In vitro Release Kinetics Study of Ranolazine from Swellable Hydrophilic Matrix Tablets

Mohammad Nezab Uddin, Ishtiaq Ahmed, Monzurul Amin Roni, Muhammad Rashedul Islam, Mohammad Habibur Rahman and Reza-ul Jalil

Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh

ABSTRACT: The objective of this study was to design oral sustained release matrix tablets of Ranolazine using hydroxypropyl methylcellulose (HPMC) as the retardant polymer and to study the effect of formulation factors such as polymer proportion and polymer viscosity on the release of drug. *In vitro* release studies were performed using USP type II apparatus (paddle method) in 900 mL of 0.1N HCl at 100 rpm for 12 hours. The release kinetics was analyzed using the zero-order, first order, Higuchi and Korsmeyer-Peppas equations to explore and explain the mechanism of drug release from the matrix tablets. In vitro release studies revealed that the release rate decreased with increase in polymer proportion and viscosity grade. Mathematical analysis of the release kinetics indicated that the nature of drug release from the matrix tablets was dependent on drug diffusion and polymer relaxation and therefore followed non-Fickian or anomalous release. The developed controlled release matrix tablets of Ranolazine prepared with high viscosity HPMC extended release up to 12 hours.

Key words: Ranolazine, Sustained release, Methocel E50 Premium LV, Methocel K100LV CR, Methocel K4M CR, Methocel K15M CR.

INTRODUCTION

Ranolazine is indicated for the treatment of chronic angina in patients who have not achieved an adequate response with other antianginal drugs. Its novel mechanism of action increases oxygen supply to the myocardium without compromising hemodynamic status[1]. Ranolazine is extensively metabolized in gut and liver and its absorption is highly variable. The apparent terminal half-life of poorly soluble ranolazine is 7 hours. The marketed preparation has 500 mg or 1000 mg active ingredient and administered twice daily.

Correspondence to:
Muhammad Rashedul Islam
E-mail: rashed1505@yahoo.com

Dhaka Univ. J. Pharm. Sci. **8**(1): 31-38, 2009 (June)

Hydroxypropyl methylcellulose (HPMC), a semi synthetic derivative of cellulose, is a swellable and hydrophilic polymer. Some research groups have worked on the usage of swellable HPMC as the retarding polymer to sustain the release of different drugs.[2-4] It is very suitable to use as a retardant material in CR matrix tablets, as it is nontoxic and easy to handle.[5] Matrix tablets prepared using HPMC on contact with aqueous fluids gets hydrated to form a viscous gel layer through which drug will be released by diffusion and/or by erosion of the matrix.[6] The release of the drug from the CR matrices is influenced by various formulation factors, such as polymer viscosity, polymer particle size, drug-to-polymer ratio, drug solubility, drug particle size, compression force, tablet shape, formulation excipients, processing techniques, and dissolution medium.[7,8] The drug release from the polymer matrix

can be due to disentanglement or diffusion, depending on the polymer molecular weight and the thickness of the diffusion boundary layer.[9,10] Polymer dissolution plays an important role in regulating the drug release in the case of lower viscosity grades of HPMC and for relatively water-insoluble drugs.[11]

The purpose of this study was to design oral sustained release tablet formulations of Ranolazine using different viscosity grades of HPMC as the release retarding polymer. The tablets were prepared by wet granulation, and their physical parameters and *in vitro* release characteristics were evaluated. The effect of formulation factors such as polymer proportion and polymer viscosity on the release characteristics was studied in order to optimize these variables.

MATERIALS AND METHODS

Drug: Ranolazine (Ranbaxy, India); **Polymers:** Methocel K4M CR Premium (Dow Chemical, USA), Methocel K15M CR Premium (Dow Chemical Co., USA), Methocel K100LV CR Premium (Dow Chemical Co., USA), Methocel E 50 Premium LV (Dow Chemical Co., USA); **Other excipients:** Lactose (Lactose company New Zealand), Microcrystalline cellulose (Ming Tai Chemical co. Ltd., Taoyuan Hsien, Taiwan), Magnesium Stearate (Dr. Paul Lohmann GmbH KG, Germany), Colloidal Silicon dioxide (Cabot India Ltd, Mumbai). **Reagent:** Hydrochloric Acid (Merck, Germany).

Preparation of dissolution medium. For the preparation of simulated gastric medium (0.1 N HCl, pH 1.3) 11.4 ml of Hydrochloric acid (32% w/v) was diluted with sufficient water to produce 1000 ml.

Preparation of matrix tablets. Active ingredient, lactose, microcrystalline cellulose, and HPMC polymer were passed through No. 40 mesh (Endecotts test sieve, UK) and mixed for 10 minutes properly. Purified water was used as granulating fluid. The wet mass were dried in an oven at 60^0C. Dried granules are sieved through No. 20 mesh SS screen (Endecotts test sieve, UK). Magnesium stearate and colloidal silicon dioxide were passed through No. 60 mesh SS screen (Endecotts test sieve, UK) and added during blending part. Tablets were compressed using rotary tablet compression machine (Manesty D type, 16 stations) with a 19.00 x 8.80 mm concave, plain faced punch and die set using 2.5 ton compression force. Each tablet weighed approximately 1.0 g and the formulations are shown in Table 1. All the preparations were stored in airtight containers at room temperature for further study.

Physical characterization of matrix tablets. Hardness was tested for 10 matrix tablets from each formulation with electronic hardness tester (ERWEKA-TBH 300, Germany) and friability was determined using Roche Friability Tester.

***In vitro* dissolution study.** All dissolution studies were carried out for sustained release Ranolazine formulations using USP dissolution tester (Erweka Model DT-700, Germany). Dissolution studies were conducted in paddle method at 100 rpm for 12 h. The dissolution medium was 0.1 N HCl and the temperature was maintained at 37°c ± 0.5°C. The amount of drug dissolved in the medium was determined by UV spectrophotometer (UV–1601 PC Shimadzu, Japan) at 271 nm.

Characterization of release kinetics. The rate of drug release from the preparation may follow zero order kinetics, first order kinetics[12] or Higuchi's model[13]. To evaluate the mechanism of drug release from the preparation, data of drug release may be plotted in Korsmeyer and Peppas equation[14,15](Equation 1), which is often used to describe the drug release behavior from polymeric systems.

$$\mathrm{Log}\left(\frac{M_t}{M_f}\right) = \mathrm{Log}\, k + n\, \mathrm{Log}\, t \quad \textbf{(1)}$$

Where M_t is the amount of drug release at time t, M_f is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the dosage form, n is the diffusional exponent indicative of the mechanism of drug release[16].

The log value of percent drug dissolved is plotted against log time for each formulation according to the equation. For a cylinder shaped matrix the value of $n \leq 0.45$ indicates Fickian (case I) release; > 0.45 but < 0.89 for non-Fickian (anomalous) release; and > 0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled drug release[17].

Mean Dissolution Time (MDT) can be calculated from dissolution data according to equation 2, where n is the release exponent and k is release rate constant.[18]

$$\mathbf{MDT} = \left(\frac{\mathbf{n}}{\mathbf{n+1}}\right)\mathbf{k}^{-1/\mathbf{n}} \qquad \textbf{(2)}$$

A higher value of MDT indicates a higher drug retaining ability of the polymer and vice-versa.

RESULTS AND DISCUSSION

Physical Characterization of the Designed Tablets. The physical appearance, tablet hardness, and friability of all tablet formulations were found to be satisfactory and reproducible as observed from the data in Table 1. Tablet hardness was found to be good (between 17 and 27 kp) depending on the compression force applied, and friability was less than 0.1% (w/w). According to these parameters wet granulation is an acceptable method for preparing good-quality matrix tablets of Ranolazine.

Release Rate Studies. The kinetic parameters and MDT values for all the formulations are given in Table 2. A plot of cumulative percentage released vs square root of time (SQRT) for matrix-embedded SR tablets of Ranolazine prepared using different proportions of HPMC 50 cps, is shown in Figure 1.

Table 1. Composition of Ranolazine matrix tablets (mg/tablet)

Formulation Code	Methocel E50 (mg)	Methocel K100LV CR (mg)	Methocel K4M CR (mg)	Methocel K15M CR (mg)	Lactose (mg)	Hardness Kp (±S.D.)	Friability (%)
F1	50	-	-	-	250	21.5 ± 0.01	<0.1
F2	100	-	-	-	200	23.4 ± 0.02	<0.1
F3	150	-	-	-	150	24.8 ± 0.02	<0.1
F4	200	-	-	-	100	25.6 ± 0.01	<0.1
F5	250	-	-	-	50	26.7 ± 0.01	<0.1
F6	300	-	-	-	0	27.3 ± 0.02	<0.1
F7	-	50	-	-	250	19.6 ± 0.01	<0.1
F8	-	100	-	-	200	18.2 ± 0.03	<0.1
F9	-	150	-	-	150	17.9 ± 0.01	<0.1
F10	-	200	-	-	100	17.6 ± 0.02	<0.1
F11	-	250	-	-	50	19.5 ± 0.01	<0.1
F12	-	300	-	-	0	20.3 ± 0.01	<0.1
F13	-	-	50	-	250	19.2 ± 0.02	<0.1
F14	-	-	100	-	200	18.2 ± 0.01	<0.1
F15	-	-	150	-	150	18.8 ± 0.01	<0.1
F16	-	-	200	-	100	19.7 ± 0.03	<0.1
F17	-	-	250	-	50	20.5 ± 0.01	<0.1
F18	-	-	300	-	0	20.9 ± 0.02	<0.1
F19	-	-	-	50	250	22.2 ± 0.01	<0.1
F20	-	-	-	100	200	21.9 ± 0.02	<0.1
F21	-	-	-	150	150	22.7 ± 0.01	<0.1
F22	-	-	-	200	100	23.9 ± 0.01	<0.1
F23	-	-	-	250	50	21.4 ± 0.03	<0.1
F24	-	-	-	300	0	23.5 ± 0.02	<0.1

Note: HPMC indicates Hydroxypropyl Methylcellulose. Each tablet contains Ranolazine 500 mg, Microcrystalline cellulose 185 mg, Colloidal silicon dioxide 5 mg, and Magnesium stearate 5 mg per tablet. Total tablet was 1.0 g.

Table 2. Kinetic parameters of Ranolazine matrix tablets.

Formulation code	Zero Order		First Order		Higuchi		Korsmeyer		MDT
	r^2	K_0	r^2	K_1	r^2	K_H	r^2	n	
F1	0.440	4.59	0.685	0.47	0.709	22.50	0.875	0.13	1.17
F2	0.579	5.35	0.910	0.21	0.828	24.72	0.959	0.20	1.68
F3	0.685	5.84	0.802	0.21	0.902	25.88	0.986	0.25	2.18
F4	0.734	6.20	0.924	0.17	0.933	27.03	0.974	0.32	2.51
F5	0.788	6.45	0.919	0.15	0.970	28.65	0.986	0.36	2.88
F6	0.848	6.86	0.849	0.17	0.985	28.55	0.994	0.41	3.23
F7	0.430	4.92	0.976	0.39	0.698	24.20	0.622	0.23	1.57
F8	0.547	5.61	0.725	0.41	0.799	26.18	0.774	0.29	1.95
F9	0.664	6.32	0.951	0.21	0.881	28.14	0.858	0.38	2.45
F10	0.725	6.69	0.976	0.14	0.915	29.02	0.888	0.45	2.87
F11	0.765	6.83	0.928	0.11	0.932	29.14	0.919	0.49	3.27
F12	0.780	6.81	0.933	0.10	0.938	28.84	0.927	0.51	3.48
F13	0.858	7.27	0.983	0.15	0.979	29.99	0.977	0.49	3.41
F14	0.858	7.23	0.998	0.12	0.975	29.80	0.968	0.55	3.73
F15	0.875	7.21	0.980	0.10	0.975	29.42	0.971	0.59	4.10
F16	0.936	6.87	0.991	0.08	0.993	27.34	0.995	0.60	4.96
F17	0.957	6.39	0.992	0.06	0.992	25.12	0.998	0.61	6.01
F18	0.958	5.41	0.994	0.05	0.991	21.27	0.990	0.57	7.93
F19	0.898	7.27	0.918	0.17	0.994	29.54	0.993	0.46	3.55
F20	0.933	7.29	0.961	0.11	0.996	29.11	0.996	0.57	4.37
F21	0.950	7.36	0.964	0.10	0.992	29.05	0.996	0.61	4.69
F22	0.949	6.76	0.981	0.07	0.991	26.70	0.995	0.61	5.38
F23	0.954	5.96	0.994	0.05	0.994	23.49	0.995	0.57	6.62
F24	0.961	5.64	0.994	0.05	0.990	22.11	0.991	0.59	7.51

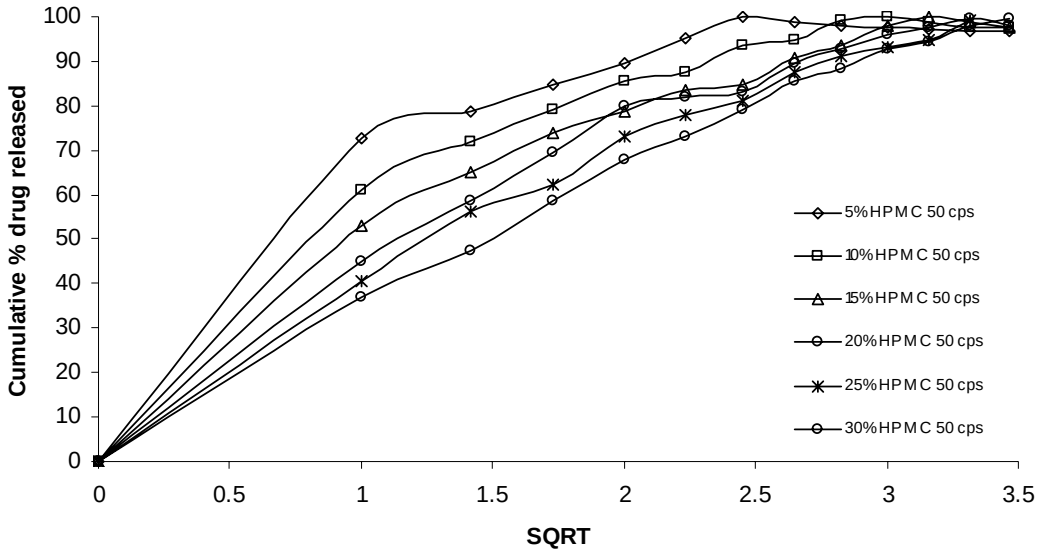

Figure 1. Higuchi plot of Ranolazine sustained release matrix tablets prepared using different proportions of hydroxypropyl methylcellulose 50 cps. Each data point represents the average of 3 tablets

The initial burst release in the first hour was followed by more controlled release in next 4-5 hours. Ultimately most of the drug was released within 5-6 hours from all formulations indicating Methocel E50 (HPMC 50 cps) is not appropriate as sustained release polymer. Drug release for the first hour varied between 37% and 72% for all the formulations containing Methocel E 50. However, in the later

stages, the release was found to be slower and more controlled in the tablets with a higher proportion of the polymer. The release of the drug from the tablets extended as the polymer proportion was increased from 5 to 30%. The MDT values increased from 1.17 hours to 3.23 hours as the polymer proportion was increased from 5 to 30%.

A plot of cumulative percentage released vs. square root of time (SQRT) for matrix-embedded SR tablets of Ranolazine prepared using different proportions of Methocel K100LV CR is shown in Figure 2. In the case of Methocel K 100 LVCR, the initial release for the first hour varied between 26 to 47% depending on the polymer proportion, but the release was found to be more controlled in the later stage in the matrix tablets with a higher proportion of the polymer. The MDT values increased significantly from 1.57 hours to 3.48 hours as the polymer proportion was increased from 5 to 30%.

A plot of cumulative percentage released vs. square root of time (SQRT) for matrix-embedded SR tablets of Ranolazine prepared using different proportions of Methocel K4M CR is shown in Figure 3. In the case of Methocel K4M CR, the initial release for the first hour varied between 19 to 32%, depending on the polymer proportion, but the release was found to be more controlled in the later stages in the tablets with a higher proportion of the polymer. The MDT values increased significantly from 3.41 hours to 7.93 hours.

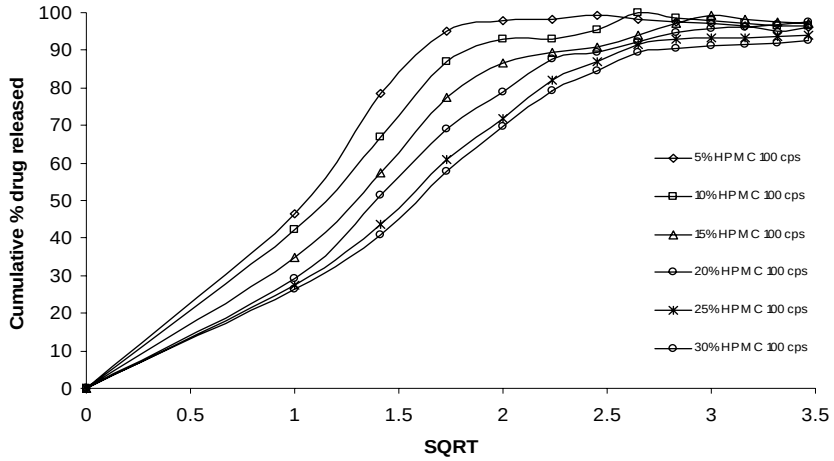

Figure 2. Higuchi plot of Ranolazine sustained release matrix tablets prepared using different proportions of hydroxypropyl methylcellulose 100 cps. Each data point represents the average of 3 tablets

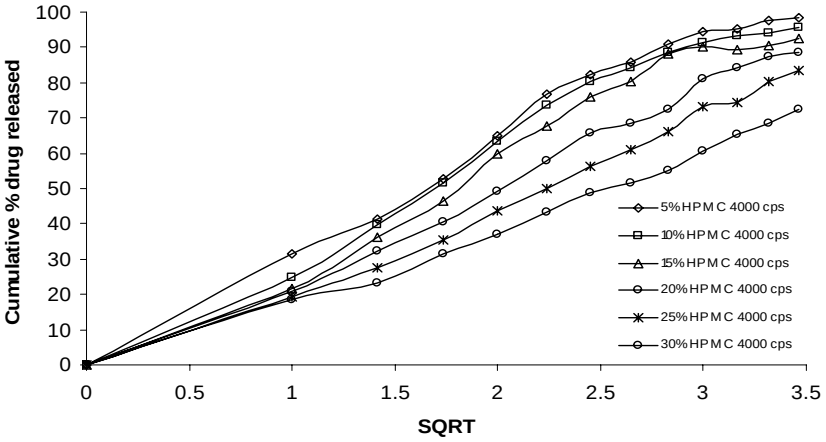

Figure 3. Higuchi plot of Ranolazine sustained release matrix tablets prepared using different proportions of hydroxypropyl methylcellulose 4000 cps. Each data point represents the average of 3 tablets

A plot of cumulative percentage released vs. Square root of time (SQRT) for matrix-embedded SR tablets of Ranolazine prepared using different proportions of Methocel K15M CR is shown in Figure 4. In the case of Methocel K4M CR, the initial release for the first hour varied between 18 to 34%, depending on the polymer proportion, but the release was found to be more controlled in the later stages in the tablets with a higher proportion of the polymer. The MDT values increased significantly from 3.55 hours to 7.51 hours.

The release rate of the drug from the matrix tablets decreased with an increase in polymer proportion because of an increase in the gel strength as well as formation of a gel layer with a large diffusional path. This could have caused a decrease in the effective diffusion coefficient of the drug and therefore a reduction in the drug release rate.[19]

The n values for all the formulations containing Methocel K4M CR and Methocel K15M CR ranged from 0.49 to 0.61 and 0.46 to 0.61 respectively, indicating that the release mechanism was Non-Fickian or anomalous release ($0.45 < n < 0.89$). The n values for formulations containing Methocel K100LV CR at polymer proportion 20, 25 and 30% were o.45, 0.49 and 0.51 respectively which again indicative of Non-Fickian release. It can be inferred that the release was dependent on both drug diffusion and polymer relaxation in case of formulations containing Methocel K4M CR (F13, F14, F15, F16, F17 and F18), Methocel K15M CR (F19, F20, F21, F22, F23 and F24) and Methocel K100LV CR (F10 , F11 and F12). n values for formulations containing lower Methocel K100LV CR proportion (F7,F8 and F9) ranged from 0.23 to 0.38, indicating that the release mechanism was dominated by Fickian diffusion phenomenon. n values for all the formulations containing Methocel E 50 ranged from 0.13 to 0.41 indicating that the release mechanism was dominated by Fickian diffusion phenomenon.

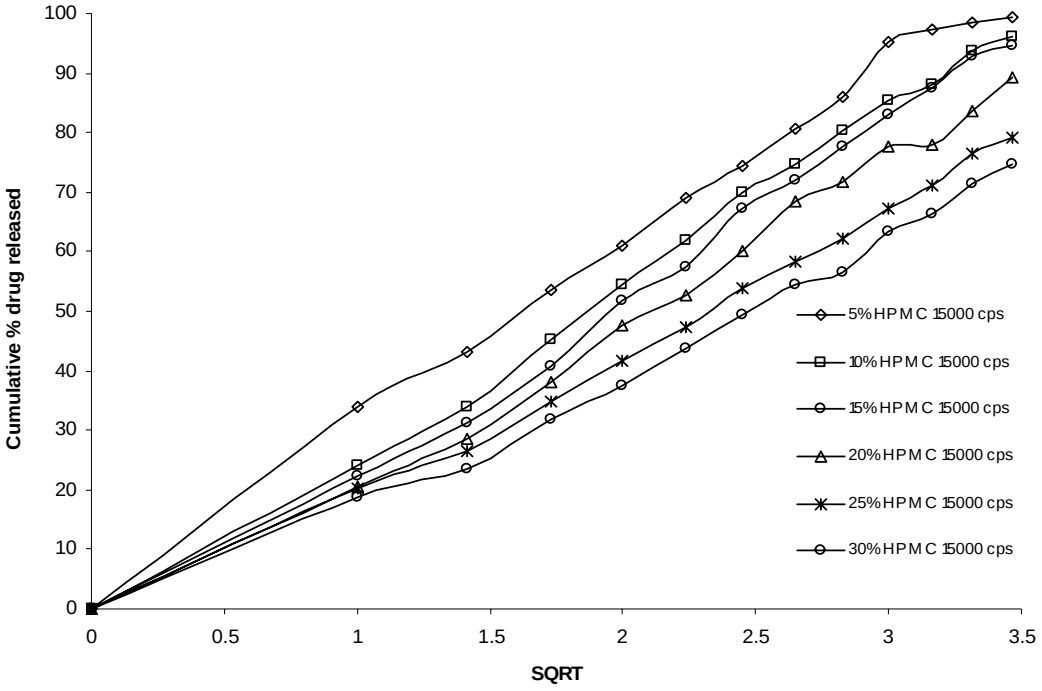

Figure 4. Higuchi plot of Ranolazine sustained release matrix tablets prepared using different proportions of hydroxypropyl methylcellulose 15000 cps. Each data point represents the average of 3 tablets

Because the values of n were close to 0.50 in most cases good correlation coefficients (r^2 values ranged from 0.975 to 0.996) were obtained for the kinetic parameters based on Higuchi's Square-Root

equation for matrix tablets containing Methocel K 4M and Methocel K 15 M. But it can not be concluded that the drug release was totally based on diffusion, which generally is the case in Higuchi's Square-Root kinetics. It was observed that the matrix tablets undergo swelling and erosion during the dissolution studies which indicated that polymer relaxation had a role in the drug release mechanism. However, it can be concluded that the effect of diffusion on drug release was more than the effect of polymer relaxation as the values of n were nearer to 0.5.

CONCLUSION

Sustained release matrix tablets of Ranolazine were prepared using four different grades of cellulose derivative- Methocel E 50, Methocel K100LV CR, Methocel K4M CR and Methocel K15M CR. Variation of polymer amount and viscosity grade significantly affected drug release from prepared matrix tablets. Higher amount of polymer decreased drug release rate and extent irrespective of its type. Release rate of the drug from the matrix tablets was significantly influenced by the proportion as well as viscosity of HPMC used. The release was dependent on drug diffusion and polymer relaxation in case of formulations containing Methocel K4M CR (F13, F14, F15, F16, F17, F18), Methocel K15M CR (F19, F20, F21, F22, F23, F24) and higher proportion of Methocel K100LV CR (F10, F11, F12). Formulations containing Methocel E 50 (F1, F2, F3, F4, F5, F6) and lower proportion of Methocel K100LV CR (F10, F11 and F12) indicating that the release mechanism was dominated by Fickian diffusion phenomenon. In case of Methocel K100 LV CR, increase in the polymer proportion caused increasing of release exponent (n) indicating the shifting of release mechanism from Fickian to Non-Fickian direction. Extensive *in vitro-in vivo* correlation studies on similar formulations are essential to establish a successful formulation from the biopharmaceutical viewpoint.

ACKNOWLEDGEMENT

The authors are thankful to Eskayef Bangladesh Ltd. for providing raw materials, reagents and equipments required for the experiment.

REFERENCES

1. Anderson, J.R., Nawarskas, J. and Ranolazine, J. 2005. A Metabolic Modulator for the Treatment of Chronic Stable Angina Cardiology in Review. **13**, 202-210.
2. Bravo, S.A., Lamas, M.C. and Salomon, C.J. 2004. Swellable matrices for the controlled-release of diclofenac sodium: formulation and in vitro studies. *Pharm Dev Technol.* **9**, 75-83.
3. Velasco, M.V., Ford, J.L., Rowe, P., Rajabi-Siahboomi, A.R. 1999. Influence of drug: hydroxypropyl methylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC matrices. *J. Control Release.* **57**: 75-85.
4. Heng, P.W.S., Chan, L.W., Easterbrook, M.G. and Li, X. 2001. Investigation of the influence of mean HPMC particle size and number of polymer particles on the release of aspirin from swellable hydrophilic matrix tablets. *J. Control Release*. **76**, 39-49.
5. Lee, B.J., Ryu, S.G. and Cui, J.H. 1999. Formulation and release characteristics of hydroxypropyl methylcellulose matrix tablet containing melatonin. *Drug Dev Ind Pharm*. **25**, 493-501.
6. Katzhendler, I., Mader, K. and Friedman, M. 2000. Structure and hydration properties of hydroxypropyl methylcellulose matrices containing naproxen and naproxen sodium. *Int J. Pharm*. **200**, 161-179.
7. Velasco, M.V., Ford, J.L., Rowe, P. and Rajabi-Siahboomi, A.R. 1999. Influence of drug: hydroxypropyl methylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC matrices. *J. Control Release*. **57**, 75-85.
8. Tapia-Albarran, M. and Villafuerte-Robles, L. 2004. Effect of formulation and process variables on the release behavior of amoxicillin matrix tablets. *Drug Dev Ind Pharm.* **30,** 901-908.
9. Narasimhan, B. and Peppas, N.A. 1996. Disentanglement and repetition during dissolution of rubbery polymers. *J. Polym. Sci. Part B: Polym Phys.* **34**, 947-961.
10. Narasimhan, B. and Peppas, N.A. 1997. Molecular analysis of drug delivery systems controlled by dissolution of the polymer carrier. *J. Pharm. Sci*. **86**, 297-304.
11. 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 of drugs from hydrophilic matrices. *Drug Dev. Ind. Pharm.* **8**, 1355-1375.

12. Wagner, j.G. 1969. Interpretation of percent dissolved –time plots derived from in vitro testing of the conventional tablets and capsules. *J. Pharm. Sci.* **58**, 1253-1257.

13. Higuchi, T. 1961. Rate of release of medicaments from ointment bases containing drugs in suspension. *J. Pharm. Sci.* **50**, 874-875

14. Peppas, N.A. 1985. Analysis of Fickian and non-Fickian drug release from polymers. *Pharm. Acta. Helv.* **60**, 110-111.

15. Harland, R.S., Gazzaniga, A., Sangalli, M.E., Colombo, P. and Peppas, N.A. 1988. Drug/polymer matrix swelling and dissolution. *Pharm. Res.* **5**, 488-494.

16. Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P. and Peppas, N.A. 1983. Mechanisms of solute release from porous hydrophilic polymers. *Int. J. Pharm.* **15**, 25-35.

17. Siepmann, J. and Peppas, N.A. 2001. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). *Adv. Drug Deliv. Rev.* **48**, 139-157.

18. Mockel, J.E. and Lippold, B.C 1993. Zero order release from hydrocolloid matrices.*Pharm. Res.* **10**, 1066-1070.

19. Katzhendler I, Mader K. and Friedman M. 2000. Structure and hydration properties of hydroxypropyl methylcellulose matrices containing naproxen and naproxen sodium. Int. J. Pharm. **200**, 161-179.