African Journal of Pharmacy and Pharmacology Vol. 5(7), pp. 862-873, July 2011
Available online http://www.academicjournals.org/ajpp
DOI: 10.5897/AJPP11.192
ISSN 1996-0816 ©2011 Academic Journals

Full Length Research Paper

Physicochemical characterization and *in-vitro* evaluation of flubiprofen oral controlled release matrix tablets: Role of ether derivative polymer ethocel

Muhammad Akhlaq[1,2]*, Gul Majid Khan[1], Abdul Wahab[1], Hamdy Abdelkader[3], Raid Alany[2] Abid Hussain[1] and Nauman Rahim Khan[1]

[1]Faculty of Pharmacy, Gomal University, D.I.Khan, KPK, Pakistan.
[2]School of Pharmacy, University of Auckland, Auckland, New Zealand.
[3]Department of Pharmaceutics, Faculty of Pharmacy, Minia University, Minia, Egypt.

Accepted 7 June, 2011

The main aim of the study was to develop once-daily controlled release matrix tablet of the selected propionic acid derivative flubiprofen (100 mg) using ethyl cellulose ether derivative release controlling polymer. Preformulation factors, including solubility, powder flowability and compressibility, and loss on drying were studied. Hausner's factor and angle of repose ranged from 1.10 to 1.25 and 25 to 29° respectively, indicating the best flowability and compressibility of the powder. Drug-polymer interaction was analyzed by particle size analysis, SEM and FTIR spectroscopy. Matrices were prepared by direct compression, with and without polymer. Effect of co-excipients like HPMC, starch and CMC, was studied on release behavior of the drug. The tablets were subjected to different physicochemical tests including hardness, friability, weight variation, % drug content, thickness and diameter with limits ranging from 6.4 ± 0.24 to 6.9 ± 0.44 kg/cm^2, 0.22 ± 0.06 to 0.77 ± 0.03 w/w, 200 ± 1.3 to 203 ± 1.0 g, 98.30 ± 0.16 to 99.70 ± 0.64%, 2.1 ± 0.032 to 2.3 ± 0.020 mm and 4.2 ± 0.001 to 4.4 ± 0.001 mm respectively. *In-vitro* drug release study was conducted in phosphate buffer (pH 7.4) and different kinetic parameters were applied. Ethocel FP polymer alone showed the best anomalous release with exponent $n =$ 0.793 with the linearity $r^2 =$ 0.992, whereas the market brand released 90% of the drug after four hours with release exponent $n =$ 0.210.

Key words: Drug delivery, flurbiprofen, ethyl cellulose ether derivative polymers, physicochemical, release kinetics.

INTRODUCTION

Controlled release drug delivery systems have attracted considerable attention from the pharmaceutical technologies in the last three decades and have made quantum advances in various dosage forms using existing and new drug molecules (Gunawan and Xu, 2008). Controlled release pharmaceutical dosage form offers more advantages over a conventional dosage form of the same drug like sustained blood levels and better patients compliance, smaller dosage unit or higher dosage per unit, easier to administer and economical to manufacture (Hanna et al., 1987). The drug can now be delivered and made bioavailable in a sustained and well-controlled manner up to a desired period of time (Skelly, 1987). Propionic acid derivatives, like flurbiprofen (FLB), are considered to be the first line drugs in the symptomatic treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. They are safe and effective analgesic and by inhibiting the prostaglandin synthesis they can interrupt the normal paracrine signaling necessary for the elaboration of inflammatory response (Brooks and Day, 1991; Qiu and Bae, 2006) having dose response trend in both sexes (Jackson and Hawkey, 1999). Flurbiprofen has been found to be one of the most

*Corresponding author. E-mail: akhlaqhayat@hotmail.com. Tel: 0064220722456.

potent members of a series of phenylalkanoic acids in various animal species in anti-inflammatory, analgesic and antipyretic tests (van Miert and van Duin, 1977). It is highly effective in the treatment of rheumatoid arthritis in man (O'Dell et al., 2001). Flurbiprofen also causes a dose dependent inhibition of collagen induced platelet aggregation in platelet rich plasma from human, rats and rabbits *in-vitro* (Nishizawa et al., 1973). Flurbiprofen is at least 99% bound to human serum albumin at therapeutic concentration. It may bind to red blood cells. Area under the plasma drug concentration versus time curve increases with increasing dose administration (Kaiser et al., 1986). Upon oral administration, the most frequently reported side effects of flurbiprofen are abdominal discomfort along with other gastrointestinal effects. It has short elimination half-life of 3.9 h and requires frequent dosing (Charoo et al., 2005). Hence, formulating FLB in controlled release solid dosage form could reduce the aforementioned side effects.

Polymer science has become the backbone for the development of new formulation for the past few years and its advances have led to the development of numerous applications in pharmaceutical sciences, as coating agent, emulsifying agent, suspending agent, adhesive and adjuvant (Qiu and Bae, 2006). Polymers have achieved greater importance in the pharmaceutical industry as drug encapsulates and vehicles of drug carriage and protecting drug during its passage through the body. Polymeric delivery systems or devices are used to ensure either a temporal or spatial control of drug delivery (Jain, 2006). Bio-functional polymers have got pharmaceutical interest in recent years and are widely used for formulation of extended or prolonged- release dosage forms (Meidan and Khan, 2007). For few decades ethyl cellulose has been used as controlled-release excipients. In most uses, ethyl cellulose has been solubilized in organic solvents and used as a film coating for tablets beads and particles to impart a controlled release or taste masking effect (Katikaneni et al., 1995). Flurbiprofen SR exhibits erosion controlled mechanism coupled with diffusion (Skoug et al., 1993). FLB market brand released 97.77% of FLB between 4 to 8 h, while ethocel FP release retarding material offered empirical approach in developing controlled release system. The present study aims to develop flurbiprofen controlled release matrix tablets using ethocel in order to reduce dosing frequency, to lesser the side effects and to improve patient compliance. The study is unique in the sense that deriving insight from the exciting research findings and advancements in the field has been made to enhance its utility and impact.

MATERIALS AND METHODS

Flurbiprofen was received as a gift from Abbot Labs, Pakistan, monobasic potassium phosphate, CMC, Starch, NaOH (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 (ethyl cellulose ether derivative) Standard 7 Premium, Ethocel 7 FP Premium and HPMC (Dow Chemical Co., Midland USA). All the chemicals used and received were of analytical grades.

Preformulation study

Solubility

The solubility study of flurbiprofen was performed by following the equilibrium solubility method in six different solvents at 37°C in a shaking water bath for 24 h. Excess amounts of drug were added to 100 ml conical flasks. After two days aliquots were withdrawn, filtered (0.22 µm) and diluted with their respective solvents. The samples were analyzed spectrophotometrically on 247 nm using concerned solvents as blank (Uekama et al., 1985).

Bulk density

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

$$\text{Bulk density} = W_s / V_s$$

Where W_s is sample weight and V_s is the sample volume.

Tape density

Tape density is the indirect measurement of flow, mixing and tableting properties of powder. It was calculated by using 10 ml measuring cylinder with 100 tapping which are sufficient to bring plateau condition (Abdelkader et al., 2008). Tapped density was calculated by the following formula:

Tapped density = Weight of mixture/volume of mixture after 100 tapings

Hausner's ratio

It is called as index of flowability and is calculated by the formula (Abdelkader et al., 2008):

$$\text{Hausner's ratio} = V_1 / V_2$$

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

Loss on drying

A porcelain dish was heated in an oven at 60°C for half an hour. It was then cooled in a desiccator. 1 g of flurbiprofen was accurately weighed and heated in oven at 60°C for 3 h, at a pressure not more than 7 kPa. After a specified period of time FLB was reweighed and limit of detection (LOD) was calculated as mass percentage (Abdelkader et al., 2008).

Angle of repose

Angle of repose was determined by Funnel and Cone method. A Petri dish was taken and its diameter was determined. A funnel was

Table 1. Experimental conditions for particle size analysis.

Material	Circulation speed	Ultrasonic	Laser T (%)	Form of distribution	RR index
Ethocel 7 FP Premium	5	02:00	86.6	Standard	1.50-0.41
Ethocel 7 Premium	5	02:00	86.7	Standard	1.50-041
Flurbiprofen	5	02:00	86.6	Standard	1.50-0.40

Table 2. Weight compositions (mg) of flurbiprofen formulations.

Formulation	Flurbiprofen	Ethocel7 FP	Ethocel 7 simple	Lactose	Mg stearate	HPMC	Starch	CMC
F-1	100	30		69	1	--	--	--
F-2	100	--	30	69	1	--	--	--
F-3	100	30	--	48.3	1	20.7	--	--
F-4	100	--	30	48.3	1	20.7	--	--
F-5	100	30	--	48.3	1	--	20.7	--
F-6	100	--	30	48.3	1	--	20.7	--
F-7	100	30	--	48.3	1	--	--	20.7
F-8	100	--	30	48.3	1	--	--	20.7
F-9	100	--	--	99	1	--	--	--

fixed above the Petri dish and accurately weighed amount of flurbiprofen (4 g) 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 the following equation (Lee and Herman, 1993).

$$Tan\theta = \frac{h}{R} \quad (1)$$

Where "h" is the height of the cone and "R" is the radius of the cone base.

Compressibility index

Compressibility index of FLB powder was determined by Carr's compressibility percentage given as (Lachman, 1987):

$$Compressibility\% = \left[\frac{Df - D\bullet}{Df}\right] \times 100 \quad (2)$$

Where "Df" is the tape bulk density "$D\bullet$" is the fluff bulk density.

Infra-red absorption spectroscopy

A computerized FTIR (iS10, Thermo Fischer Scientific, USA) was used to study the possible drug-polymer interaction. Sample of approximately 10 mg was placed at the plate and enough pressure was applied to obtain the sharp peaks at suitable intensity. Spectroscopy of FLB, Polymer and FLB-Polymer physical mixture was carried out in the range of 500 to 4000 cm^{-1} to detect the possible interaction of drug and polymer (Ranjha et al., 2009).

Scanning electron microscopy

SEM images of FLB and FLB-EC physical mixture were taken to analyze the surface morphology of drug and its physical mixture at two different magnifications.

Particle size analysis

Particle size (Horiba Particle size analyzer, LA 300, Japan), of FLB and ethocel polymer was analyzed, using distilled water as circulation medium at refractive index of 1.50 to 0.41 in order to study the effect of particle size on the compaction of tablets and release behavior of flurbiprofen thereafter. The experimental conditions are given in Table 1(Andrýsek, 2001).

Preparation of matrix tablets

FLB 100 mg tablets, with polymer and without polymer, were prepared by direct compression method, using Single Punch Machine Model No. AR 400 (Erweka GMBH, Germany), applying 450 kg force for about 2 s. The tablets compositions are given in Table 2.

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.

Hardness

The hardness of the tablets was determined by using Hardness tester (Erweka, Germany) and was reported in kg.

Weight variation

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

Friability test

For each formulation 10 tabs were weighed, placed in Friabilator (Erweka, Germany) and were subjected to 100 rotations in 4 min. The tablets were reweighed and friability was calculated along with mean and the standard deviation.

$$Friability = \frac{W_1 - W_2}{W_1} \times 100 \quad (3)$$

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

Content uniformity test

30 tabs were selected randomly from each formulation, 10 tabs were assayed individually. All of the tested tablets contained more than 99% of active FLB. For determining the drug content collectively, three tablets of were crushed and powder, equivalent to 100 mg of FLB, was dissolved in phosphate buffer pH 7.4, and was analyzed spectrophotometrically at 247 nm after sufficient dilutions with the respective solvent.

In-vitro drug release study

Drug release study was performed according to USP Apparatus 1, using 8-station dissolution apparatus Pharma Test Model # PTWS-11/P, TPT (Hamburg, Germany). Each flask was filled up to 900 ml dissolution medium of 0.2 M phosphate buffer solution pH 7. 4 kept at 37 ± 0.1℃ and stirred at 100 rpm (Perfect sink conditions). Tablets were placed in different baskets and at predetermined time intervals of 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18 and 24 h, a 5 ml sample was taken with syringe using 0.45 µm filter and was replaced with the same fresh medium. Samples were analyzed at 247 nm with the help of UV- Visible Spectrophotometer UV-1601 (Shimadzu, Japan). The mean of three tablets was used to evaluate the drug release for each of the formulations.

Drug release kinetics

To study the release kinetics, data obtained from *in-vitro* drug release studies were plotted in various kinetics models:

Zero-order:

$$W = k_1 t \quad (4)$$

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

First order:

$$\ln(100 - W) = \ln 100 - k_2 t$$

Where k_2 is the first order constant and ln100 is the initial concentration of drug.

Hixson Crowell's equation or Erosion model:

$$(100 - W)^{1/3} = 100^{1/3} - k_3 t$$

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

Higuchi's model:

$$W = k_4 t^{1/2}$$

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

Korsmeyer-Peppas equation:

$$M_t / M_\infty = k_5 t^n$$

Where M_t / M_∞ is the fractional solute release, k_5 is power law constant of drug-polymer system, whereas n is an exponent that indicates drug release mechanism from matrix.

RESULTS AND DISCUSSION

Preformulation studies

Solubility studies

Flurbiprofen is a monoprotic drug having pKa value 4.22 ± 0.03. Its solubility ranged from 1.474 to 6.961, which was maximum at a pH 10 (Anderson and Conradi, 1985). Solubility values at pH 1.2, 6.8, 7, 7.2, 7.4 and at pH 10 were found to be 1.474, 4.308, 4.800, 5.868, 6.661 and 6.961. Both the measured drug solubility and pKa are in good agreement. The drug solubility was increased at pH 6.8 and above having maximum value at pH 10 because of drug ionization, while at pH 1.2 it was low due to un-ionized form of FLB present in the solution as shown in Figure 1 (Li and Zhao, 2003).

Table 3 shows poured density, tapped density, Hausner's ratio, angle of repose, compressibility index and loss on drying. Poured density ranged from 0.228 to 0.398 while tapped density ranged from 0.312 to 0.582,

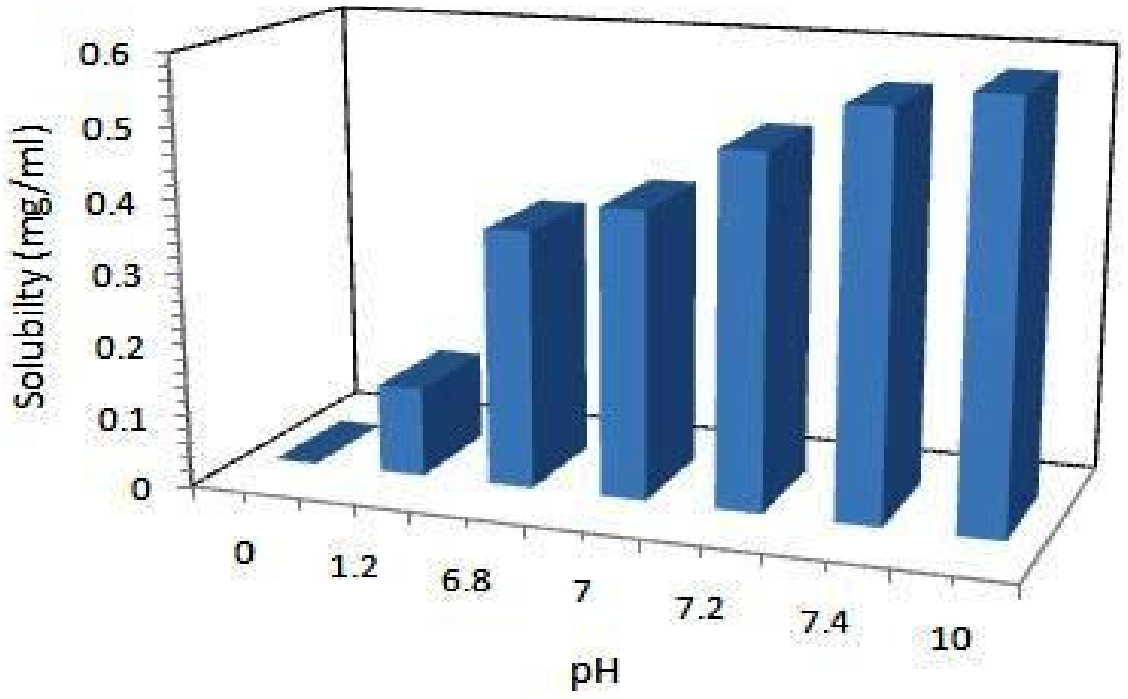

Figure 1. Solubility of flurbiprofen at various pH values.

Table 3. Results of evaluation tests performed on flurbiprofen powder and physical mixture.

Formulation	Bulk density(g/cm³)	Tapped density(g/cm³)	Hausner Factor	Angle of repose (θ)	Compressibility (%)	Loss on drying (%)
Pure drug	0.228	0.582	1.10	29.64	55.25	0.1
F-1	0.334	0.312	1.11	27	15.29	0.2
F-2	0.387	0.348	1.15	25	17.52	0.2
F-3	0.367	0.320	1.21	24	16.44	0.1
F-4	0.398	0.362	1.11	22	19.11	0.3
F-5	0.376	0.335	1.17	27	18.23	0.2
F-6	0.304	0.361	1.14	25	20.52	0.2
F-7	0.295	0.354	1.22	25	18.19	0.2
F-8	0.342	0.412	1.25	26	19.02	0.3
F-9	0.311	0.391	1.18	26	19.73	0.3

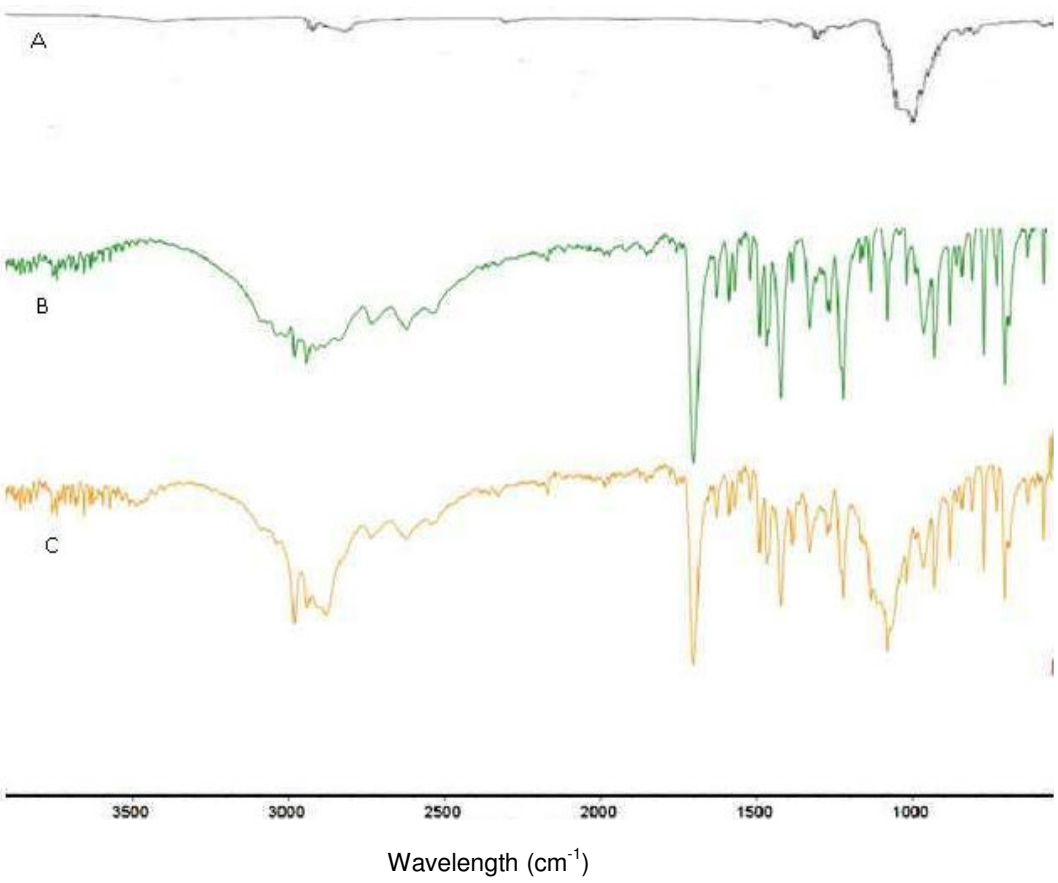

Figure 2. FTIR spectra of polymer (A), flurbiprofen (B) and FLB-polymer (C).

indicating that there is no conclusive effect of physical mixing upon the particle size. HF values ranged from 1.10 to 1.25 indicating good flow properties of powder. Angle of repose was found to be 29.64° for FLB powder. Angle of repose for physical mixtures ranged from 22 to 27° indicating fair flow properties of the physical mixture. The frictional force in the loose powder was in acceptable range but the addition of polymer and excipients improved the powder flow and reduced the cohesive force among the particles up to negligible extent during compression (Sharma, 2008). Compressibility index developed by Carr, from the bulk densities of FLB indicating indirect measurement of flow property of powdered drug, its bulk density, size and shape, moisture content surface area, was calculated by Equation 2. Percentage compressibility of FLB powder was 55.25% which was in good agreement with angle repose, while that for the physical mixtures ranged from 15.29 to 20.52% indicating the improved compressibility and flowability of physical mixtures (Lachman, 1987; Raghuram, 2003). LOD was found to be 0.10% for FLB powdered drug while that for physical mixtures was also found to be in accordance with USP standards ranging from 0.1 to 0.3% (Reddy et al., 2003), indicating that FLB powder had moisture content up to acceptable limit which was good for compression to make uniform matrices.

FTIR spectra analysis

FTIR spectroscopy of polymer (a), drug (b) and physical mixture (c) was conducted to investigate possible drug-polymer interaction. FLB spectra showed principal peaks at 1695 (C=O), 1220 (C–F), 707, 930, 773 and 960 cm^{-1} due to asymmetric stretching of carbonyl, hydroxyl and single bonds (Shrivastava et al., 2009; Ranjha et al., 2010). Spectra showed minor changes in the absorbance pattern especially in the region of 1000 to 1700 cm^{-1} and 2500 to 3000 cm^{-1} This alteration could be due to variations in the resonance structure, stretching and bending, rotation of a part of molecule or certain bonds or minor distortion of bond angle (Shrivastava et al., 2009), as shown in the Figure 2.

Scanning electron microscopy

Figure 3 shows SEM images of FLB and FLB-Polymer

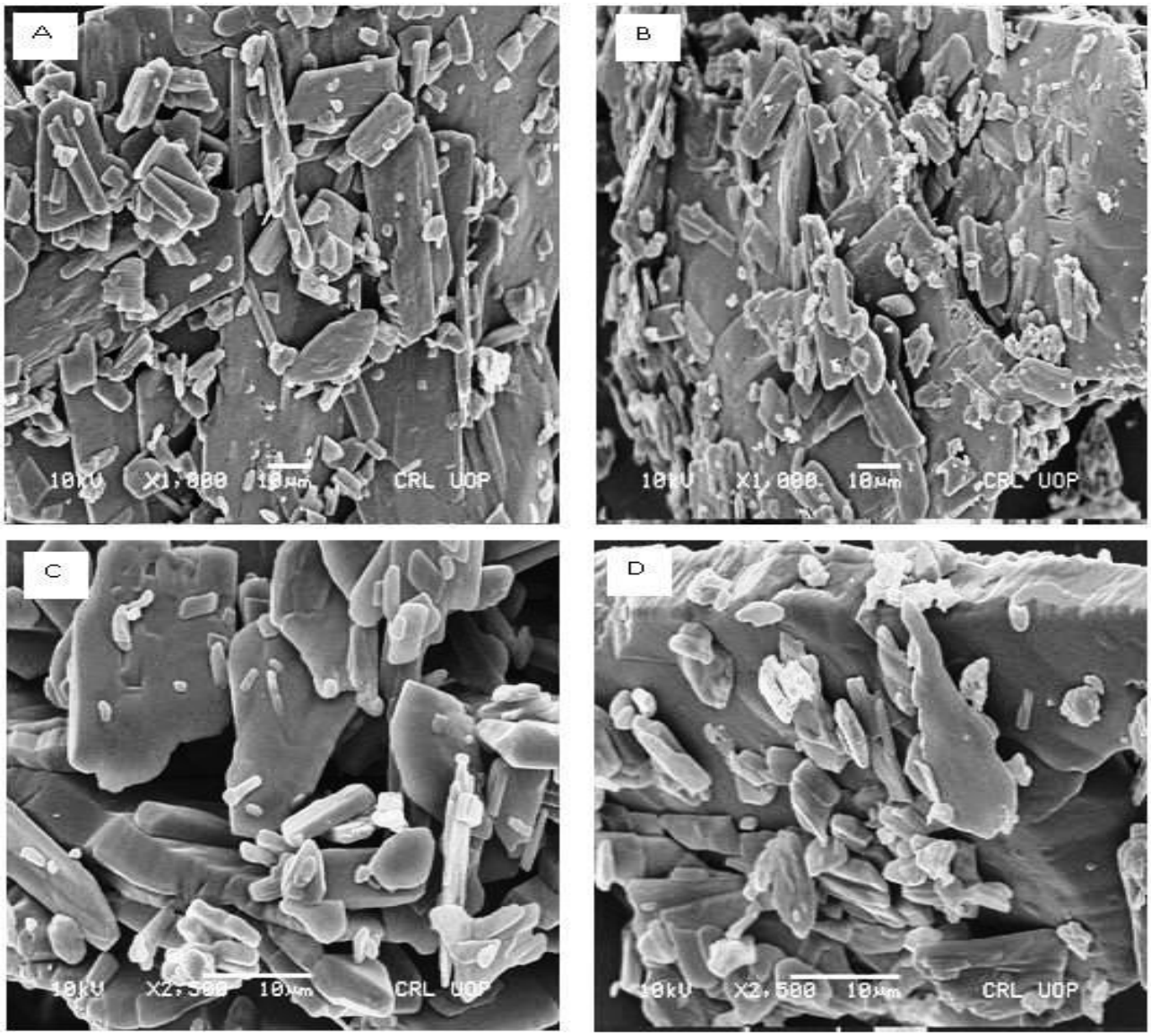

Figure 3. Scanning Electron Microscope images of FLB AND FLB-Polymer mixture at two different magnifications, (A) FLB at ×1000, (C) FLB at ×2500, (B) FLB-Polymer at ×1000 & (D) FLB-Polymer at ×2500.

physical mixture at two different resolutions. FLB and polymer could be seen separated having no chemical interaction or permanent attachment in case of their physical mixture. It could also be observed that there is complete physical miscibility of FLB with ethyl cellulose polymer.

Physical characteristics of tablets

Physical characteristics of the tablets are given in the Table 4, including hardness, friability, weight variation, % drug content, thickness and diameter. Hardness of the tablets ranged from 6.4 ± 0.24 to 6.9 ± 0.44 kg/cm^3, which was suitable to reduce the tendency to cap, as thickness affects the internal stress of the tablet. Polymer viscosity and concentration have increasing effect upon the size of tablet because the polymer may have low binding force (Abdelkader et al., 2007). Friability calculated was in the acceptable range of 0.22 ± 0.06 to 0.77 ± 0.03 w/w, and it increased with the increase of polymer grade and concentration. Weight variation test showed that all of the tablet were in the acceptable range of 200 ± 1.3 to 203 ± 1.0 mg. Content uniformity test fell in the best suitable range of 98.70 ± 0.04 to 99.70 ± 0.64% for 100 mg FLB tablets, whereas the drug content for FLB pure drug showed 99.0±0.42% of drug contents. Thickness and diameter ranged from 2.1 ± 0.032 mm to

Table 4. Physical properties of standard tablets expressed as mean ± SD.

Formulation	Hardness(kg/cm²)	Friability(w/w)	Weight variation (mg)	% Drug content	Thickness (mm)	Diameter (mm)
F-1	6.5 ± 0.37	0.77 ± 0.03	200 ± 1.3	99.10 ± 0.04	2.1 ± 0.041	4.2 ± 0.004
F-2	6.8 ± 0.41	0.62 ± 0.02	201 ± 1.8	98.20 ± 0.49	2.2 ± 0.045	4.3 ± 0.001
F-3	6.9 ± 0.44	0.53 ± 0.11	202 ± 1.1	99.70 ± 0.64	2.1 ± 0.040	4.2 ± 0.003
F-4	6.5 ± 0.34	0.71 ± 0.05	200 ± 1.6	99.80 ± 0.10	2.3 ± 0.007	4.2 ± 0.001
F-5	6.5 ± 0.45	0.22 ± 0.06	203 ± 0.3	99.30 ± 0.16	2.3 ± 0.020	4.2 ± 0.002
F-6	6.4 ± 0.24	0.46 ± 0.10	203 ± 1.0	99.40 ± 0.25	2.2 ± 0.041	4.2 ± 0.002
F-7	6.8 ± 0.32	0.73 ± 0.09	203 ± 0.4	98.30 ± 0.16	2.2 ± 0.002	4.3 ± 0.001
F-8	6.6 ± 0.54	0.36 ± 0.08	202 ± 1.2	98.70 ± 0.04	2.1 ± 0.032	4.4 ± 0.001
F-9	6.4 ± 0.26	0.73 ± 0.02	201 ± 2.1	99.50 ± 0.36	2.1 ± 0.040	4.2 ± 0.002

2.3 ± 0.020 (Table 4).

Dissolution studies

Figures 5, 6 and 7 shows that F-1 containing only ethocel FP polymer-based matrices released 95.25% of drug after 24 h, while those with ethocel simple coarser polymer released 98.12% after 8 h respectively, indicating that FP polymer released the drug in a well-controlled manner. Simple coarser ethocel polymer with same viscosity but higher particle size released maximum amount of the drug up to 8 h indicating that polymer particle size could be the main release determining factor, while polymer with fine particles might contribute to increased compressibility and produce more uniform matrices with uniform channels for water to diffuse and to dissolve the drug in a controlled manner. Particle sizes of flurbiprofen, ethocel FP and simple polymer were found to be 22.52, 5.26 and 58.32 µm respectively indicating that fine particle might retard the drug release rate from matrices as shown in Figure 4 (Katikaneni et al., 1995). Decrease in particle size might have decreased the porosity and hence increased the tourtosity and diffusion path of the matrix tablets. While HPMC-based matrices released 97.79 and 98.83% after 24 and 6 h for each formulated with ethocel FP and simple respectively. HPMC in combination with ethocel FP polymer released FLB in controlled manner. In small quantities HPMC can act as channeling agent, and can enhance the release rates (Maggi et al., 2000, Velasco et al., 1999). Starch-based tablets released 98.99 and 98.89% FLB after 2 h for each ethocel FP and simple polymer respectively. Because polyvalent cations of starch might swell in water by about 5 to 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). CMC-based matrices released 99.81 and 99.90% after 2 h for each ethocel FP and simple polymers. CMC-based matrices markedly increased the release rate because the disintegration and swellability character of CMC might be contributed to this effect (Khan, 1975; Khan and Jiabi, 1998). Figure 7 shows that matrices formulated without polymer burst and released 99.0% of the drug in 1 h, while FLB 200 mg market brand released 97.77% of drug within 9 h.

Release kinetics

FLB release data was evaluated by zero-order, first-order and Higuchi models. As the dissolution of controlled release matrices followed the anomalous (combination of diffusion and erosion) release of drug so the Higuchi model failed to explain the release behavior, therefore Korsmeyer equation was applied to the dissolution of drug from the matrices, Which is always used to describe anomalous the release behavior from the matrices (Abdelkader et al., 2007). Korsmeyer model describes the release of the drug from matrices while n is the release exponent that actually characterizes the release mechanism of the drug. If $n = 0.45$, then the release is Fickian and if $0.45 \leq n \leq 0.89$ then it is non-Fickian. While0.98 value of n exponent indicates typical zero-order release (Merchant, 2006). The release data was fitted to Equation 7 as shown in the Table 5. Exponent n for F-1 0.793 followed by the best linearity $r^2 = 0.992$ indicated anomalous release coupled by diffusion and erosion. While

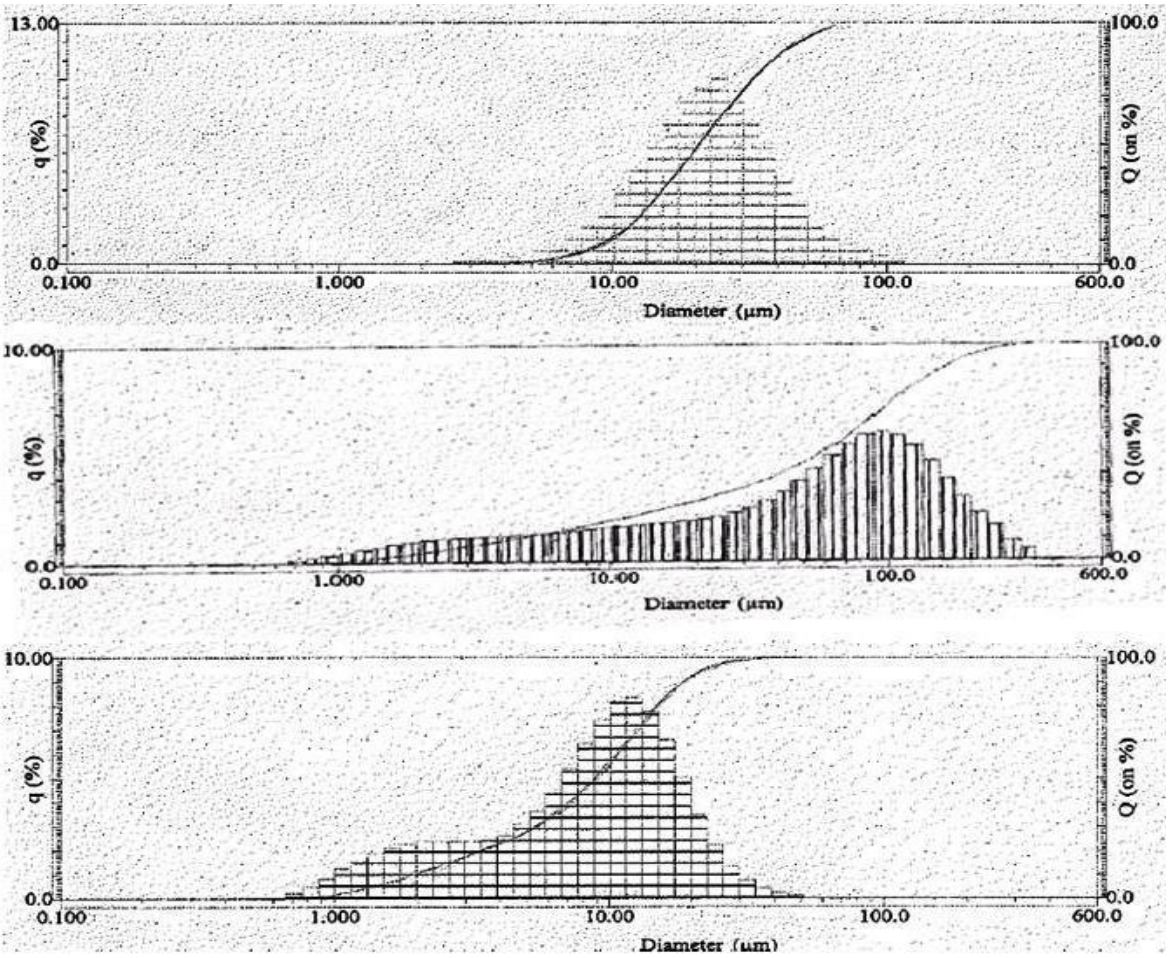

Figure 4. Particle size distribution of ethocel FP (A), ethocel simple (B) and FLB (C).

that for F-2 formulated with ethocel simple polymer gave n exponent 0.731 indicating anomalous release as well. It could be observed that matrices with FP polymer remained intact during the dissolution and gave the highest release exponent value 0.793 whereas the tablet formulations F-4, 6 and 8 with ethocel simple coarser polymer disintegrated slowly as shown in the figure (Dabbagh et al., 1996). The release data of HPMC-based matrices, F-3 and F-4 gave the release exponent n = 0.673 for each FP and simple granular forms indicating anomalous release behavior**.** Drug release data of starch-based formulations F-7 and F-8 was fitted to Equation 8 and it gave the release exponent n values 0.053 and 0.037, indicating maximum release with first hour. Starch is water swellable in nature and is not suitable for controlled release formulations (Khan and Jiabi, 1998). Figures 5 and 6 show that 70% drug was released within 1 h indicating that the combination of starch with ethocel FP polymer markedly increased the drug release from matrices.

CMC-based matrices released 80% drug within first hour showing release exponent n for F-7 and F-8, 0.22 and 0.016 respectively. It was could be observed that the rapid disintegration of CMC (Khan, 1975) released 99% drug within 2 h as shown in the Figures 5 and 6. Low swellabilty of CMC might be contributed to the marked increase in the drug release rate (Abdelkader et al., 2007). Release exponent for F-9 was too small to show the controlled release, that is, 0.0032 behavior of FLB. FLB market brand gave n value 0.210 with $r^2 = 0.902$ indicating that the drug release did not follow the zero-order kinetics and released maximum amount with 9 h.

Conclusions

It has been observed that ethyl cellulose ether derivative polymer of viscosity Grade 7 can be used in directly compressed controlled release matrices tablets of slightly soluble non-steroidal anti-inflammatory drugs such as flurbiprofen. Inherently cross-linked structure of ethyl cellulose polymer could form uniform channels in the

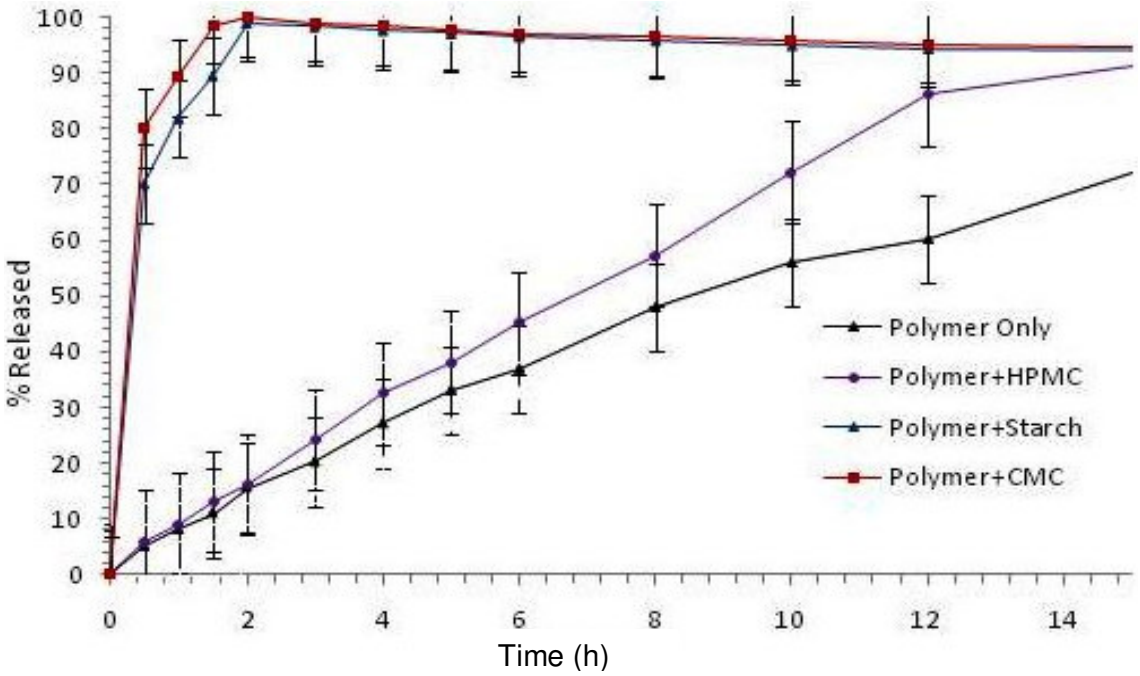

Figure 5. FLB release profile from matrices containing ethocel FP polymer with different exciepents.

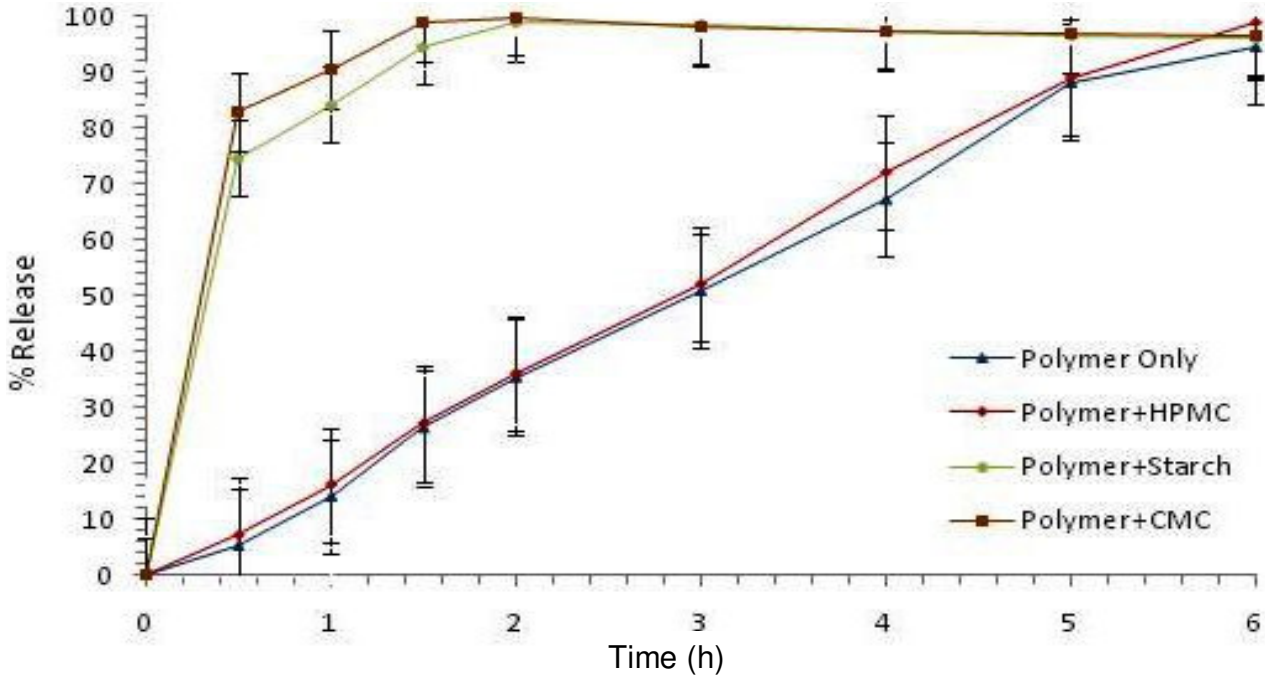

Figure 6. FLB release profile from matrices containing Ethocel simple coarser polymer with different excipients.

matrix system to release the drug in a well-controlled manner. Polymer particle size and concentration are the main drug release determining factors from the matrices. Coexcipients like CMC and Starch markedly increased the release rate. FLB-market brand released maximum amount of drug within 9 h. Drug release mechanism from matrices could be changed by changing the polymer particle size and its concentration in various modes.

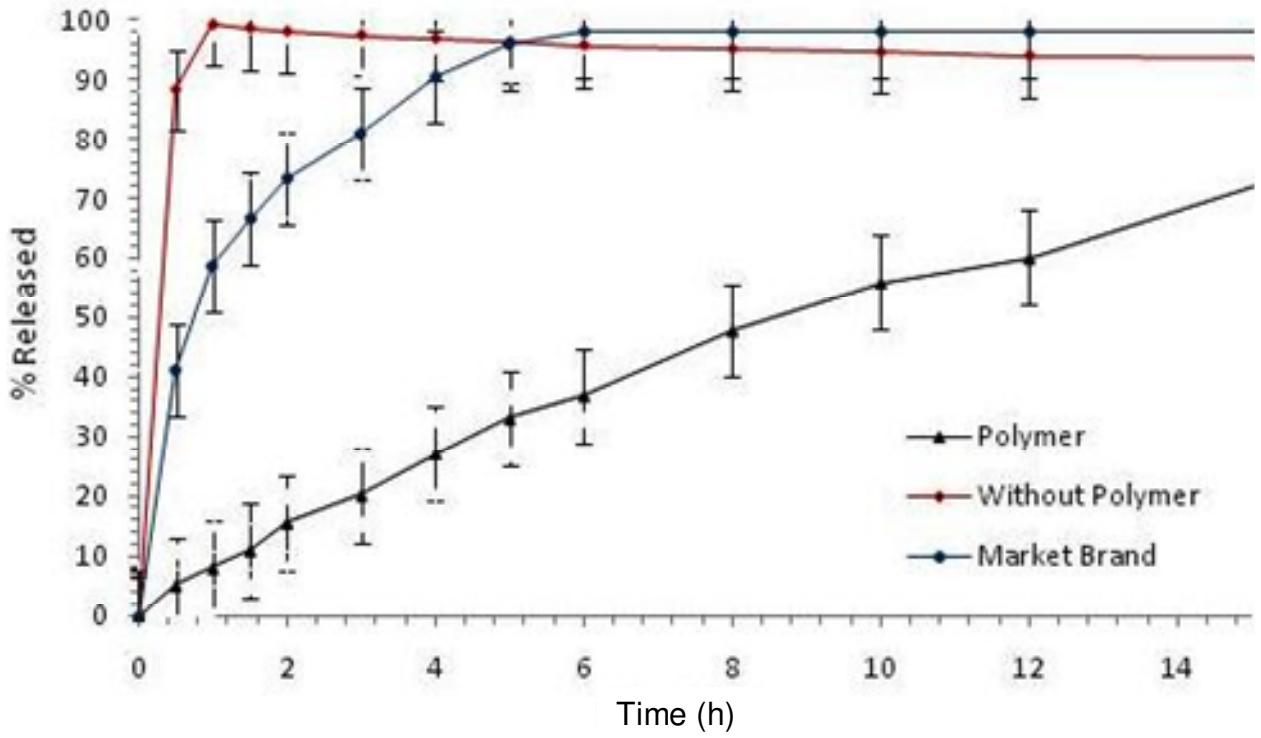

Figure 7. FLB release profile from matrices containing Ethocel FP polymer, without polymer and from market brand.

ACKNOWLEDGMENTS

The authors are thankful to the Higher Education Commission of Pakistan.

REFERENCES

Abdelkader H, Abdalla O, Salem H (2007). Formulation Of Controlled-Release Baclofen Matrix Tablets: Influence Of Some Hydrophilic Polymers On The Release Rate And In Vitro Evaluation. Aaps Pharm. Sci. Tech., 8: 156-166.

Abdelkader H, Youssef AO, 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 Pharm. Sci. Tech., 9: 675-683.

Anderson BD, Conradi RA (1985). Predictive Relationships In The Water Solubility Of Salts Of A Nonsteroidal Anti-Inflammatory Drug. J. Pharm. Sci., 74: 815-820.

Andrýsek T (2001). The Role of Particle Size Distribution On Bioavailability Of Cyclosporine: Novel Drug Delivery System. Biomed., 145: 3-8.

Brooks P, Day R (1991). Nornal Anti-Inflammatory Drugs: Differences And Similarities. N. Eng. J. Med., 324: 1716-25.

Charoo Na, Anwer A, Kohli K, Pillai Kk, Rahman Z (2005). Transdermal Delivery Of Flurbiprofen: Permeation Enhancement, Design, Pharmacokinetic, And Pharmacodynamic Studies In Albino Rats. Pharm. Dev. Technol., 10: 343-351.

Dabbagh MA, Ford Jl, Rubinstein MH, Hogan JE (1996). Effects of Polymer Particle Size, Compaction Pressure And Hydrophilic Polymers On Drug Release From Matrices Containing Ethylcellulose. Int. J. Pharm., 140: 85-95.

Flubiprofen, Loss On Drying. Available At Http://Www.Sinoapi.Com/Pharmacopoeia/Jp15/Jp5104-49-4.Pdf. Accessed December 10, 2010.

Gunawan P, Xu R (2008). Direct Control of Drug Release Behavior From Layered Double Hydroxides Through Particle Interactions. J. Pharm. Sci., 97: 4367-4378.

Hamid AM, Harris MS, Jaweria T, Rabia IY (2006). Once-Daily Tablet Formulation and In Vitro Release Evaluation of Cefpodoxime Using Hydroxypropoyl Methyl Cellulose: A Technical Note. AAPS Pharm Sci. Tech, p. 7.

Hanna G, Berwyn P, Vadino Aw, Bridgewater N J (1987). Controlled Release Dosage Forms Comprising Hyroxipropylmethylcellulose United States Patent.

Jackson Lm, Hawkey Cj (1999). Nsaids And The Gi Tract—Potential Hazards And Benefits. Apoptosis, 4: 397-402.

Jain Kn (2006). Polymers In Pharmaceutical Sciences. Pharmaceutical Product Development 1st Ed. New Delhi, Satish Kumar Jain, 585-670.

Kaiser DG, Brooks CD, Lomen PL (1986). Pharmacokinetics of flurbiprofen. The American Journal of Medicine, 80, 10-15.

Katikaneni Pr, Upadrashta Sm, Neau Sh, Mitra Ak (1995). Ethylcellulose Matrix Controlled Release Tablets Of A Water-Soluble Drug. Int. J. Pharm., 123: 119-125.

Khan Gm, Jiabi Z (1998). 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. J. Controlled Release, 54: 185-190.

Khan Karc. (1975). Evaluation of Different Viscosity Grades of Sodium Carboxymethylcellulose as Tablet Disintegrants. Pharm. Acta. Helv., 50: 99-102.

Lachman Llh, Kanig Jl (1987). The Theory and Practice Of Industrial Pharamcy, Philadelphia, Pa: Lea And Febiger, Pp. 317-318.

Lee J, Herman JH (1993). Angle of Repose and Angle of Marginal Satbility: Molecular Dynamics of Granular Particles. J. Phys. A: Math. Gen., 26: 373-383.

Li P, Zhao L (2003). Solubilization Of Flurbiprofen In Ph-Surfactant Solutions. J. Pharm. Sci., 92: 951-956.

Maggi L, Bruni R, Conte U (2000). High Molecular Weight Polyethylene Oxides (Peos) As An Alternative To Hpmc In Controlled Release Dosage Forms. Int. J. Pharm., 195: 229-238.

Meidan Vm, Khan Gm (2007). Drug Release Kinetics from Tablet

Matrices Based Upon Ethylcellulose Ether-Derivatives: A Comparison Between Different Formulations. Informa Healthcare.
Nishizawa EE, Wynalda DJ, Suydam DE, Molony BA (1973). Flurbiprofen, a New Potent Inhibitor of Platelet Aggregation. Thrombosis Res., 3: 577-588.
Qiu L, Bae Y (2006). Polymer Architecture and Drug Delivery. Pharm. Res., 23: 1-30.
Raghuram RK Srinivas M, Srinivas R (2003). Once-Daily Sustained-Release Matrix Tablets Of Nicorandil: Formulation and *in vitro* Evaluation. Aaps Pharm. Sci. Tech. (Serial Online), p. 4.
Ranjha N, Khan H, Naseem S (2010). Encapsulation and Characterization of Controlled Release Flurbiprofen Loaded Microspheres Using Beeswax as an Encapsulating Agent. J. Materials Sci.: Materials In Medicine, 21: 1621-1630.
Ranjha Nm, Khan I, Naseem S (2009). Encapsulation And Characterization Of Flurbiprofen Loaded Poly(Є-Caprolactone)–Poly(Vinylpyrrolidone) Blend Micropheres By Solvent Evaporation Method. J. Sol-Gel Sci. Technol., 50: 281-289.
Reddy K, Mutalik S, Reddy S (2003). Once-Daily Sustained-Release Matrix Tablets of Nicorandil: Formulation and *in Vitro* Evaluation. Aaps Pharm. Sci. Tech., 4: 480-488.
Sharma S (2008). New Generation of Tablet: Fast Dissolving Tablet. Latest Reviews: Pharmainfo.Net, 6.
Shrivastava KS, Jain D, Shrivastava KP, Trivedi P (2009). Flurbiprofen-And Suprofen-Dextran Conjugates: Synthesis, Characterization And Biological Evaluation. Trop. J. Pharm. Res., P. 8
Skoug Jw, Mikelsons Mv, Vigneron Cn, Stemm Nl (1993). Qualitative Evaluation Of The Mechanism Of Release Of Matrix Sustained Release Dosage Forms By Measurement Of Polymer Release. J. Controlled Release, 27: 227-245.
Uekama K, Imai T, Maeda T, Irie T, Hirayama F, Otagiri M (1985). Improvement Of Dissolution And Suppository Release Characteristics Of Flurbiprofen By Inclusion Complexation With Heptakis(2,6-Di-O-Methyl)-B-Cyclodextrin. J. Pharm. Sci., 74: 841-845.
van Miert AS, van Duin CT 1977). The Antipyretic Effect of Flurbiprofen. Eur. J. Pharm., 44: 197-204.
Velasco MV, Ford Jl, Rowe P, Rajabi-Siahboomi AR (1999). Influence of Drug:Hydroxypropylmethylcellulose Ratio, Drug and Polymer Particle Size and Compression Force on The Release of Diclofenac Sodium From Hpmc Tablets. J. Controlled Release, 57: 75-85.
Visavarungroj N, Remon JP (1990). Crosslinked Starch as a Disintegrating Agent. Int. J. Pharm., 62: 125-131.