international Journal of Pharmaceutical research and Applications
Volume 6, Issue 6, pp: 434-442 www.ijprajournal.com ISSN: 2456-4494

The Release Effect of Ticlopidine HCl from Different Dimension of HydroxyPropyl MethylCellulose (HPMC) Tablets

Yuh-Tyng Huang[1], Wen-Ho Chuo[2], Yung-Kuang Lo[3],Thau-Ming Cham*[1,4]
[1,] *Departmane of Pharmaceutical Science and Technology, Chung Hwa University of Medical Technology, Tainan, Taiwan*
[2] *Department of Pharmacy, Tajen University, Pingtung, Taiwan*
[3]*Department of pharmacy, Chia Nan University of Pharmacy&Science, Tainan, Taiwan*
[4]*School of pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan*
Corresponding Author: Thau-Ming Cham

Submitted: 22-11-2021 Revised: 04-12-2021 Accepted: 06-12-2021

ABSTRACT: Five different punch diameters, four different viscosity grades of hydroxypropyl methylcellulose (HPMC), an excipient (lactose), and a model drug (ticlopidine HCl) were used to investigate the effect on the drug released from the HPMC matrix tablets prepared at 100 Kg/cm2. The results showed that a higher drug release rate was obtained for smaller tablet dimensions, as well as formulations with lower HPMC/lactose ratio and lower HPMC viscosity grades. In addition, the mechanisms of drug release from HPMC matrix tablets were analyzed by simple exponential equation $\frac{Mt}{M\infty} = Kt^{n}$ and equation $\frac{Mt}{M\infty} = K_1\sqrt{t} + K_2 t$, respectively. The results showed that the mechanism of drug release followed the anomalous (non-Fickian) diffusion.

KEYWORDS: hydroxypropyl methylcellulose, tablet dimensions, simple exponential equation, lactose, non-Fickian diffusion

I.INTRODUCTION

In recent years, drug controlled release systems were developed extensively. Advantages of drug controlled release systems mainly include improves drug performance, i.e. concentration levels are maintained in the desired range and are protected from degradation, decreased side effects, elimination of patient discomfort and compliance, cost less expense and wastefulness in comparison to the researching of a new drug, and maintained of therapeutic concentration during the night. Solid polymers for controlled release systems were extended into the field of medicine in 1960s. Many polymers occur naturally, e.g. cellulose. Hydroxy propyl methyl cellulose (HPMC) is one of a number of cellulose ethers that has been manufactured from cotton waste or wood pulp. HPMC offers the advantages of being non-toxic, non-irritant, high-biocompatibility and relatively inexpensive, it can be directly compressed into matrices and the many grades available allow a wide latitude in the ability to tailor desired drug-release profiles [1].

HPMC is important in extended-release formulations, especially as a hydrophilic matrix system for oral sustained release preparation. The release of drug from the matrix system can be determined by the solubility of the drug [2,3]. Other variables such as HPMC concentration, HPMC viscosity grades, dosage size, manufacturing process and percentage of a water-soluble co-excipient may also affect the release of drug from the HPMC matrices system [1, 4, 5]. However, the compaction pressure has little impact on the drug release rate [6, 7]. The drug release from HPMC matrices system had also been interpreted by mathematical models [8, 9,10]. However, up to now, it has been less studied than that exploring effect of drug release and formulations from different dimension (as well as same total dose) of HPMC tablets placed in the vessel for in-vitro dissolution test (the imitation circumstances of G-I tract in vivo).

In the pharmaceutical market, a pharmaceutical product Dilacor XR consist 3 or 4 tablets in a capsule. This product has both advantages of single dosage form (tradition tablet) and multiple dosage form (capsule), such as it has more predictable gastric emptying and dispersion in the gastrointestinal tract, and the reduced risk of “dose dumping”, i.e. failure of the system leading to immediate release of the drug, as well as it has more simple fabrication process than that prepared multiple dosage form (capsule). This product consists of three layers tablet and delivers diltiazem for 24 hours to controlling mild-to-moderate hypertension [11].

In the present study, a water-soluble drug (Ticlopidine HCl) was chosen as model drug to

international Journal of Pharmaceutical research and Applications
Volume 6, Issue 6, pp: 434-442 www.ijprajournal.com ISSN: 2456-4494

prepare different dimension (as well as same total dose) of HPMC tablets and placed them in the vessel for in-vitro dissolution test to estimate drug release condition. Moreover, the effect of some variables, such as tablet dimension, HPMC grades, and ratio of lactose in the formulation on the release of ticlopidine HCl from HPMC tablet matrices also have been investigated. The drug release mechanism was interpreted using mathematical models. Finally, we hope that in vitro data of this study can apply to reference basis for in-vivo test in the further.

II.Materials and Methods

Materials

Ticlopidine HCl (Alfa chemicals, Italy, batch number: 998165), monohydrate lactose (New Zealand Lactose Co., Ltd., New Zealand), HPMC K100, K4M, K15M and K100M (Dow Chemical Co., USA), Aerosil 200 (Degussa, Germany). And other chemicals were analytic grade.

Preparation of ticlopidine HCl tablets

The formulations of the ticlopidine HCl tablets are listed in Tables 1. The required quantities of formulations were sieved through a 40 mesh screen and blended for 15 minutes. And then, powder mixture was transferred into the given diameter die (Table 2) and compressed manually on a hydraulic press (Carver, USA) at 100 Kg/cm2.

In vitro dissolution studies of ticlopidine HCl tablets

In vitro release studies of ticlopidine HCl tablets were carried out with USP XXIII dissolution apparatus (DT-610, JASCO Co., Ltd., Japan) in 900 ml 0.1 N HCl maintained at 37 ± 0.5 ℃ as dissolution medium, and the paddle speed was 50 rpm. Samples of the drug solution passed through a 30-50 μm filter at 10, 20, and 30 min, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hr were collected using an automatic fractional collector (DIS-422, JASCO Co., Ltd., Japan). The amount of the dissolved drug was determined spectrophotometrically (UV-700, JASCO Co., Ltd., Japan) at 235 nm. No interference due to either the dissolved HPMC, lactose, Aerosil 200 or magnesium stearate occurred. Six replicates for each kind of tablets were tested. The number of each kind of tablets placed in the vessel for dissolution test was listed in Table 2. Each tablet was enclosed within a helical wire sinker to prevent the tablet stick to the bottom of vessel and to each other as well, while there were two or more than two tablets in the same vessel (Figure 1).

Average surface areas of ticlipidine HCl tablets

The dimension of the each tablet was measured prior to dissolution studies using a micrometer and ten replicates for each kind of tablets were measured. The surface areas of the flat-faced tablets were computed subsequently.

III.Results and Discussion

Effect of helical wire sinker on dissolution test

Statistical analysis of data was performed by the pairwise approach, the 〝different factor, *f1*〞 and 〝similarity factor, *f2*〞 . The *f2* value between 50 and 100 suggests that the dissolution profiles are similar. And *f1* value describes the relative error between two dissolution profiles, and it should be less than 15 for a similarity of the two profiles [12]. In accordance with pairwise approach that *f2* and *f1* values are 72.51 and 8.58, respectively, indicating that the dissolution profiles of the tablets with or without a helical wire sinker are similar. Therefore, a helical wire sinker was used to enclose the tablet for dissolution test throughout the study.

Effect of tablet dimensions on the release of ticlopidine HCl tablets

Figure 2 depicts the effect of tablet dimension on the release of ticlopidine HCl from HPMC K15M tablets. It shows that when the dose of ticlopidine HCl was constant, the number of tablets placed in the vessel were more for smaller size tablets, the release of ticlopidine HCl was faster. On the contrary, the release of ticlopidine HCl was slower for larger size tablets. When the release rate of ticlopidine HCl from HPMC K15M tablets was plotted against the total calculated surface area of the tablets prior to dissolution test, it was a directly proportional relationship (Figure 3). Similar results had been reported previously for the release of promethazine from HPMC matrices system [5].

Effect of HPMC viscosity grade on the release of ticlopidine HCl tablets

The release of ticlopidine HCl from 12.5 mm HPMC tablets was governed by the viscosity grade of the HPMC used in the formulation 1 (Figure 4). The release rate of ticlopidine HCl decreased as the HPMC viscosity increased. This was presumably due to HPMC K100 had a higher porosity and a lower tortuosity polymeric nature on comparison to the other three grades of HPMC used in this study. Also, HPMC K100 has a lower gel strength, which

international Journal of Pharmaceutical research and Applications
Volume 6, Issue 6, pp: 434-442 www.ijprajournal.com ISSN: 2456-4494

will allow rapid diffusion of the drug. A comparatively faster erosion of the HPMC K100 tablet would also enhance the release of the drug [13, 14].

Effect of HPMC / lactose ratio on the release of ticlopidine HCl tablets

results to presume that increase in the HPMC concentration would also increase the viscosity of the surrounding fluid, which would increase the gel-strength, and thus both the tortuosity of the matrix tablet was increased and the diffusion path of the drug was extended, so the drug released was slower. Lactose is a water-soluble diluent that decreased the tortuosity of the matrix tablet and diffused outward forming channels. Therefore, tablet formulations that compose a higher ratio of lactose, the release rate of drug will be faster [15].

Study of mechanism on the release of ticlopidine HCl tablets

When a matrix tablet comes into contact with an aqueous solution, the tablet surface becomes wet, and the polymer starts to partially hydrate to form a gel layer. There follows an expansion of the gel layer when water permeates into the tablet increasing the thickness of the gel layer and soluble drug diffuses through the gel barrier. For a long time, tablet outer layers become erosion and finally tablet core has dissolved [6].

The release mechanisms from controlled release polymeric matrices can be described by the equation (1) [10]

$$\frac{Mt}{M\infty} = Kt^{n} \quad \text{----------(1)}$$

$\frac{Mt}{M\infty}$ is the percentage of drug released at time t, K is a kinetic constant incorporating structural and geometric characteristics of the tablets and n is the diffusional exponent indicative of the release mechanism. In theory, equation (1) should be applicable to the first 60% of fractional release from matrix tablets for computation. For n value equal to 0.50 is defined Fickian diffusion drug release, n value between 0.5~1 is defined non-Fickian (anomalous) drug release and n value equal to 1.0 is defined Case II transport that refer to Zero-order.

However, in most hydrophilic matrix tablets usually exist to couple the rates of Fickian diffusion and polymer relaxation, which the intermediate situation was termed anomalous (non-Fickian) drug diffusion [8].

In this study, examination of the dissolution parameters derived from that results indicated the release of ticlopidine HCl follows the non-Fickian

Incorporation of lactose in the HPMC K100 tablet formulation would increase the release rate of ticlopidine HCl (Figure 5). A higher proportion of lactose in the HPMC K100 matrices system gives a faster release of ticlopidine HCl. This is much more significant for larger size tablets than that of smaller size tablets (Figure 6). In accordance with these mechanism, as the n values were between 0.5~1(Table 3).

The mechanism of drug release via polymer relaxation and Fickian diffusion has been described by the equation (2).

$$\frac{Mt}{M\infty} = K_1\sqrt{t} + K_2 t \quad \text{----------(2)}$$

$\frac{Mt}{M\infty}$ is the percentage of drug released at time t, and both K1 and K2 are constants describing the diffusion-controlled release mechanism and Case II transport (polymer relaxation) release mechanism, respectively.

Vigoreaux and Ghaly [16] used computer software PCNONLIN Version 4.0 to fit drug release data in equation (2). The PCNONLIN was designed to solve general nonlinear regression problems that possible to estimate the percent of drug released by Fickian diffusion and the percent of drug released by polymer relaxation.

The estimative K1 and K2 values obtained when the drug release data was fitted to equation (2). According to the results that K1 values were greater than K2 values, which indicated in anomalous release system, the percentage of drug released by Fickian diffusion predominately (Table 4).

IV.Conclusions

In this study, the percentage release of ticlopidine HCl is directly proportional to the calculated contact surface area of the tablets. The release rate of ticlopidine HCl decreased as the HPMC viscosity and HPMC/lactose ratio increased. Decrease HPMC viscosity and HPMC/lactose ratio in the formulations also increase the release rate of ticlopidine HCl. The release of ticlopidine HCl follows the non-Fickian (anomalous) diffusion mechanism.

References

[1] Alderman, D. A. 1984. A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. Int. J. Pharm. Tech. Prod. Mfr. 5: 1-9.

[2] Vazquez, M. J., Perez-Marcos, B., Gomez-Amoza, J. L., Martinez-Pacheco, R., Souto, C. and Concheiro, A. 1992. Influence of

technological variables on release drugs from hydrophilic matrices. Drug Dev. Ind. Pharm. 5: 1355-1375.

[3] Williamsa, H. D., Ward, R., Hardy, I. J., and Melia, C. D. 2010. The effect of sucrose and salts in combination on the drug release behaviour of an HPMC matrix. Eur. J. Pharm. Biopharm. 76: 433-436.

[4] Doelker, E. L. 1987. Water-swollen cellulose derivatives in pharmacy. In "Peppas, N. A. (ed) Hydrogels in Medicine and Pharmacy". Vol. 2. pp. 115-160. Polymers, CRC Press, Boca Raton, FL.

[5] Sung, K. C., Nixon, P. R., Skoug, J. W., Ju, T. R., Gao, P., Topp, E. M. and Patel, M. V. 1996. Effect of formulation variables on drug and polymer release from HPMC-based matrix tablets. Int. J. Pharm. 142: 53-60.

[6] Ford, J. L., Rubinstein, M. H. and Hogan, J. E. 1985. Formulation of sustained release promethazine hydrochloride tablets using hydroxypropyl- methylcellulose matrices. Int. J. Pharm. 24: 327-338.

[7] Velasco, M. V., Ford, J. L., Rowe, P. and Rajabi-Siahboomi, A. R. 1999. Influence of drug:hydroxypropylmethylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets. J. Control. Release. 57: 75-85.

[8] Lee, P.I. 1985. Kinetics of drug release from hydrogel matrices. J. Control. Release. 2: 277-288.

[9] Peppas, N. A. and Sahlin, J. J. 1989. A simple equation for the description of solute release. III. Coupling of diffusion and relaxation. Int. J. Pharm. 57: 169-172.

[10] Ritger, P. L. and Peppas, N. A. 1987. A simple equation for description of solute release. II. Fickian and anomalous release from swellable devices. J. Control. Release. 5: 37-42.

[11] Choi, D. H. and Jeong S. H. 2011. Multi-Layered Matrix Tablets with Various Tablet Designs and Release Profiles. Int J. Pharm. Investig. 41: 263-272.

[12]Pillay, V. and Fassihi, R. 1998. Evaluation and comparison of dissolution data derived from different modified release dosage forms: an alternative method. J. Control. Release. 55: 45-55.

[13] Cao, Q. R., Choi, H. G., Kim, D. C. and Lee, B. J. 2004. Release behavior and photo-image of nifedipine tablet coated with high viscosity grade hydroxypropylmethylcellulose: effect of coating conditions. Int. J. Pharm. 274, 107–117.

[14] Pekel, N., Yoshii F., Kume, T. and Güven O. 2004. Radiation crosslinking of biodegradable hydroxyl propyl methylcellulose. Carbohydr. Polym. 55, 139–147

[15] Sakata, Y. and Yamaguchi, H. 2011. Effects of calcium salts on thermal characteristics of hydroxypropyl methylcellulose films. J. Non. Cryst. Solids. 357, 1279~1284.

[16] Vigoreaux, V. and Ghaly, E.S. 1994. Fickian and relaxation contribution quantification of drug release in a swellable hydrophilic polymer matrix. Drug Dev. Ind. Pharm. 20, 2519-2526.

international Journal of Pharmaceutical research and Applications
Volume 6, Issue 6, pp: 434-442 www.ijprajournal.com ISSN: 2456-4494

Table 1. Formulations 1, 2, 3 and tablet weight (mg) for five tablet dimensions

Formulations	Diameter (mm)	HPMC[a] (mg)	Lactose (mg)	Aerosil 200 (mg)	Mg-stearate (mg)	Tablet weight (mg)
F1	12.5	245	—	2.5	2.5	500
F2	12.5	163.5	81.5	2.5	2.5	500
F3	12.5	122.5	122.5	2.5	2.5	500
F1	11	122.5	—	1.25	1.25	250
F2	11	81.75	40.75	1.25	1.25	250
F3	11	61.25	61.25	1.25	1.25	250
F1	10	81.6	—	0.833	0.833	166.6
F2	10	54.48	27.16	0.833	0.833	166.6
F3	10	40.82	40.82	0.833	0.833	166.6
F1	8	61.3	—	0.625	0.625	125
F2	8	40.88	20.38	0.625	0.625	125
F3	8	30.63	30.63	0.625	0.625	125
F1	7	24.5	—	0.25	0.25	50
F2	7	16.35	8.15	0.25	0.25	50
F3	7	12.25	12.25	0.25	0.25	50

Table 2. Number and weight of tablet for each dimension

Diameter (mm)	12.5	11	10	8	7
Tablet weight (mg)	500	250	166.6	125	50
Number of tablet	1	2	3	4	10

Table 3. Dissolution parameters for three formulations of ticlopidine HCl tablets obtained by linear regression based on $\frac{Mt}{M\infty} = Kt^{n}$

Type of HPMC		K4M			K15M			K100M			K100		
Diameter (mm)		*n*	*K*	r	*n*	*K*	r	*n*	*K*	r	*n*	*K*	r
	12.5	0.6	16.56	0.9991	0.65	13.61	0.9970	0.67	13.64	0.9990	0.67	17.81	0.9999
	11	0.55	26.73	0.9999	0.60	20.09	0.9987	0.63	19.86	0.9960	0.76	21.70	0.9989
F1	10	0.57	30.20	0.9996	0.59	24.04	0.9988	0.58	25.23	0.9990	0.60	28.84	0.9999
	8	0.51	37.15	0.9957	0.56	28.13	0.9967	0.57	26.36	0.9966	0.62	39.81	0.9920
	7	0.56	44.67	0.9977	0.52	44.67	0.9976	0.48	44.57	0.9975	0.53	52.48	0.9998
Diameter (mm)		*n*	*K*	r	*n*	*K*	r	*n*	*K*	r	*n*	*K*	r
	12.5	0.58	20.15	0.9989	0.62	17.22	0.9990	0.66	18.78	0.9940	0.73	20.70	0.9996
	11	0.57	26.79	0.9998	0.60	22.68	0.9999	0.62	21.66	0.9990	0.64	28.18	0.9900
F2	10	0.54	30.97	0.9999	0.58	28.95	0.9992	0.62	25.53	0.9995	0.72	37.15	0.9997
	8	0.53	35.48	0.9998	0.56	30.20	0.9965	0.52	28.18	0.9996	0.63	45.71	0.9993
	7	0.51	53.70	0.9997	0.48	51.17	0.9999	0.50	46.77	0.9997	0.55	69.18	0.9960
Diameter (mm)		*n*	*K*	r	*n*	*K*	r	*n*	*K*	r	*n*	*K*	r
	12.5	0.66	20.09	0.9995	0.65	17.75	0.9971	0.68	18.07	0.9999	0.73	26.30	0.9999
	11	0.53	33.88	0.9997	0.61	22.05	0.9951	0.64	23.61	0.9996	0.74	33.89	0.9997
F3	10	0.54	41.02	0.9999	0.58	29.51	0.9997	0.58	26.93	0.9999	0.65	45.71	0.9997
	8	0.52	46.77	0.9992	0.60	30.90	0.9997	0.64	30.20	0.9990	0.61	48.98	0.9992
	7	0.52	67.92	0.9998	0.51	53.95	0.9999	0.53	46.88	0.9999	0.45	89.13	0.9994

international Journal of Pharmaceutical research and Applications
Volume 6, Issue 6, pp: 434-442 www.ijprajournal.com ISSN: 2456-4494

Table 4. Dissolution parameters for three formulations of ticlopidine HCl tablets obtained by non-linear regression based on $\frac{Mt}{M\infty} = K_1\sqrt{t} + K_2 t$

Type of HPMC		K4M			K15M			K100M			K100		
Diameter (mm)		K_1	K_2	correlation	K_1	K_2	correlation	K_1	K_2	correlation	K_1	K_2	correlation
	12.5	18.71	2.14	0.9980	14.53	1.23	0.9970	12.71	2.16	0.9990	13.05	4.70	0.9999
	11	21.96	3.81	0.9990	19.74	1.45	0.9990	18.71	2.14	0.9980	13.99	8.15	0.9980
F1	10	11.48	2.24	0.9980	22.41	2.05	0.9990	22.60	2.85	0.9990	26.35	0.45	0.9940
	8	28.79	7.80	0.9960	28.80	2.14	0.9970	23.95	2.52	0.9980	36.32	0.00	0.9770
	7	42.19	2.46	0.9970	42.49	0.00	0.9750	41.90	0.004	0.9710	48.84	0.00	0.9910
Type of HPMC		K4M			K15M			K100M			K100		
Diameter (mm)		K_1	K_2	correlation	K_1	K_2	correlation	K_1	K_2	correlation	K_1	K_2	correlation
	12.5	19.01	1.70	0.9980	15.92	2.06	0.9990	19.76	1.53	0.9910	11.57	8.73	0.9999
	11	24.41	2.47	0.9990	19.80	2.98	0.9990	18.85	3.22	0.9990	23.12	3.75	0.9780
F2	10	28.94	0.00	0.9890	26.55	2.42	0.9990	21.96	3.81	0.9990	19.17	18.20	0.9990
	8	32.80	0.00	0.9920	29.76	0.00	0.9820	27.35	2.09	0.9999	31.89	13.47	0.9999
	7	49.19	0.00	0.9900	47.82	0.00	0.9890	43.35	0.002	0.9890	68.25	0.54	0.9990
Type of HPMC		K4M			K15M			K100M			K100		
Diameter (mm)		K_1	K_2	correlation	K_1	K_2	correlation	K_1	K_2	correlation	K_1	K_2	correlation
	12.5	16.08	4.35	0.9990	17.58	1.80	0.9970	13.49	4.77	0.9990	18.38	5.06	0.9950
	11	31.30	2.43	0.9999	14.80	6.23	0.9980	18.64	4.99	0.9990	28.05	2.92	0.9920
F3	10	37.72	3.10	0.9999	25.92	0.81	0.9940	23.12	3.60	0.9999	39.00	2.89	0.9950
	8	43.65	2.76	0.9999	28.34	0.19	0.9940	26.34	1.27	0.9950	45.16	0.048	0.9820
	7	65.13	2.55	0.9999	50.36	0.00	0.9890	43.54	0.00	0.9890	93.30	0.004	0.9990

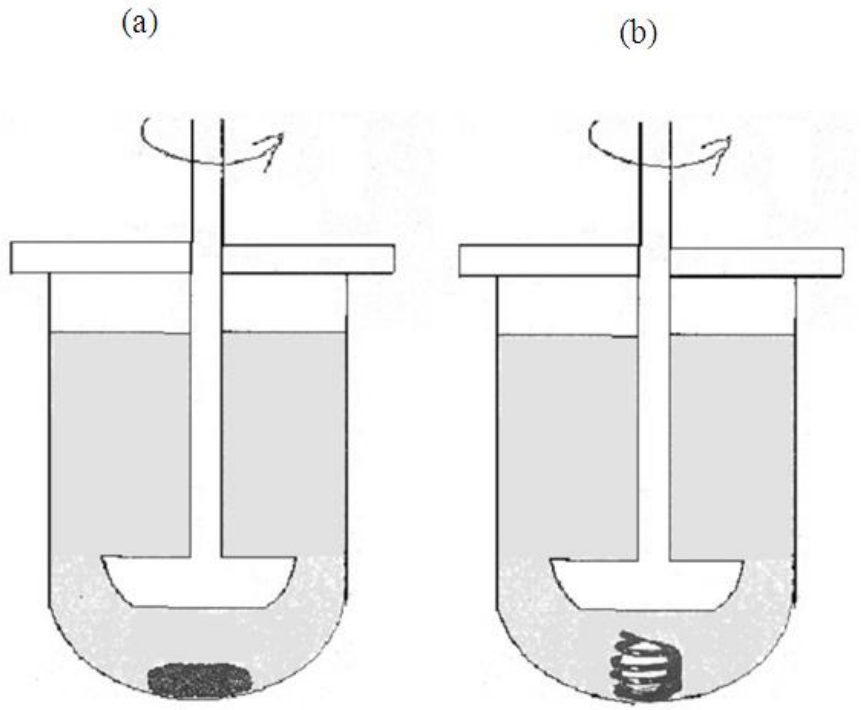

Figure 1. (a) Tablet with one surface sticking to the bottom of the vessel.
(b) Tablet enclosed within a helical wire sinker to prevent sticking to the bottom of the vessel (n = 6)

international Journal of Pharmaceutical research and Applications
Volume 6, Issue 6, pp: 434-442 www.ijprajournal.com ISSN: 2456-4494

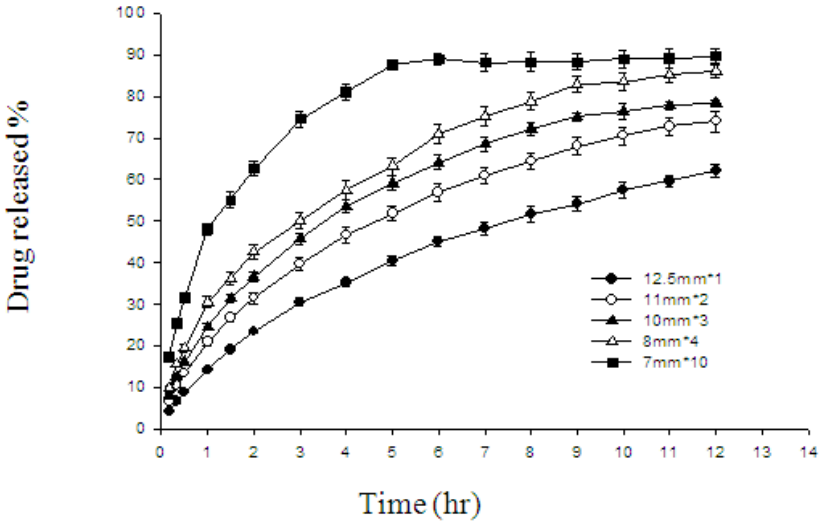

Figure 2. Effect of tablet dimension on the % release of ticlopidine HCl from HPMC K15M tablets

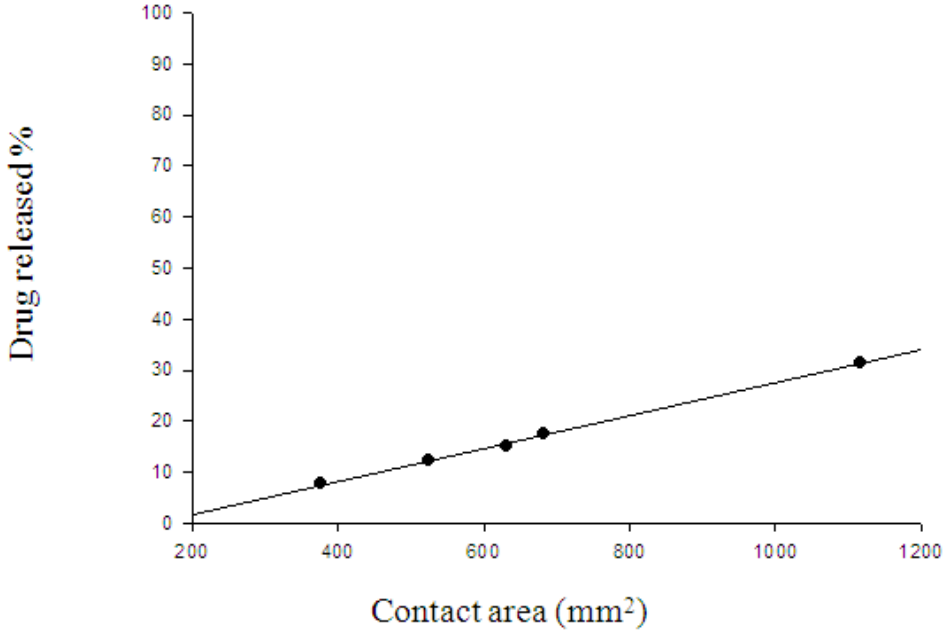

Figure 3. Dissolution rate of ticlopidine HCl tablet VS calculated contact area of tablets prepared by HPMC K15M

international Journal of Pharmaceutical research and Applications
Volume 6, Issue 6, pp: 434-442 www.ijprajournal.com ISSN: 2456-4494

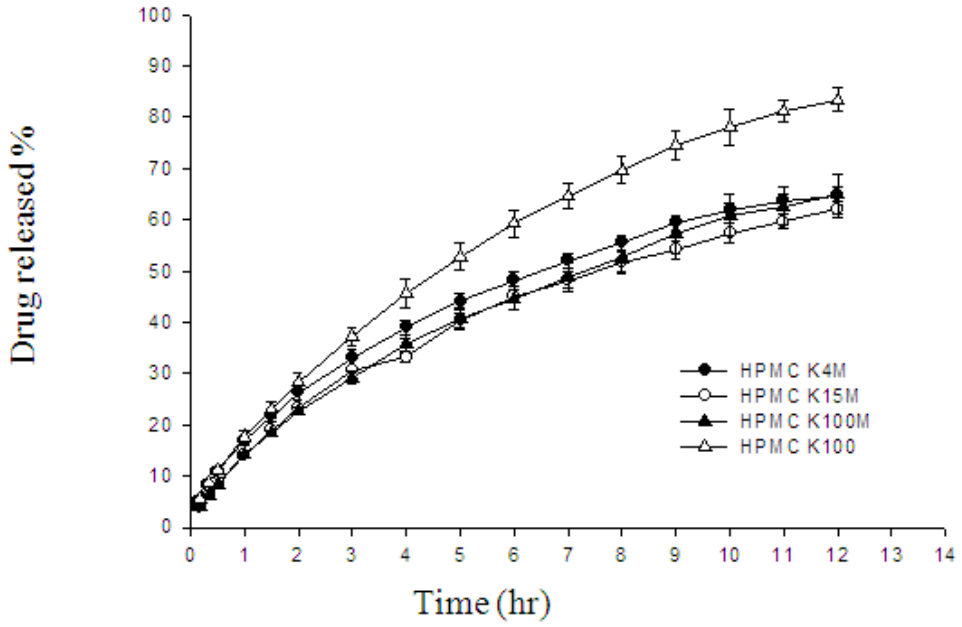

Figure 4. Effect of HPMC viscosity grades on the % release of ticlopidine HCl from tablets (diameter, 12.5 mm) of formulation

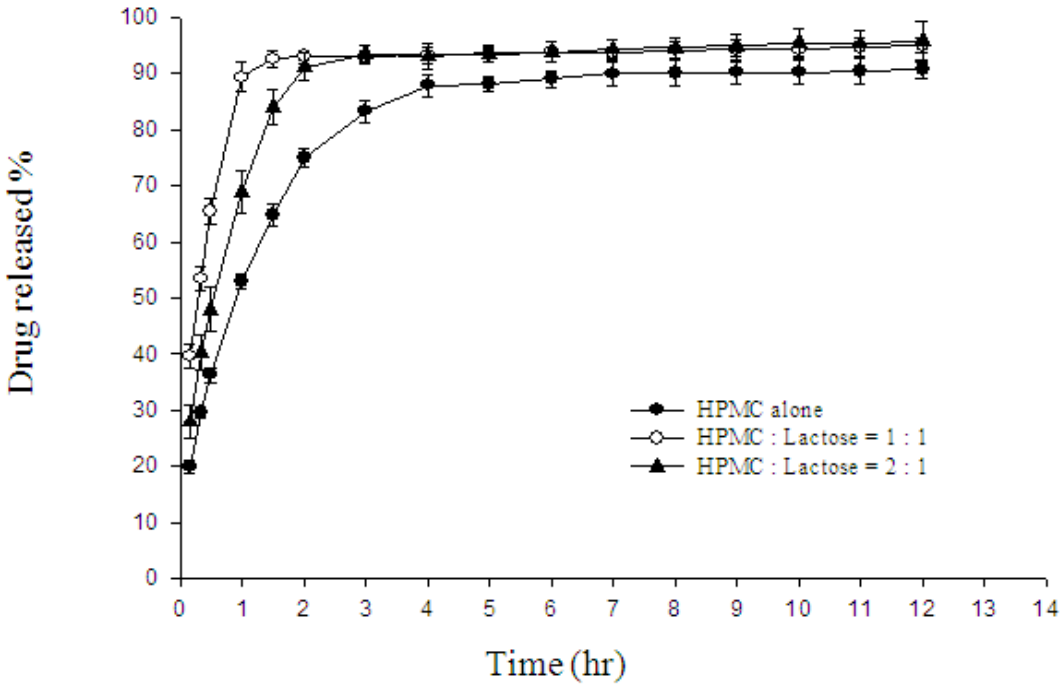

Figure 5. Dissolution profile of ticlopidine HCl tablets (diameter, 7 mm) prepared by HPMC K100

international Journal of Pharmaceutical research and Applications
Volume 6, Issue 6, pp: 434-442 www.ijprajournal.com ISSN: 2456-4494

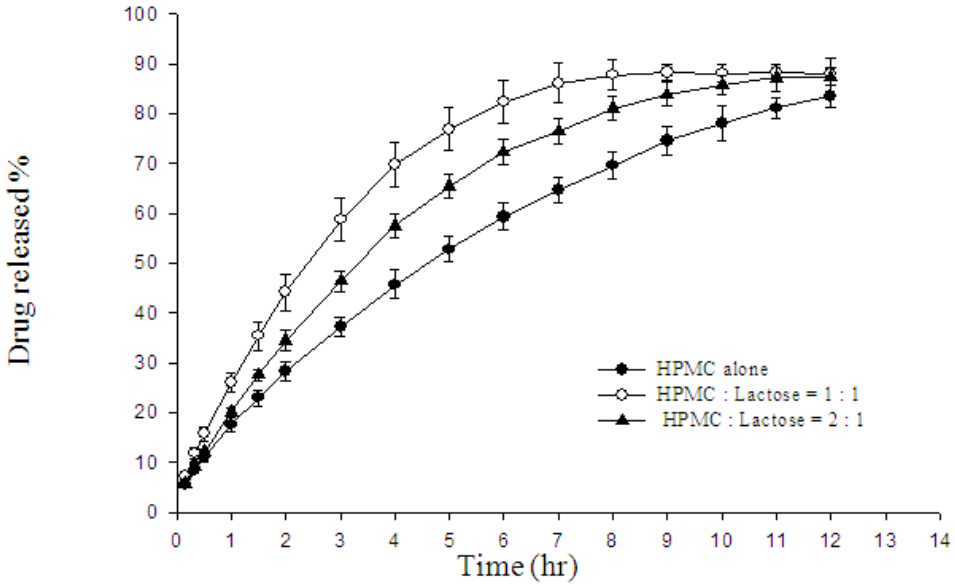

Figure 6. Dissolution profile of ticlopidine HCl tablets (diameter, 12.5 mm) prepared by HPMC K100