Pak. J. Pharm. 20-23 (1 & 2)
23-29, 2007-2010

ISSN: 1019-956X

FORMULATION AND *IN-VITRO* EVALUATION OF FLURBIPROFEN CONTROLLED RELEASE MATRIX TABLETS USING CELLULOSE DERIVATIVE POLYMERS

Muhammad Akhlaq*, Gul Majid Khan, Abdul Wahab, Abid Hussain, Arshad Khan, Asif Nawaz and Kifayat Ullah Shah

Faculty of Pharmacy, Gomal University, Dera Ismail Khan, Pakistan

ABSTRACT

The study aims to design once-daily controlled release hydrophilic hydrophobic matrix tablets of flurbiprofen with cellulose derivative polymers using direct compression technique. Preformulation factors including bulk density, tapped density, Hausner's factor, angle of repose and compressibility index were evaluated for flurbiprofen powder drug and physical mixtures. Tablets were compressed using a single punch machine and various physical parameters were tested including hardness, friability, weight variation, content uniformity, thickness and diameter. All of the tests for starting material fell in the acceptable British Pharmacopoeial limits. *In-vitro* release study was conducted in phosphate buffer solution, pH 7.4 and different kinetics parameters were applied on dissolution data. Dissolution study showed a controlled release profile for formulations F-1 and F-2, containing ethylcellulose and hydroxypropylmethylcellulose and released 98.29 and 97.49% drug after 12 and 18 hrs, respectively. The release exponent, "n" for F-1 and F-2 indicated an anomalous release behavior with the values 0.599 and 0.776 and the linearity of 0.986 and 0.971, respectively.

Keywords: Flurbiprofen, Cellulose derivative polymer, *In-vitro* release kinetics, Controlled release

INTRODUCTION

Matrix tablet is a unit dosage form that contains hydrophilic or hydrophobic polymers, uniformly mixed with a selected model drug and other excipients such as matrix forming agent, filler, binder and lubricant (Siepmann and Peppas, 2001; Tiwari *et al.,* 2003). While manufacturing such type of systems, a selected drug is properly distributed and embedded throughout the polymer matrix. The designed matrix can then be compressed into tablets and subjected to release studies (Abdelbary and Tadros, 2008).

It could be observed that when a controlled release anti-inflammatory tablet is ingested, the drug is released slowly as a result of slow drug dissolution, and swelling and erosion of the polymer matrix (Bravo *et al.,* 2002; Bravo *et al.,* 2004). A desired plasma profile can generally be achieved by using different release controlling polymers such as ethylcellulose, hydoxypropylmethylcellulose, etc. Usually free drug is released promptly and serves as the loading dose. The entrapped drug is released gradually over a certain period of time providing a constant plasma level of therapeutic entity (Roy and Shahiwala, 2009).

Hydrophilic and hydrophobic cellulose polymers such as hydroxylpropylmethyl cellulose, carboxymethylcellulose (Khan and Jiabi, 1998) and ethylcellulose ether derivative polymers (Crowley *et al.,* 2004) are commonly used in the pharmaceutical industries to design and formulate controlled release matrix tablets. Drug release is governed by the rate of hydration and water penetration into the matrix, polymer solubility and erosion, the porosity of the matrix (how deeply the water penetrates) and the solubility of the drug (amount of water needed to release the drug) (Sinha Roy and Rohera, 2002). Now-a-days there is an increased

***Corresponding author's Address:** Muhammad Akhlaq, Faculty of Pharmacy, Gomal University, D.I Khan (Pakistan), Email: akhlaqhayat@hotmail.com

awareness of the potential relevance of modified-release matrix of sparingly soluble drugs such as flurbiprofen. These can be prepared by mixing the drug with hydrophobic polymer. These hydrophobic matrices help to slow the rate of drug dissolution and hence, prolong its release (Streubel *et al.,* 2000; Khan, 2001). These systems may either be hydrophilic or hydrophobic depending upon the drug carriers. Role of ethylcellulose ether derivative polymer has been evaluated by Katikaneni (Katikaneni *et al.,* 1995), to control the release of pseudophenadrine from the matrix tablets. Direct compression was found to be the best method to sustain the release rate effectively over a period of 10 hours (Varshosaz *et al.,* 2006). The study aims to design, evaluate and formulate once-daily flurbiprofen controlled release matrix tablets by direct compression technique.

MATERIALS AND METHODS

Materials

Flurbiprofen was received as a gift from Abbott Laboratories, Pakistan. Monobasic potassium phosphate, carboxymethylcellulose (CMC), starch and sodium hydroxide (NaOH) (E. Merck, Germany) were received as gift from Wilshire Pharmaceutical, Lahore. Lactose, magnesium stearate (BDH Chemical Ltd, Pool England), were purchased from Sohail chemical, Rawalpindi, Pakistan. Ethocel (ethylcellulose ether derivative polymer) and hydroxyl propylmethyl cellulose (HPMC) were purchased from Dow Chemicals (Dow Chemical Co., Midland USA). All chemicals used were of analytical grade.

Preformulation studies

The pure drug and physical mixtures were subjected to prefolurmlation studies. The following parameters were evaluated.

Poured bulk density

Bulk density was determined by the following formula (Abdelkader *et al.,* 2008).

$$\text{Tapped Density} = \frac{W_s}{V_s} \qquad \text{Equation 1}$$

Where W_s is sample weight and V_s is the initial volume of powder before tapping.

Tapped density

Tap density is the indirect measurement of flow, mixing and tabletting properties of powder. It was calculated by using 10 ml measuring cylinder with 100 tapings, sufficient to bring plateau condition (Abdelkader *et al.,* 2008). Tapped density was calculated using the Equation 1 but replacing V_s as the volume of samples after 100 tapings.

Hausner's ratio

Hausner's ratio is called as index of flowability and is calculated by Equation 2 (Abdelkader *et al.,* 2007).

$$\text{Tapped Density} = \frac{V_1}{V_2} \qquad \text{Equation 2}$$

Where V_1 is the volume before taping and V_2 is the volume after tapping.

Loss on drying (LOD)

A porcelain dish was heated in an oven at 60°C for half an hour. It was then cooled in a desiccator. One gram of flurbiprofen was accurately weighed, taken in pre-heated and cooled porcelain dish and was heated in oven at 60°C for 3 hours, at a pressure not more than 7 kPa. After a specified period of time the drug was reweighed and LOD was calculated as mass percentage (Abdelkader *et al.,* 2007).

Angle of repose

Angle of repose of powder drug was determined by fixed funnel and cone method. A petri dish was taken and its diameter was determined. A funnel was fixed above the petri dish and 4 g of flurbiprofen was poured from funnel with its tip at 2 cm height 'H' until the apex of the heap formed reached the lower end of the funnel. The mean diameter, 2R, of the base for the powder cone was measured and the angle of repose was calculated by Equation 3 (Lee and Herman, 1993).

$$\text{Tan}\theta = \frac{H}{R} \qquad \text{Equation 3}$$

Where H is the height of the cone and R is the radius of the cone base.

Compressibility index

Compressibility index of drug powder was determined by Carr's compressibility percentage as given in Equation 4 (Lachman *et al.,* 1987).

$$\text{Compressiility}\,\% = \left[\frac{D_f - D_i}{D_f}\right] \times 100 \qquad \text{Equation 4}$$

Where D_f is the tape bulk density and D_i is the fluff bulk density.

Preparation of matrix tablets

Tablets containing fixed amount of 100mg of flurbiprofen were prepared by direct compression and wet granulation methods with varied composition of polymers and excipients as given in Table I. The powder was sieved through sieve, mesh # 40. The drug and the required amounts of excipients were mixed thoroughly and compressed directly (Avachat and Kotwal, 2007), using single punch applying 450 kg force for about 2 seconds (Katikaneni *et al.,* 1995, Khan and Zhu, 1998).

Table I: Compositions of 100 mg flurbiprofen matrix tablets

Formulation	Ethylcellulose	Lactose	Mg stearate	HPMC	Starch	CMC
F-1	20	79	1	--	--	--
F-2	20	55.3	1	23.7	--	--
F-3	20	55.3	1	--	23.7	--
F-4	20	55.3	1	--	--	23.7

Physical characteristics of matrix tablets

Thickness and diameter

The thickness and diameter of the tablets were determined by using vernier caliper (123M-150), presented in millimeters with their mean and standard deviation SD.

Hardness

The hardness of the tablets was determined by using tablet hardness tester (Erweka, Germany) and was reported in Kg/cm^3.

Weight variation

Ten (10) tablets were used to study weight variation of flurbibrofen tablets using Electronic Balance Model No, AX-200 (Shimadzu, Japan) and the values were given in milligrams with their mean and standard deviation SD.

Friability test

For each formulation 10 tablets were weighed, placed in Friabilator (Erweka, Germany) and were subjected to 100 rotations in 4 minutes. The tablets were re-weighed and friability was calculated, using Equation 5 along with mean and the standard deviation SD.

$$\text{Friability} = \frac{W_1 - W_2}{W_1} \times 100 \quad \text{Equation 5}$$

Where W_1 is the initial weight and W_2 is the final weight of the tablets.

Content uniformity test

From the randomly selected 30 tablets of each formulation, 10 tablets were assayed individually. All of the tested tablets contained more than 99% of active flurbibrofen. In order to determine the drug content collectively, three tablets of each formulation were crushed. Powder equivalent to 100 mg of the drug was dissolved in phosphate buffer, pH 7.4, and was analyzed spectrophotometrically at 247 nm after sufficient dilution with the respective solvent of phosphate buffer solution pH 7.4.

***In-vitro* drug release study**

Drug release study was performed according to USP method. Each vessel was filled with dissolution medium (up to 900 ml), 0.2 M phosphate buffer solution, pH 7.4 maintained at 37 ± 0.1°C and stirred at 100 rpm (perfect sink conditions). Tablets were placed in different baskets. At predetermined time intervals of 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 18.0 and 24.0 hrs, a 5 ml sample was taken with syringe using 0.45 μm filter and was replaced with the fresh medium. Samples were analyzed at 247 nm, using UV- visible spectrophotometer UV-1601 (Shimadzu, Japan). Mean release of three tablets was used to evaluate the drug release for each of the formulations (Velasco *et al.,* 1999).

Drug release kinetics

To interpret the drug release rate from matrix tablets, the data obtained from *in-vitro* drug release studies was plotted in various kinetics models as given in Equations 6-10).

$$\text{Zero-order, } W = k_1 t \quad \text{(Equation 6)}$$

Where k_1 is the zero-order rate constant expressed in the units of concentration/time and " t " is the time in hours.

$$\text{First order, } \ln(100 - W) = \ln 100 - k_2 t \quad \text{(Equation 7)}$$

Where k_2 is the first order constant and ln 100 is the initial drug concentration.

Hixson Crowell's or erosion model,

$$(100 - W)^{1/3} = 100^{1/3} - k_3 t \quad \text{(Equation 8)}$$

Where k_3 is the rate constant for Hixson Crowell's equation, $(100\text{-}W)^{1/3}$is the initial concentration while $100^{1/3}$ is the amount of drug released in time t.

$$\text{Higuchi's model, } W = k_4 t^{1/2} \quad \text{(Equation 9)}$$

Where k_4 reflects the design variable of the system and is constant while t is the time in hours.

$$\text{Korsmeyer-Pappas equation, } \frac{M_t}{M_\infty} = k_5 t^n \quad \text{(Equation 10)}$$

Where $\frac{M_t}{M_\infty}$ is the fractional solute release, k_5 is the power law constant of drug-polymer system and n is an exponent that indicates drug release mechanism from the polymer matrix.

RESULTS AND DISCUSSION

Physical characteristics of starting material

The preformulation factors, including bulk density, tapped density, Hausner's ratio, angle of repose and compressibility index, were studied to evaluate the flowability and compressibility of powder formulations (El-Kamel, 2008, Taylor *et al.,* 2000). Table II shows the physical characteristics of the raw flurbibrofen powder and starting materials. The bulk and tapped density of the drug powder ranged from 0.346 to 0.381 and 0.347 to 0.921, respectively, indicating that there is no conclusive effect of physical mixing upon the particle size and mixing of the drug powder with excipients. Tapped density for powder drug was improved after the addition of excipients and fell in the USP acceptable limit, which might be resulted in uniform physical mixture with better flowability and compressibility.

Hausner's factor for flubibrofen powder was found to be 2.630 which might be contributed to its poor flow properties because of interparticular friction in powder, while Hausner's factor for the physical mixtures ranged from 1.017 to 1.035, indicating good flow properties of powder mixture with reduced friction. Angle of repose was measured as 32.64° for drug powder and for physical mixtures was found to be ranging from 21° to 26° indicating fair flow properties of the physical mixtures.

The functional force between the particles in loose powder was acceptable but the addition of polymer and excipients improved powder flow properties and reduced the cohesive force among the particles up to negligible extent during compression (Sharma, 2008). Percent compressibility indicates the indirect measurement of flow property, bulk density, size and shape, moisture content and surface area. Percent compressibility of flurbibrofen powder was calculated by Equation 5 and was found to be 48.72% which was in close agreement with angle repose, while that for physical mixtures ranged from 17.21-19.32%, indicating improved compressibility and flowability of physical mixtures (Lachman *et al.,* 1987).

Physical characteristics of tablets

Physical characteristics, including hardness, friability, weight variation, % drug content, thickness and diameter of flurbiprofen matrix tablets are given in the Table III. Hardness of the tablets ranged from 6.4 ± 0.40 kg/cm^3 to 6.9 ± 0.42 kg/cm^3, which was suitable to reduce the tendency of tablet capping. Friability was found to be in acceptable range of 0.32 ± 0.09 to 0.87 ± 0.05 w/w. Weight variation test showed that all of the tablets were in the acceptable range of 201 ± 0.8 to 203 ± 0.8mg. Content uniformity test fell in the best suitable range of 99.10 ± 0.04% to 99.70 ± 0.34% for 100 mg flurbiprofen tablets, whereas the drug content for pure drug showed 99.0 ± 0.01% of drug purity. Thickness and diameter affect the internal stress of the tablet and are counted in drug handling. Thickness and diameter ranged from 2.1 ± 0.5 mm to 2.2± 0.5 mm and 4.2 ± 0.2 mm to 4.4 ± 0.10mm and were found to be in acceptable USP range.

Table II: Physical characteristics of starting material and granules

Formulation	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Hausner Factor	Angle of repose (θ)	Compressibility (%)
Pure Drug	0.351	0.921	2.630	32.64	48.72
F-1	0.346	0.352	1.017	21	17.21
F-2	0.373	0.385	1.032	25	19.32
F-3	0.335	0.347	1.035	26	15.28
F-4	0.381	0.394	1.034	22	18.15

Table III: Hardness, Friability, Weight variation, Drug content Thickness and Diameter of the prepared tablets, expressed as Mean ± SD

Formulation	Hardness (kg/cm^3)	Friability (%)	Weight variation (mg)	Drug content (%)	Thickness (mm)	Diameter (mm)
F-1	6.7 ± 0.25	0.72 ± 0.08	201 ± 0.7	99.10 ± 0.08	2.2 ± 0.3	4.4 ± 0.2
F-2	6.9 ± 0.42	0.32 ± 0.09	202 ± 0.8	99.10 ± 0.04	2.2 ± 0.5	4.4 ± 0.1
F-3	6.8 ± 0.38	0.87 ± 0.05	203 ± 0.8	99.70 ± 0.34	2.2 ± 0.4	4.2 ± 0.2
F-4	6.4 ± 0.40	0.77 ± 0.04	201 ± 1.2	99.90 ± 0.10	2.1 ± 0.5	4.3 ± 0.0

Dissolution studies

Figure 1, shows that F-1 containing only ethylcellulose polymer released 98.29% of drug after 12 hrs, indicating that ethycellolse polymer released the drug in a well-controlled manner. Ethylcellulose polymer particles might contribute to the increased compressibility and produce more uniform matrices with uniform channels for water to diffuse and to dissolve the drug in a controlled manner (Katikaneni *et al.,* 1995). F-2, the HPMC-based matrices released 97.49% of drug after 18 hours. It has been observed that small quantities of HPMC can act as channeling agent, and can enhance the release rates (Velasco *et al.,* 1999; Maggi *et al.,* 2000). F-3, starch-based tablets released 98.43% of drug after 4 hrs. Polyvalent cations of starch might swell in water by about 5-10% at 37°C and because of this characteristic it might break up the polymeric membrane, hence released maximum amount of the drug from matrices (Visavarungroj and Remon, 1990). F-4, CMC-based matrices released 99.30% after 2 hrs. it could be

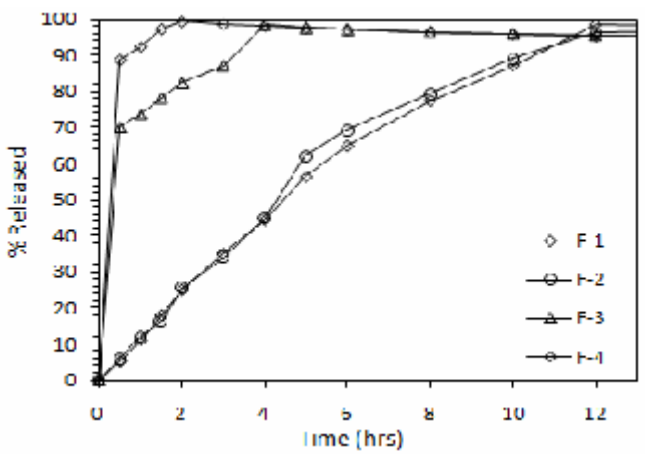

Figure 1: Comparative percent release of flurbibrofen from different matrix tablet formulations

observed that CMC-based matrices markedly increased the release rate, because of the disintegration and swellability character of CMC, it might be contributed to this effect (Khan and Rhodes, 1975; Khan and Jiabi, 1998).

Release kinetics

Flurbibrofen release data was evaluated by zero-order, first-order and Higuchi models. As the dissolution of controlled release matrix tablets followed the anomalous release behavior (combination of diffusion and erosion), hence the Higuchi model failed to explain the release mechanism. Therefore, Korsmeyer equation was applied to the dissolution data, which is used to describe anomalous the release behavior from the matrix tablets (Abdelkader *et al.,* 2007). Korsmeyer model describes the release of the drug from matrices, while "n" is the release exponent that characterizes the release mechanism of the drug from the tablets. When n = 0.45, the release is Fickian and non-Fickian when $0.45 \leq n \leq 0.89$. While 0.98 value of "n" exponent indicates typical zero-order release (Hamid *et al.,* 2006). The release data was fitted to Equation 10, and the findings are shown in the Table IV. Release exponent "n" for F-1 0.599 followed by the best linearity $r^2 = 0.986$, indicated anomalous release behavior coupled with diffusion and erosion. F-2, formulated with ethycellulose and HPMC polymers produced the release exponent as 0.776, indicating anomalous release. All the matrix tablets were observed to be remained intact during the dissolution. F-3 and F-4, starch and CMC based formulations disintegrated rapidly and gave the release exponents of 0.036 and 0.007, respectively, as shown in the Table IV (Dabbagh *et al.,* 1996).

CONCLUSION

Ethylcellulose ether derivative polymer was effective release controlling polymer for flurbiprofen matrix tablet. HPMC also retarded the release rate of drug when combined with ethycellulose. In future, we intend to investigate the *in-vivo* behavior of the formulation in animals.

Table IV: Release kinetics of various formulations.

Formulation	**$W = k_1 t$**	**$(100-w) = \ln 100 - k_2 t$**	**$(100-w)^{1/3} = 100^{1/3} - k_3 t$**	**$W = k_4 t^{1/2}$**	**$(M_t/M_\infty = k_5 t^n)$**
	K_1±SD	**r^1**	**k_2±SD**	**r^2**	**k_3±SD**
F-1	8.096±0.395	0.909	0.258±0.005	0.820	0.298±0.036
F-2	8.055±0.366	0.962	0.185±0.045	0.835	0.219±0.019
F-3	3.778±2.658	0.182	1.031±0.552	0.029	1.045±0.565
F-4	1.487±4.278	0.024	1.295±0.738	0.013	1.226±0. 693

REFERENCES

Abdelbary, G.A. and Tadros, M.I. (2008). Design and *in vitro*/*in vivo* evaluation of novel nicorandil extended release matrix tablets based on hydrophilic interpolymer complexes and a hydrophobic waxy polymer. *European Journal of Pharmaceutics and Biopharmaceutics*. 69, 1019-1028.

Abdelkader, H., Abdalla, O. and Salem, H. (2007). Formulation of controlled-release baclofen matrix tablets: Influence of some hydrophilic polymers on the release rate and in vitro evaluation. *AAPS PharmSciTech*. 8, 156-166.

Abdelkader, H., Abdalla, Y.O. and Salem, H. (2008). Formulation of controlled-release baclofen matrix tablets II: Influence of some hydrophobic excipients on the release rate and in vitro evaluation. *AAPS PharmSciTech*. 9, 675-683.

Avachat, A. and Kotwal, V. (2007). Design and evaluation of matrix-based controlled release tablets of diclofenac sodium and chondroitin sulphate. *AAPS PharmSciTech*, 8, 51-56.

Bravo, S.A., Lamas, M.C. and Salomón, C.J. (2002). *In-vitro* studies of diclofenac sodium controlled-release from biopolymeric hydrophilic matrices. *Journal of Pharmacy and Pharmaceutical Sciences.* 5, 213-219.

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. *Pharmaceutical Development and Technology*. 9, 75-83.

Crowley, M.M., Schroeder, B., Fredersdorf, A., Obara, S., Talarico, M., Kucera, S. and Mcginity, J.W. (2004). Physicochemical properties and mechanism of drug release from ethyl cellulose matrix tablets prepared by direct compression and hot-melt extrusion. *International Journal of Pharmaceutics*. 269, 509-522.

Dabbagh, M.A., Ford, J.L., Rubinstein, M.H. and Hogan, J.E. (1996). Effects of polymer particle size, compaction pressure and hydrophilic polymers on drug release from matrices containing ethylcellulose. *International Journal of Pharmaceutics*. 140, 85-95.

El-Kamel, A.H. (2008). Improvement of physico-chemical and biopharmaceutical properties of flurbiprofen using melt sonocrystallization technique. *Drug Development Research*. 69, 34-41.

Hamid, A. Merchant, H.M.S., Tazeen, J. and Yousuf, R.I. (2006). Once-daily tablet formulation and in vitro release evaluation of cefpodoxime using hydroxypropoyl methyl cellulose: A technical note. *AAPS PharmSciTech*. 7.

Katikaneni, P. R., Upadrashta, S. M., Neau, S. H. and Mitra, A. K. (1995). Ethylcellulose matrix controlled release tablets of a water-soluble drug. *International Journal of Pharmaceutics*. 123, 119-125.

Khan, G.M. (2001). Controlled release oral dosage forms: Some recent advances in matrix type drug delivery systems. *The Science*. 1, 350-354.

Khan, G.M. and Zhu, J.B. (1998a). Ibuprofen release kinetics from controlled-release tablets granulated with aqueous polymeric dispersion of ethylcellulose II: Influence of several parameters and coexcipients. *Journal of Controlled Release*. 56, 127-134.

Khan, G.M. and Jiabi, Z. (1998b). Formulation and in vitro evaluation of ibuprofen-carbopol® 974P-NF controlled release matrix tablets III: Influence of co-excipients on release rate of the drug. *Journal of Controlled Release.* 54, 185-190.

Khan K.A, Rhodes, C.T. (1975). Evaluation of different viscosity grades of sodium carboxymethylcellulose as tablet disintegrants. *Pharmceutica Acta Helvetica*. 50, 99-102.

Lachman, L., Lieberman, H.A. and Kanig, J. L. (1987). The Theory and Practice of Induatrial Pharmacy. Philadelphia, PA: Lea and Fabiger;. 317-318.

Lee, J. and Herman, J.H. (1993). Angle of repose and angle of arginal satbility: Molecular dynamics of granular particles. *J of Physics A: Mathical and General.* 26, 373-383.

Maggi, L., Bruni, R. and Conte, U. (2000). High molecular weight polyethylene oxides (PEOs) as an alternative to HPMC in controlled release dosage forms. *International Journal of Pharmaceutics.* 195, 229-238.

Roy, P. and Shahiwala, A. (2009). Multiparticulate formulation approach to pulsatile drug delivery: Current perspectives. *Journal of Controlled Release*. 134, 74-80.

Sharma, S. (2008). New generation of tablet: Fast dissolving tablet. Latest Reviews: Pharmainfo.net, 6.

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

Sinha Roy, D. and Rohera, B.D. (2002). Comparative evaluation of rate of hydration and matrix erosion of HEC and HPC and study of drug release from their matrices. *European Journal of Pharmaceutical Sciences*. 16, 193-199.

Streubel, A., Siepmann, J., Dashevsky, A. and Bodmeier, R. (2000). pH-independent release of a weakly basic drug from water-insoluble and water-soluble matrix tablets. *Journal of Controlled Release*. 67, 101-110.

Taylor, M., Ginsburg, J., Hickey, A. and Gheyas, F. (2000). Composite method to quantify powder flow as a screening method in early tablet or capsule formulation development. *AAPS PharmSciTech*. 1, 20-30.

Tiwari, S., Murthy, T., Raveendra Pai, M., Mehta, P. and Chowdary, P. (2003). Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. *AAPS PharmSciTech*. 4, 18-23.

Varshosaz, J., Tavakoli, N. and Kheirolahi, F. (2006). Use of hydrophilic natural gums in formulation of sustained-release matrix tablets of tramadol hydrochloride. *AAPS PharmSciTech.* 7, E168-E174.

Velasco, M.V., Ford, J.L., Rowe, P. and Rajabi-Siahboomi, A.R. (1999). Influence of drug, hydroxy-propylmethylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets. *Journal of Controlled Release*. 57, 75-85.

Visavarungroj, N. and Remon, J.P. (1990). Crosslinked starch as a disintegrating agent. *International Journal of Pharmaceutics*. 62, 125-131.