2 M d. pH media of ionic strength 0.4 M. Standard deviations smaller than the symbol size were not shown on the graphs

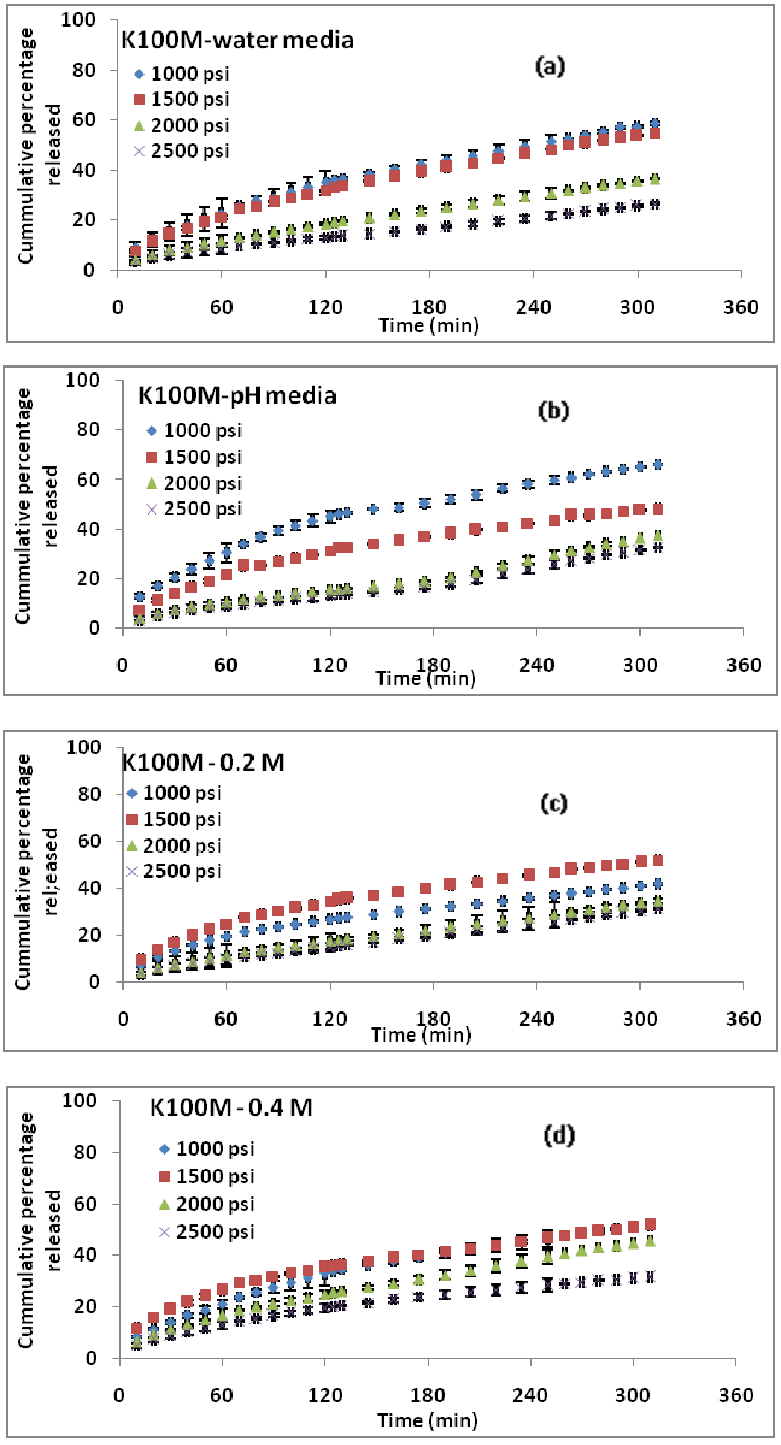

Figure 6: The effect of compaction force on the influence of media ionic strength on hydrochlorothiazide release HPMC K100M matrices in pH 1.2-7.5 a. water media b. pH media c. pH media of ionic strength 0.2 M d. pH media of ionic strength 0.4 M. Standard deviations smaller than the symbol size were not shown on the graphs

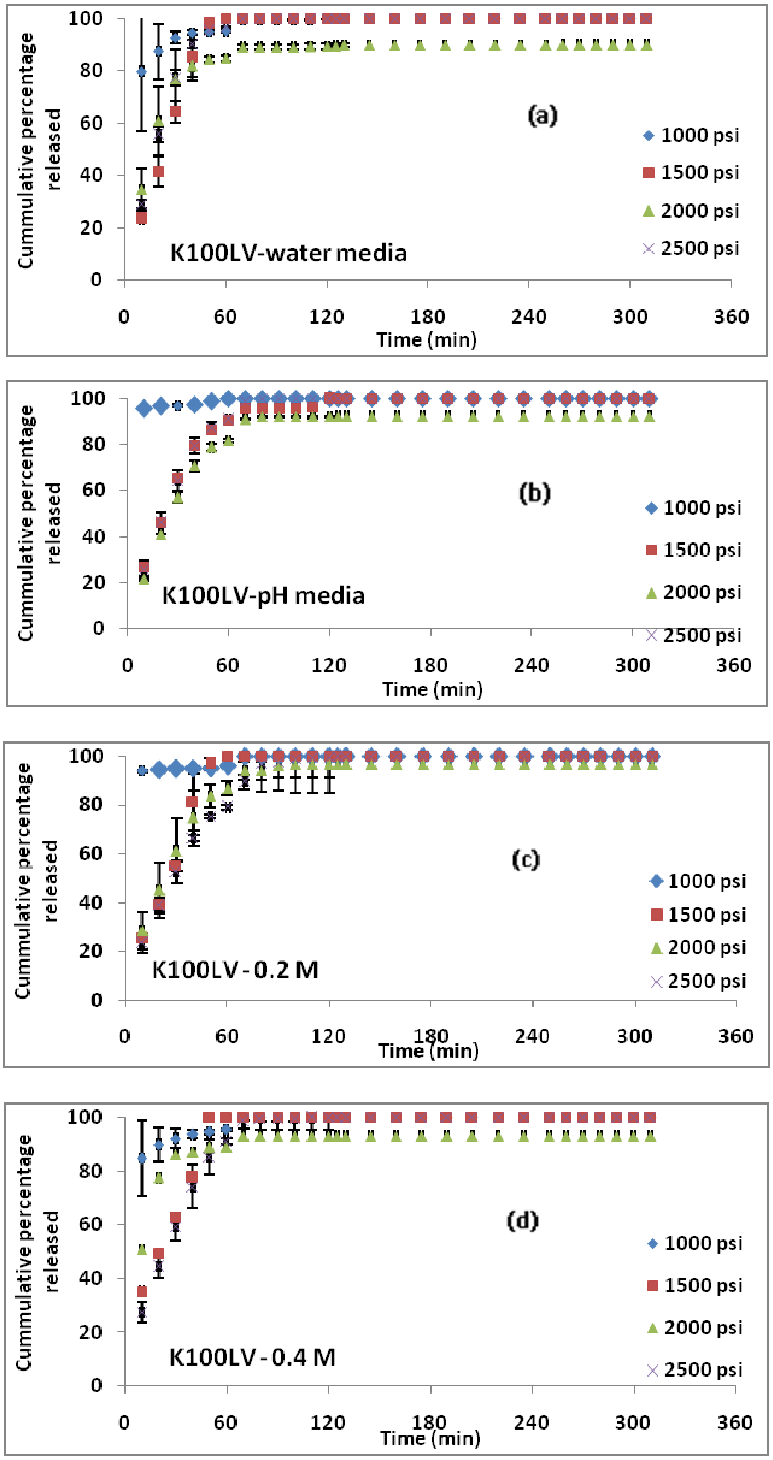

Figure 7: The effect of compaction force on the influence of media ionic strength on diltiazem HCl release HPMC K100LV matrices in pH 1.2-7.5 a. water media b. pH media c. pH media of ionic strength 0.2 M d. pH media of ionic strength 0.4 M. Standard deviations smaller than the symbol size were not shown on the graphs

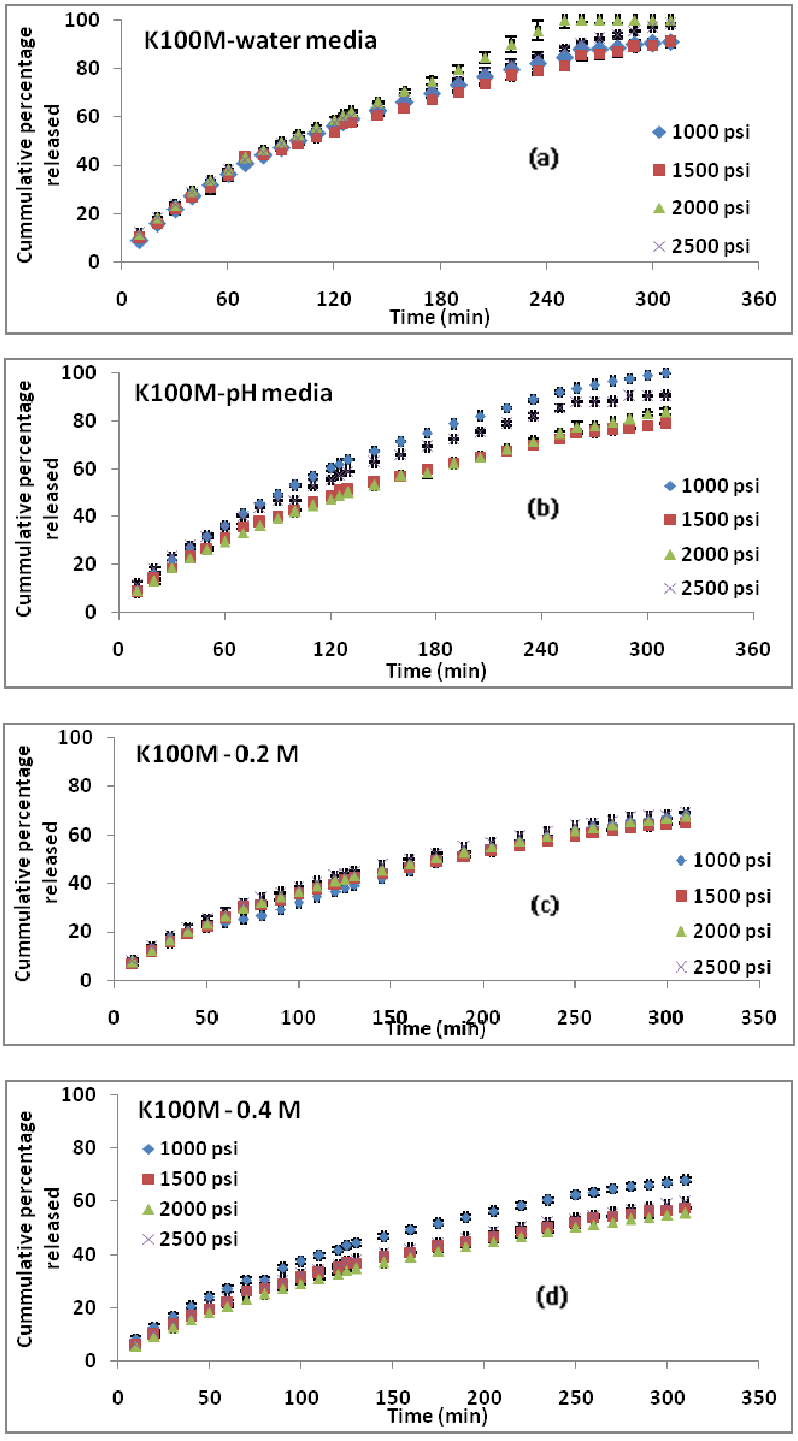

Figure 8: The effect of compaction force on the influence of media ionic strength on diltiazem HCl release HPMC K100M matrices in pH 1.2-7.5 a. water media b. pH media c. pH media of ionic strength 0.2 M d. pH media of ionic strength 0.4 M. Standard deviations smaller than the symbol size were not shown on the graphs.

These values however suggested Fickian diffusion to be occurring at these profiles (n=0.25 to 0.41). Apart from the descending order of agitation (30-5 dpm) for the K100M diltiazem HCl matrix compressed at 1000 psi where drug release was too quick for the n value to be obtained, all kinetics of drug release for the diltiazem HCl K100M tablet matrices displayed anomalous transport as its dominating kinetics of drug release (Table 6).

3.2. The effect of compaction force on the influence of ionic strength

Figures 5-8 shows the influence compaction force and ionic strength on drug release from theophylline and diltiazem HCl tablets made using different viscosity HPMC (K100LV and K100M) in the drug: polymer ratio of 4:1. Just like in the case of agitation, the K100LV tablet

matrices for both drugs released quicker than the K100M tablets matrices. Drug release for both HPMC polymers incorporated with the model drugs were generally in the order of 1000 psi > 1500 psi > 2000 psi > 2500 psi. This meant a decrease in drug release occurred as the compression force for the tablet making process was increased. An increase in the compression force from 1000 psi to 1500 psi was able to suppress the burst effect from the theophylline and diltiazem HCl K100LV matrices. This was more significant for the latter. As such drug release was in the water media > pH media > pH media (ionic strength 0.2 M) > pH media (ionic strength 0.4 M). The similarity factor analysis was carried out using drug release at 1500 psi (5.5 kN) in the media tested to determine if release rates at the different compression forces were similar and whether ionic strength had an effect on it. The fast drug release for the theophylline and diltiazem HCl K100LV tablet matrices in all the ionic strength media tested meant it was not possible to obtain f_2 values for these release profiles. With the exception of dissimilarity occurring in pH media (f_2=44) for theophylline K100M compacts compressed at 1000 psi, the three other ionic media tested showed similarity at the 1000 psi compaction pressure (f_2=55-77) (Table 7). Also drug release in pH media (ionic strength 0.4) for theophylline K100M compacts compressed at 2000 psi showed similarity (f_2=53) (Table 7). The diltiazem HCl K100M tablets matrices on the other hand showed similarity at all the compaction forces and pH of different ionic concentration strengths tested (f_2=50-91) (Table 8).

The kinetics of drug release showed that there was an increase in the n value as compression force was increased for the theophylline tablet matrices. This was evident only at the water and pH media ionic strength levels. For example, K100LV theophylline compacts compressed at 1000 psi had n values of 0.47 and 0.38 in the water media and pH media ionic strengths respectively (Table 9). An increase in compression to 1500 psi, increased the n values in the aforementioned media to 0.51 and 0.42 respectively. An even further increase in compression increased the contribution of Case-II transport as opposed to Fickian diffusion occurring for these matrices to 0.64 and 0.63 respectively, and so for. Again this gave evidence that compaction can affect the release mechanism of tablet matrices. The strength of the K100M gel and their resilience made it difficult to establish such trends as n values obtained very similar at the levels discussed. It was however noted that compressions at 2000 psi and 2500 psi also gave very similar n values (Table 9). Values for *n* were unobtainable for the diltiazem HCl K100LV matrices compressed at 1000 psi (Table 10). This was due to the quick drug release profiles obtained here. Fickian diffusion only occurred for two drug release profiles (K100LV compressed at 1000 psi with drug release in pH media and K100M compressed at 2000 psi with drug release in pH media of 0.4 M ionic concentration strengths). With the exception of these two drug release profiles, all the formulated diltiazem HCl matrices (K100LV and K100M) compacted at the different pressures were dominated by anomalous transport. It was not possible to establish a real trend in the values of n obtained for their drug release patterns (Table 10).

4. Conclusion

An increase in the compression of the tablet matrices for the K100LV theophylline and diltiazem HCl tablet matrices resulted in a significant difference in their drug release profiles both in the agitation sequence and with the influence of ionic concentration strength. The K100M tablet matrices for the theophylline and diltiazem HCl were generally unaffected. Evidence from these experiments also suggests that where there is a drive towards obtaining zero order release, compression plays an important role as seen in the values of n obtained for the K100LV tablet matrices. With regards to the higher molecular of more viscous polymers, the strength of the gel seem to be more of a determinant factor. This investigation also highlights the importance of controlling drug release in the desired dissolution medium as agitation could significantly influence the drug release resulting in a possible toxicity or making drug not available at the required site. This being clear in the ability of compression force to suppress burst release.

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