

Full Length Research Paper

Pre-formulation investigation and *in vitro* evaluation of directly compressed ibuprofen-ethocel oral controlled release matrix tablets: A kinetic approach

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The objective of this study was to develop directly compressed oral controlled-release ibuprofen matrix tablets containing hydrophobic polymer (Ethocel[®]) of different viscosity grades (Ethocel[®] standard 7P, 7FP, 10P, 10FP 100P and 100FP). As ibuprofen like other non-steroidal anti-inflammatory drugs has dosage frequency and severe gastrointestinal tract (GIT) complications and patient non-compliance, so to avoid these problems, controlled release matrices were developed. Before development of matrix tablets, pre-formulation studies were performed for the determination of physicochemical interaction between polymer, drug and co-excipients, using differential scanning calorimetry (DSC) and Fourier transform infrared (FT-IR) and no interaction was found. Controlled-release matrix tablets were formulated by direct compression method. Effect of partial replacement of lactose by different co-excipients such as HPMC K100M, starch and CMC on the release of drug was also studied. The tablets were subjected to different physicochemical, dimensional and quality controlled tests, such as drug content, weight variations, friability, hardness, thickness and diameter, all these tests were within United States Pharmacopoeia (USP) range. The *in vitro* release profile in phosphate buffer (pH 7.4) for all formulations containing polymer and co-excipients was compared with a formulation developed without polymer and co-excipients for 24 h. Different kinetics models were used, such as first-order equation, zero-order equation, Higuchi equation, Hixon Crowel's equation and Korsmeyer-Peppas to study and investigate the release mechanism. It was concluded that formulations containing different grades of ethylcellulose polymer showed prolonged release for 6 to 18 h, but the formulation containing polymer Ethocel[®] standard FP7 premium without co-excipient showed controlled release for 24 h, which can be used to develop controlled release matrices of ibuprofen with optimum release kinetics. All those formulations containing co-excipients showed enhanced release rate.

Key words: Ethocel[®] standard FP premium, Ethocel[®] standard premium, ibuprofen, matrix tablets, co-excipients, controlled release.

INTRODUCTION

Efforts and struggles of human being have been focused on the development of a system to deliver the active pharmaceutical ingredients (APIs) to the site of action with reduced side effects, minimum dosage frequency, maximum patient compliance and low development cost.

As the development cost and duration to introduce a new chemical entity in dosage form in market is approximately \$ 500 million and 10 to 12 years, respectively, while for the development of novel drug delivery system (NDDS) of existing chemical entity, the development cost and duration is approximately \$ 20 to 50 million and 3 to 4 years, respectively (Verma et al., 2002). Among the various NDDS available in market, per oral controlled drug delivery systems hold the major market share, because of their obvious advantages of ease of administration and

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better patient compliance (Verma and Garg, 2001). Controlled drug delivery systems as compared to immediate drug delivery systems provide desired concentration of drug at the absorption site allowing maintenance of plasma concentration within the therapeutic range, reducing the dosing frequency and greater patient compliance (Akhtlaq et al., 2011; Verma et al., 2002). There are different controlled and modified release systems and devices like, reservoir devices, monolithic devices (matrix systems), pendent, enteric films, osmotically controlled devices, electrically stimulated devices and hydrogels, etc., (<http://www.initium.demon.co.uk>, 2011; Rafiq et al., 2010). In the present study, matrix system was selected, because it is an easy to manufacture and popular on a commercial scale in industries (Kar et al., 2009). Incorporation of drug within a matrix offers a better means of controlling the drug release. Controlled release matrices are also cost effective (Muhammad et al., 2010). For the preparation of controlled release matrices, direct compression method was used, because direct compression method is becoming popular for the manufacturing of controlled release tablets and as compare to wet granulation, it is not a complicated method (Mark et al., 2009). It is the process in which tablets are compressed directly from mixture of the drug and excipients without any preliminary treatment (BP, 2004). It is economical and not time consuming and no more steps are required like wet granulation (Yasmeen et al., 2005). Direct compression offers higher efficacy as compared to wet granulation (Zang et al., 2003). Direct compression method is better than wet granulation method, because the unnecessary contact of any drug to heat and moisture is not good (Shangraw, 1998).

The Non-steroidal anti-inflammatory drug, ibuprofen was selected as a suitable candidate in this study. As ibuprofen is propionic acid derivate, which is used for the treatment of rheumatoid arthritis, osteoarthritis, post-operative pain and for reduction of fever and inflammation ((Baum et al., 1985; Herzfeldt and Kümmel, 1983).

The short plasma half-life of 1 to 3 h, GIT irritation following oral administration, dosage frequency and patient non-compliance make it an ideal candidate for controlled-release matrices.

In this study for the preparation of controlled release matrices hydrophobic polymer ethyl cellulose derivatives were used, because ethyl cellulose polymer shows the sustained release properties when the tablets are formulated by direct compression method (Brabander et al., 2003). Mostly, for the extended release formulation, it is used as controlling agent (Scott et al., 2008).

The hydrophilic polymer, hydroxypropyl methyl cellulose (HPMC), sodium corboxy methyl cellulose (CMC) and starch were used as co-excipients to show the effect on the release of drug from hydrophobic matrices.

MATERIALS AND METHODS

Ibuprofen (gifted by drug testing laboratory, Peshawar, Pakistan), Ethocel standard premium 7, 10, 100 and Ethocel standard FP premium 7, 10, 100 (Dow chemical company), HPMC K100M PE (Dow chemical), Na-CMC (Merck), Starch (Merck), Monobasic potassium phosphate (Merck.), NaOH (Merck), Deionized water, UV/Visible double beam spectrophotometer (UV1601, Shimadzu, Japan), Pharma test dissolution apparatus PTWS-11/P, TPT (Germany), Hardness tester (Erweka, Germany), Friabilator (Erweka, Germany), Vernier caliper (Germany), Analytical balance (AX-200, Shimadzu, Japan), micropipette, pH-meter (Denver, USA), Syringes (Otsuka, Pakistan), Single punch tablets compression machine (AR 400, Erweka, Germany), Beakers, Volumetric flasks and Test tubes, (Pyrex, Japan).

Pre-formulation studies for investigation of interaction

For investigation of physicochemical interactions, DSC and FT-IR studies were performed.

Differential scanning calorimetry (DSC) studies

The differential scanning calorimetry (DSC) studies were performed for investigation of ibuprofen interaction with polymers and excipients, using DSC instrument (Mettler Toledo DSC 822e, Greifensee, Switzerland) equipped with Star[®] computer program. Approximately 3 to 6 mg of sample was weighed in aluminum pan and then sealed with punched lid. The temperature range was kept at 20 to 300°C, with heating rate of 10°C/min under nitrogen gas flow.

Fourier transform infrared (FT-IR) studies

For further conformation, FT-IR spectra of pure ibuprofen and its mixture with polymers and different excipients was taken to observe the drug-polymer and excipient interaction, using FT-IR SpectrumOne spectrophotometer (Perkin Elmer, UK) in the range of 650 to 4000 cm⁻¹. The sample of several milligrams was placed on the stage of machine and then, handle of the machine was placed on the sample for generation of enough pressure and sharp peaks with reasonable intensities were obtained. The spectra obtained were the result of 4 scans at 1 cm⁻¹ resolution.

Formulation of directly compressed matrix tablets of ibuprofen

Matrix tablets of Ibuprofen were prepared using polymers (Ethocel[®] standard premium and Ethocel[®] standard FP premium) of different viscosity grades as controlled-releasing agents. HPMC K100M, CMC, starch and lactose were used as co-excipient to determine their influence on the release patterns and release mechanism of the drugs, and magnesium stearate was use as lubricant. Direct compression method was used for the preparation of matrix tablets and drug-to-polymer ratio (D:P) was kept 10:3.

All ingredients except magnesium stearate were mixed according to dilution principle of powders, and then, polybags were used for further mixing. After this, for thorough mixing, the powder mixtures were passed through No. 30-mesh size screen and then, the required amount of magnesium stearate (0.5%) was added as lubricant and was well mixed. Later on each resultant mixture was passed twice through the same mesh screen, and then each mixture was directly compressed into tablets, using single punch machine (Erweka, Germany) equipped with 8 mm punch and die set. The composition of various formulations is given in the Table 1.

Table 1. Different ibuprofen matrix tablets composition.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20	F21	F22	F23	F24	F25
Ibuprofen	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Ethocel® Standard FP7 Preimum	--	30	--	--	--	--	--	30	--	--	--	--	--	30	--	--	--	--	--	30	--	--	--	--	--
Ethocel® Standard FP10 Preimum	--	--	30	--	--	--	--	--	30	--	--	--	--	--	30	--	--	--	--	--	30	--	--	--	--
Ethocel® StandardFP100 Preimum	--	--	--	30	--	--	--	--	--	30	--	--	--	--	--	30	--	--	--	--	--	30	--	--	--
Ethocel® Standard 7 Preimum	--	--	--	--	30	--	--	--	--	--	30	--	--	--	--	--	30	--	--	--	--	--	30	--	--
Ethocel® Standard 10 Preimum	--	--	--	--	--	30	--	--	--	--	--	30	--	--	--	--	--	30	--	--	--	--	--	30	--
Ethocel® Standard 100 Preimum	--	--	--	--	--	--	30	--	--	--	--	--	30	--	--	--	--	--	30	--	--	--	--	--	30
HPMCK100M	--	--	--	--	--	--	--	20.7	20.7	20.7	20.7	20.7	20.7	--	--	--	--	--	--	--	--	--	--	--	--
Lactose	99	69	69	69	69	69	69	48.3	48.3	48.3	48.3	48.3	48.3	48.3	48.3	48.3	48.3	48.3	48.3	48.3	48.3	48.3	48.3	48.3	48.3
Starch	--	--	--	--	--	--	--	--	--	--	--	--	--	20.7	20.7	20.7	20.7	20.7	20.7	--	--	--	--	--	--
Mg-stearate	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Na-CMC	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	20.7	20.7	20.7	20.7	20.7
Total weight	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

Physicochemical evaluation of matrix tablets

In order to assess whether the tablets fulfill the desired specifications, different physical and dimensional tests, such as weight variation, thickness and diameter, hardness test, content uniformity and friability were performed, as mentioned subsequently.

Weight variation test

For this purpose, 20 tablets were taken from each batch and weighed individually, using analytical balance (AX-200, Shimadzu, Japan). The mean and standard deviation were calculated, using computer based excel programme and the results were recorded accordingly.

Thickness and diameter

The thickness and diameter of 20 tablets from each batch were observed by vernier caliper (Vernier caliper, Germany) and then, mean and standard deviation were calculated.

Crushing strength or hardness test

For this test, 10 tablets were taken from each batch and

their hardness was determined by using hardness tester (Erweka, Germany). The mean and standard deviation were calculated and noted accordingly.

Friability test

To determine the friability of the prepared matrix tablets, pre-weighed/de-dusted 20 tablets (W_1) from each formulation were used. For this test, Roche friabilator (Erweka, Germany) was used at speed of 25 rpm for 4 min. Then, the tablets were de-dusted well with the help of a blower and re-weighed (W_2) to determine the loss in their weight. Friability was calculated using the following formula:

$$\% F = \frac{W_1 - W_2}{W_1} \times 100$$

where W_1 = Initial weight of tablets; W_2 = Final weight of tablets.

Content uniformity assay

For this purpose, 10 tablets were taken randomly from each batch and pulverized into powder, using pastle and

mortar. The powder samples equivalent to 20 mg of the drug were transferred to a volumetric flask (100 ml), followed by addition of a small volume of phosphate buffer (pH 7.4) to hydrate the samples and final volume was made upto the mark. The samples were shaken for some time to dissolve the drug completely and were passed through membrane filter paper (0.45 μ m). The absorbance values of standard ibuprofen and the samples were determined at λ_{max} 223 nm, using double beam spectrophotometer (UV-1601, Shimadzu, Japan). Three reading were taken and then, the mean and standard deviation were calculated.

In vitro dissolution studies

In vitro dissolution studies were conducted for the determination of drug release rate from the formulations to USP method-1 (basket method), using eight stations dissolution apparatus, Pharma test (PTWS-11/P, TPT, Hunburg, Germany) and the rotation speed of basket was set at 100 rpm. Each station or flask of the dissolution apparatus was filled with 900 ml of 0.2M phosphate buffer (pH 7.4) used as dissolution medium to study the release rate and pattern of drug from tablets matrices up to 24 h. The temperature of dissolution medium was kept $37 \pm 0.5^\circ\text{C}$. Samples of 5 ml were withdrawn at pre-determined

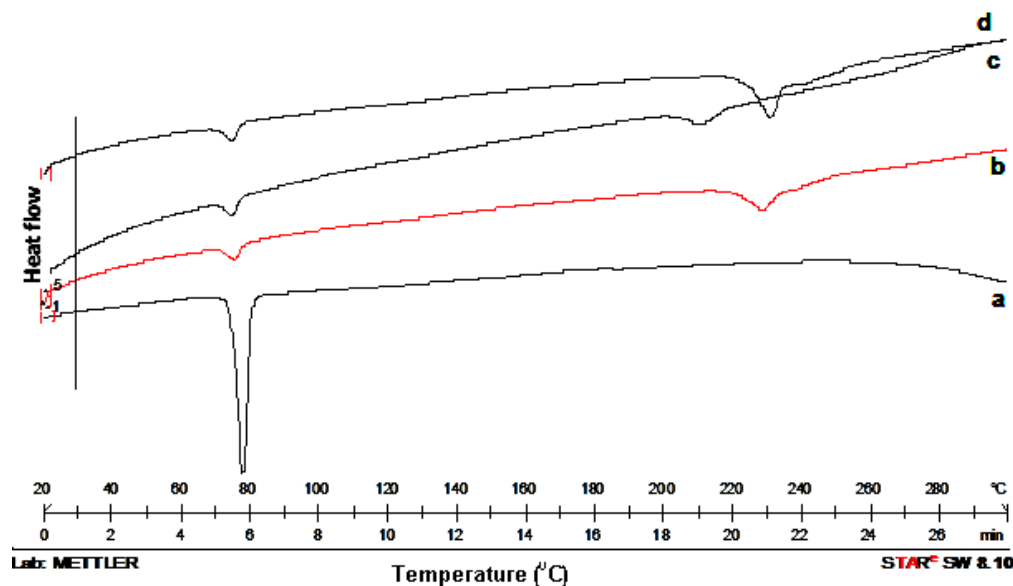


Figure 1. DSC thermogram of pure ibuprofen (a) and physical mixtures of ibuprofen with polymer ethylcellulose, magnesium stearate and lactose, using co-excipients; HPMC (b); starch (c); and CMC (d).

time of interval 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18 and 24 h with the help of syringes consisting of 0.45 μm filters. After each sampling, equal volume of fresh dissolution medium was replaced to maintain the dissolution medium constant. Then, all samples were diluted with the same buffer solution. The absorbance values of model drug (Ibuprofen) were recorded, using spectrophotometer (UV/Visible-1601, Shimadzu, Japan) at λ_{max} 223. Finally, percent release of drugs was calculated, using their respective calibration standard curves. The release study for all formulations was conducted in triplicate.

Drug release kinetics

The following various kinetic models and equations were applied on the data obtained from *in vitro* dissolution studies of different matrix tablets formulations to determine the release kinetics:

1. Zero-order kinetics (Xu and Sunada, 1995; Najib and Suleiman, 1985)

$$W = k_1 t \quad (1)$$

2. First-order kinetics equation (Merchant et al., 2006; Avachat and Kotwal, 2007; Donbrow and Samueloy, 1980; Higuchi, 1963).

$$\ln(100-W) = \ln 100 - k_2 t \quad (2)$$

3. Hixon Crowel's equation (Erosion model) (Costa et al., 2003).

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

4. Higuchi's square of time equation (Diffusion model) (Higuchi, 1963; Korsmeyer et al., 1983).

$$W = k_4 t^{1/2} \quad (4)$$

5. Power law equation or Korsmeyer-Peppas equation for mechanism of drug release (Brabander et al., 2003; Korsmeyer et al., 1983; Riter and Peppas, 1987).

$$M_t / M_\infty = k_5 t^n \quad (5)$$

where M_t/M_∞ is the fraction of drug release at time t . k_1 to k_4 are release rate constants for equations used and these rate constants depend on the kinetics models used and k_5 is the constant comprising the structural and geometric characteristics of the device, W is the percent of drug release at time t and n is the diffusion exponent of the release kinetics used to characterize the transport mechanism. For cylindrical matrix tablets, if the n value is equal to 0.45, then it indicates that the drug release mechanism is Fickian diffusion, and if the n value is more than 0.45 and less than 0.89, it indicates that it is non-Fickian or anomalous in diffusion. However, if the n value is 0.89, it is the indication of case II transport or the typical zero order release (Siepmann and Peppas, 2001), while if it is greater than 0.89, it is the super case II transport (Vueba et al., 2004).

Statistical analysis

Statistical analysis was performed, using computer based excel programme for calculation of mean and standard deviation.

RESULTS AND DISCUSSION

Pre-formulation evaluation for physicochemical interaction

For determination of any interaction, DSC and FT-IR studies were performed.

Differential scanning calorimetry (DSC) studies

To investigate the interactions of ibuprofen with polymers and different excipients, DSC studies were conducted. Figure 1 shows DSC curves of pure ibuprofen and its

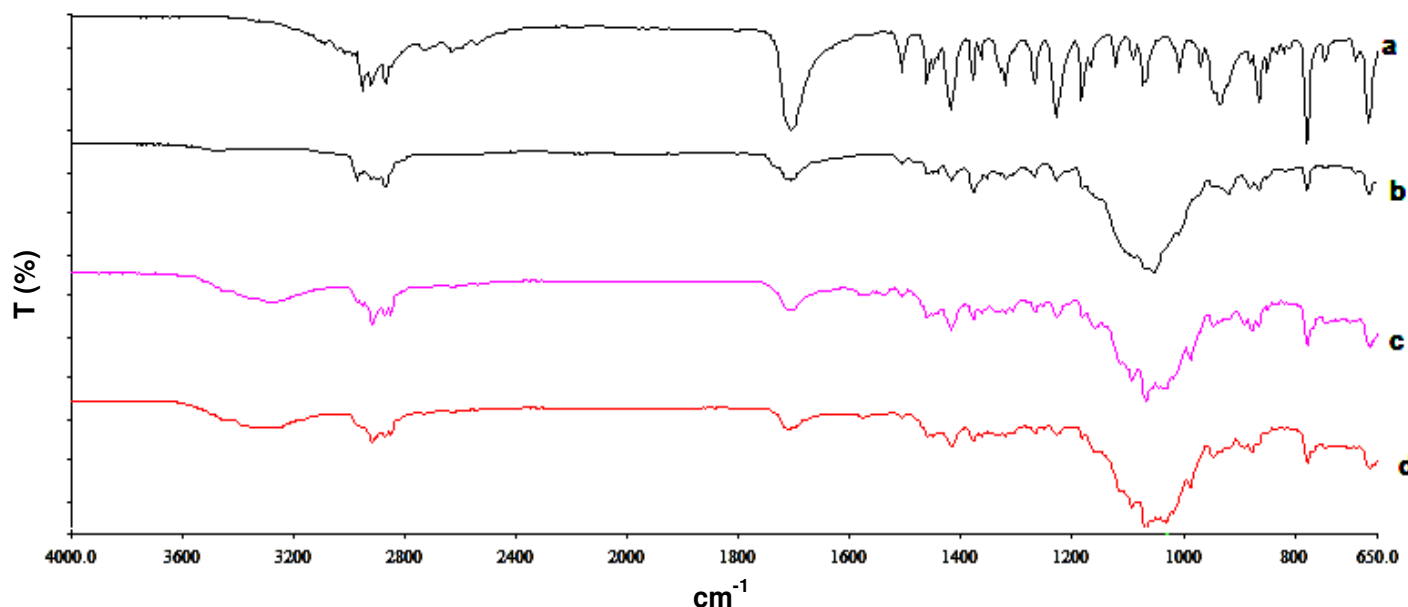


Figure 2. FT-IR spectra of of pure ibuprofen (a) and physical mixtures of ibuprofen with polymer ethylcellulose, magnesium stearate and lactose, using co-excipients; HPMC (b); starch (c); and CMC (d).

physical mixtures with polymer ethyl cellulose ether and different co-excipients. A sharp endothermic peak at 76.94°C was observed for pure ibuprofen at the temperature corresponding to its melting point (Figure 1a). As shown, the endothermic peak of ibuprofen in its mixtures with either the polymers or the coexcipients did not show any major change as compared to that of the pure drug (Figure 1a to d), indicating no possible interaction.

Fourier transform infrared (FT-IR) studies

For further analysis, FT-IR spectra of pure ibuprofen and their respective physical mixtures were also taken to assure the compatibility between pure drug and its physical mixtures with polymer ethylcellulose and different excipients, such as lactose, magnesium stearate, hydroxypropylmethylcellulose (HPMC), starch and carboxymethylcellulose (CMC). The FT-IR spectrums of pure ibuprofen, its physical mixture with polymer ethylcellulose ether and different excipients, such as lactose, magnesium stearate, hydroxypropylmethylcellulose (HPMC), starch and carboxymethylcellulose (CMC) are shown in Figure 2a to c. Pure ibuprofen showed sharp characteristic peaks at 1706 cm^{-1} which corresponds to the carboxyl acid (COOH) present in ibuprofen. Other smaller peaks in the region (1200 to 1000 cm^{-1}) are the indication of benzene ring (Socrates, 1994). As the sharp, characteristic peaks of ibuprofen did not change in physical mixture with polymer and different excipients, indicating no possible interaction.

Preparation and physicochemical evaluation of ibuprofen matrices

As for the preparation of controlled-release formulations, different methods and approaches are used, such as coating technology, osmotically controlled devices, slow eroding devices and matrix systems of swellable or nonswellable polymers (Rafiq et al., 2010), but in the present study directly compressed matrix tablets were prepared using directly compressed method. This method was used, because, it is not time consuming, economical, no preliminary treatment is required and easy to handle (Yasmeen et al., 2005; Zang and Chakrabarti, 2003). Matrix tablets were developed and formulated, using different grades of ethylcellulose polymer and co-excipients with drug-polymer ratio 10: 3 as shown in Table 1. After development, all formulations were evaluated physicochemically and the results obtained are shown in Table 2. The matrix tablets of ibuprofen containing different polymers and co-excipients showed that the drug content for all formulations ranged 98.09 ± 2.322 to $100.03 \pm 2.131\%$, indicating uniform amount of drug in all formulations. The formulated matrix tablets provided good weight variation and hardness, ranging from 199.05 ± 0.421 to 200.15 ± 0.432 and 6.98 ± 0.041 to 7.995 ± 0.032 , respectively, which are within United States Pharmacopoeia range, and other physical characteristics, such as thickness and diameter were also evaluated and found within acceptable limits of USP as shown in Table 2. The matrices also passed the friability test ($F < 1\%$), indicating that all formulations are within USP25 limits (Guyot and Fawaz, 2000).

Table 2. Physicochemical properties of ibuprofen matrix tablets formulation.

Batch code	Dug content (%)	Weight variation	Thickness (mm)	Diameter (mm)	Hardness (Kg/cm ³)	Friability (%)
	n = 3	n = 20	n = 20	n = 20	n = 10	n = 3
	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)
F1	100.03 ± 2.131	200.1 ± 0.442	3.5 ± 0.122	7.99 ± 0.0221	7.03 ± 0.092	0.31 ± 0.05
F2	98.09 ± 2.825	200.02 ± 0.303	3.4 ± 0.022	7.995 ± 0.032	7.16 ± 0.096	0.12 ± 0.01
F3	98.22 ± 1.387	199.1 ± 0.321	3.49 ± 0.031	7.995 ± 0.05	7.13 ± 0.045	0.12 ± 0.06
F4	99.22 ± 1.321	199.9 ± 0.506	3.42 ± 0.022	7.995 ± 0.02	7.11 ± 0.098	0.18 ± 0.01
F5	99.231 ± 2.043	199.7 ± 0.403	3.5 ± 0.032	7.99 ± 0.035	6.99 ± 0.049	0.25 ± 0.04
F6	99.311 ± 1.912	200.01 ± 0.521	3.505 ± 0.039	7.995 ± 0.02	7 ± 0.085	0.23 ± 0.04
F7	98.09 ± 2.322	199.8 ± 0.507	3.5 ± 0.035	7.99 ± 0.035	7 ± 0.085	0.21 ± 0.01
F8	100.01 ± 2.194	200.15 ± 0.432	3.49 ± 0.031	7.99 ± 0.038	7.11 ± 0.045	0.25 ± 0.04
F9	99.08 ± 1.365	200.05 ± 0.321	3.49 ± 0.031	7.99 ± 0.032	7.12 ± 0.075	0.23 ± 0.04
F10	100.01 ± 1.153	199.8 ± 0.543	3.4 ± 0.034	7.99 ± 0.033	7.12 ± 0.096	0.21 ± 0.01
F11	99.025 ± 2.143	199.05 ± 0.421	3.5 ± 0.032	.99 ± 0.036	6.98 ± 0.041	0.13 ± 0.02
F12	98.22 ± 1.387	200.01 ± 0.521	3.51 ± 0.031	7.99 ± 0.032	7 ± 0.085	0.16 ± 0.03
F13	99.211 ± 2.165	199.9 ± 0.506	3.5 ± 0.031	7.99 ± 0.024	7 ± 0.085	0.16 ± 0.04
F14	99.09 ± 2.212	199.1 ± 0.432	3.41 ± 0.31	7.99 ± 0.025	7.12 ± 0.037	0.12 ± 0.01
F15	99.011 ± 3.106	199.1 ± 0.459	3.45 ± 0.023	7.99 ± 0.024	7.13 ± 0.046	0.12 ± 0.01
F16	99.02 ± 2.171	199.05 ± 0.35	3.49 ± 0.032	7.985 ± 0.03	7.12 ± 0.099	0.17 ± 0.01
F17	99.311 ± 3.125	199.83 ± 0.423	3.5 ± 0.032	7.99 ± 0.038	7 ± 0.085	0.19 ± 0.03
F18	99.05 ± 2.355	200 ± 0.454	3.51 ± 0.031	7.995 ± 0.02	7.01 ± 0.076	0.21 ± 0.04
F19	100.03 ± 2.102	200.1 ± 0.498	3.5 ± 0.037	7.985 ± 0.03	6.98 ± 0.048	0.29 ± 0.05
F20	99.08 ± 2.211	199.85 ± 0.323	3.4 ± 0.032	7.985 ± 0.03	7.11 ± 0.049	0.12 ± 0.05
F21	99.012 ± 2.198	200.07 ± 0.354	3.4 ± 0.032	7.99 ± 0.032	7.11 ± 0.077	0.15 ± 0.03
F22	99.231 ± 2.217	199.95 ± 0.54	3.4 ± 0.045	7.99 ± 0.033	7.11 ± 0.075	0.15 ± 0.01
F23	99.032 ± 2.213	200.04 ± 0.321	3.495 ± 0.039	7.995 ± 0.03	6.99 ± 0.043	0.29 ± 0.02
F24	99.152 ± 3.19	199.75 ± 0.543	3.49 ± 0.31	7.995 ± 0.02	7.02 ± 0.096	0.21 ± 0.02
F25	100.012 ± 2.15	200.05 ± 0.365	3.5 ± 0.034	7.99 ± 0.032	6.99 ± 0.099	0.27 ± 0.02

***In-vitro* release study of ibuprofen matrix tablets**

Figures 3, 4, 5 and 6 depicted percentage release of ibuprofen from matrix tablets containing different viscosity grades of ethylcellulose polymer, such as Ethocel[®] standard premium 7, 10, 100 and Ethocel[®] standard FP premium, 7, 10 and 100 and co-excipient with drug to polymer ratio 10: 3. As shown in Figure 3, the drug (Ibuprofen) was released from the formulation F1 after 0.5 h, because it was only containing lactose and no polymer was used to retard the release of drug. As shown in the same figure, slow release of ibuprofen was observed from the formulations F2, F3, F4, F5, F6 and F7, because these formulations were containing different viscosity grades of ethyl cellulose polymer as drug retarding agent. The drug (Ibuprofen) was release from the formulation F3, F4, F5, F6 and F7 before 24 h, but 87.66% of the drug was release from the formulation F2 after 24 h, because in this formulation Ethocel[®] standard FP7 premium polymer was used. This extended release effect of polymer Ethocel[®] standard FP7 premium due to

the small particles size of the polymer as compared to other grades of ethylcellulose, such as Ethocel[®] standard FP 10 premium, Ethocel[®] standard FP 100 premium, Ethocel[®] standard 7 premium, Ethocel[®] standard 10 premium and Ethocel[®] standard 100 premium. The same findings were observed by Khan and Meidan (2007), so, these results conform the findings of their work. Figures 4, 5 and 6 depict the release of ibuprofen from other formulations containing different viscosity grades of ethyl cellulose polymer and co-excipients, such as hydroxypropylmethylcellulose (HPMC K100M), starch and carboxymethylcellulose (CMC). More extended release was observed in the formulations containing HPMC K100M as compared to formulations containing starch and CMC. As shown in Figure 4, 90% of the drug was released from formulations F8 to F13 in 6 to 8 h. As compared to the release from formulation F2 containing Ethocel[®] standard FP7 premium without co-excipient, the release from these formulations was fast, and the more extended release as compared to starch and CMC may be due to the less hydration capacity of HPMC K100M

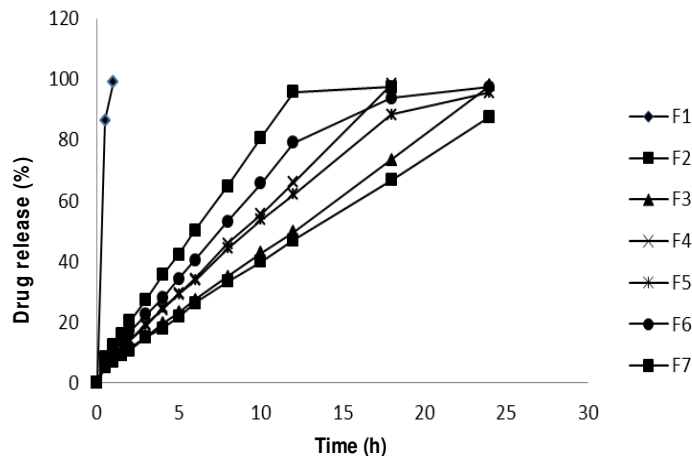


Figure 3. Drug release profiles of ibuprofen from different grades of ethylcellulose polymer.

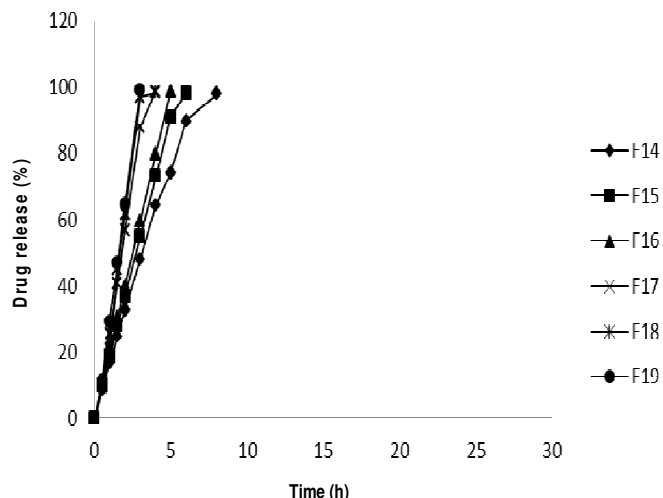


Figure 5. Drug release profile of ibuprofen from different grades of ethylcellulose polymer in presence of co-excipient starch.

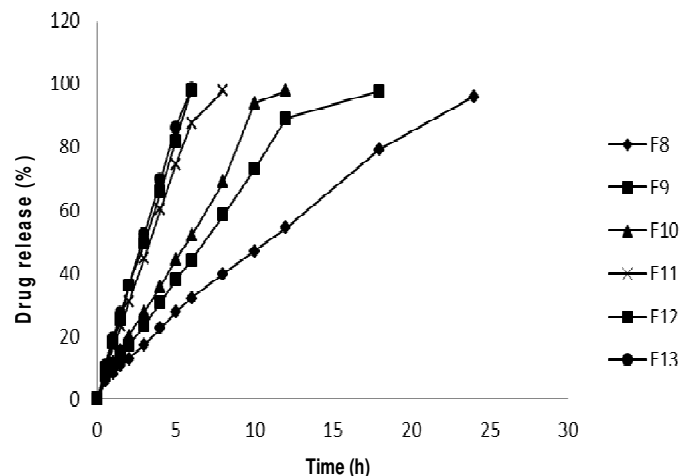


Figure 4. Drug release profile of ibuprofen from different grades of ethylcellulose polymer in presence of co-excipient K100M.

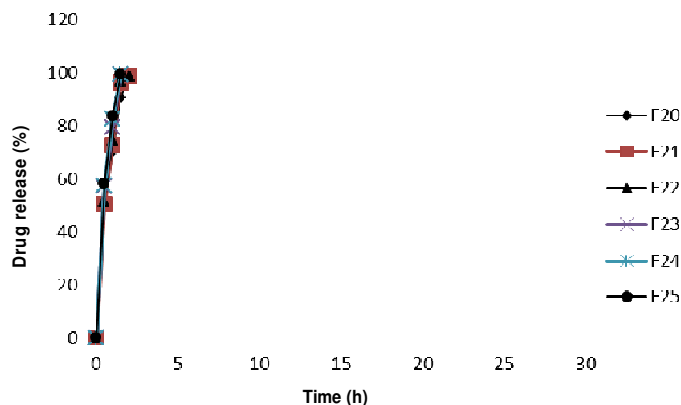


Figure 6. Drug release profile of ibuprofen from different grades of ethylcellulose polymer in presence of co-excipient CMC.

(Luana et al., 2004). However, the higher release as compared to formulations containing Ethocel[®] standard FP7 Premium without co-excipient may be due to the development of osmotic pressure, because HPMC creates osmotic forces following penetration of water within matrices. These results, also conform with the results of these findings (Alderman, 1984; Ford *et al.*, 1987; Khan and Zhu, 1998a, b; Gohal et al., 2003), that HPMC in small quantity may act as channeling agent and can increase the release rate. Figure 5 shows ibuprofen release from the formulations containing starch as co-excipient. As more than 90% of drug was released within 3 to 8 h, it may be that starch is insoluble in water and due to insoluble nature of starch, it may cause non-uniformity of polymeric material around the drug, and due to this property, mostly imperfection in membranes take

place which causes the quick release of drug from tablets. It is also because of the water swillable nature of starch that the same findings were observed by Khan and Zhu (1998b); and for this reason, the enhancement of drug from formulations containing starch could be the water-swillable property of starch. As such, due to this property, it might cause the rupture of the polymeric membrane, and enhance the drug release rate. The same findings were observed when CMC was used as co-excipient as shown in Figure 6, because the drug was released from the formulations containing CMC within 2 h. These results might be attributed to the relatively lower viscosity of CMC which led to low swillability and rapid dilution and erosion of the diffusion gel layer (Alderman, 1984; Hamdy et al., 2007). It may be due to the disintegrating property of CMC (Khan and Rhodes, 1975; Shah and Jarwoski, 1981), because the disintegration properties

Table 3. Different kinetic models applied to determine the release profile of ibuprofen from different formulations consisting ethylcellulose polymer of different viscosity grades and co-excipients HPMC K100M, starch, CMC and formulation consisting only.

Formulation IBF:Ethocel	W = k1t		(100-W) = ln100 - k2t		(100 - W) ^{1/3} = 100 ^{1/3} -k3t		W = k4t ^{1/2}		Mt/M _∞ = k5tn		
	k1 ± SD	r1	k2 ± SD	r2	k3 ± SD	r3	k4 ± SD	r4	k5 ± SD	r5	n
F1	1.345 ± 6.532	0.0361	1.303 ± 1.434	0.2432	1.368 ± 1.321	0.1522	1.041 ± 5.432	0.0262	0.000 ± 0.000	0.3808	0
F2	3.613 ± 0.490	0.9932	0.075 ± 0.039	0.9935	0.089 ± 0.026	0.9901	4.532 ± 2.016	0.9992	0.557 ± 1.103	0.9995	0.855
F3	3.887 ± 0.347	0.9746	0.072 ± 0.032	0.9856	0.098 ± 0.030	0.9845	4.967 ± 2.490	0.9846	0.412 ± 0.774	0.9944	0.762
F4	4.726 ± 1.558	0.9882	0.100 ± 0.046	0.9082	0.128 ± 0.033	0.9021	5.539 ± 3.251	0.8922	0.196 ± 0.403	0.9935	0.772
F5	4.568 ± 1.160	0.9853	0.096 ± 0.033	0.9652	0.119 ± 0.027	0.9762	5.362 ± 2.171	0.9854	0.208 ± 0.412	0.9941	0.758
F6	5.315 ± 1.909	0.941	0.112 ± 0.030	0.9247	0.148 ± 0.036	0.9163	5.910 ± 2.361	0.9751	0.080 ± 0.165	0.9912	0.722
F7	6.4 ± 2.999	0.9604	0.145 ± 0.047	0.7892	0.183 ± 0.039	0.8661	6.623 ± 3.597	0.9654	0.043 ± 0.089	0.9899	0.716
F8	4.299 ± 0.753	0.9921	0.089 ± 0.036	0.9908	0.108 ± 0.026	0.9951	5.171 ± 1.880	0.9923	0.310 ± 0.631	0.9961	0.761
F9	5.887 ± 2.546	0.9522	0.124 ± 0.039	0.743	0.158 ± 0.030	0.9387	6.344 ± 3.270	0.9513	0.089 ± 0.176	0.9887	0.759
F10	6.631 ± 3.904	0.9473	0.159 ± 0.070	0.7937	0.191 ± 0.048	0.8604	6.792 ± 4.973	0.9479	0.057 ± 0.120	0.9901	0.748
F11	8.806 ± 7.046	0.9163	0.247 ± 0.111	0.8821	0.289 ± 0.075	0.8176	7.911 ± 6.275	0.9061	0.018 ± 0.045	0.9184	0.666
F12	9.431 ± 8.732	0.8648	0.286 ± 0.145	0.755	0.318 ± 0.110	0.8275	8.099 ± 7.695	0.8654	0.011 ± 0.029	0.9824	0.623
F13	9.321 ± 8.519	0.8523	0.304 ± 0.151	0.7637	0.335 ± 0.116	0.8312	8.038 ± 7.643	0.8552	0.008 ± 0.021	0.9791	0.6
F14	9.098 ± 7.628	0.9107	0.254 ± 0.112	0.8882	0.298 ± 0.078	0.9202	8.056 ± 6.628	0.9119	0.018 ± 0.050	0.9743	0.657
F15	9.501 ± 9.110	0.8352	0.304 ± 0.148	0.7697	0.338 ± 0.121	0.8221	8.126 ± 8.081	0.8343	0.011 ± 0.030	0.9764	0.607
F16	9.649 ± 10.376	0.7982	0.350 ± 0.205	0.6645	0.372 ± 0.154	0.7509	8.161 ± 9.170	0.7965	0.008 ± 0.023	0.9759	0.58
F17	11.367 ± 15.197	0.6923	0.452 ± 0.314	0.689	0.474 ± 0.229	0.7189	9.041 ± 12.102	0.6959	0.015 ± 0.052	0.9485	0.537
F18	11.412 ± 18.118	0.6152	0.472 ± 0.333	0.4383	0.479 ± 0.279	0.536	8.840 ± 14.366	0.6144	0.010 ± 0.031	0.9715	0.515
F19	11.543 ± 17.572	0.6103	0.530 ± 0.412	0.3591	0.516 ± 0.308	0.4994	8.883 ± 13.956	0.6112	0.007 ± 0.024	0.9517	0.469
F20	8.141 ± 16.140	0.4125	0.628 ± 0.628	0.3982	0.892 ± 0.652	0.3958	5.719 ± 11.434	0.4128	0.000 ± 0.000	0.844	0.128
F21	7.74 ± 17.846	0.2849	0.906 ± 0.720	0.0804	0.901 ± 0.722	0.1635	5.344 ± 12.144	0.2749	0.000 ± 0.000	0.7818	0.106
F22	7.593 ± 17.725	0.2712	0.920 ± 0.746	0.06	0.912 ± 0.740	0.142	5.238 ± 12.599	0.2717	0.000 ± 0.000	0.7728	0.101
F23	6.926 ± 16.420	0.3339	0.673 ± 0.678	0.4048	1.027 ± 0.835	0.2624	4.867 ± 11.625	0.3331	0.000 ± 0.000	0.7495	0.092
F24	6.577 ± 16.778	0.2127	1.036 ± 0.932	0.0079	0.990 ± 0.860	0.0685	4.524 ± 11.921	0.2123	0.000 ± 0.000	0.7051	0.075
F25	6.446 ± 16.686	0.1987	1.034 ± 0.939	0.0049	0.993 ± 0.870	0.0587	4.419 ± 11.861	0.2984	0.000 ± 0.000	0.6972	0.071

might be attributed to this effect. Furthermore, this drastic release may be due to the water soluble property of CMC, because the same findings were observed by Khan and Zhu (1998b) that water soluble co-excipient may break up the polymeric membrane due to the creation of osmotic forces within matrices, causing the higher

release rate of the drug.

Kinetic release study of ibuprofen matrix tablets

Equations 1 to 5 were used to interpret the release

the rate of ibuprofen from matrix tablets containing different viscosity grades of polymer ethyl cellulose and co-excipients. Table 3 shows the rate constants, r^2 for zero order, first order, Higuchi and Hixon Crowel's equations and "n" values for power law of the formulated matrix tablets. On the basis of r^2 values obtained from different kinetics

equations, the ibuprofen release from formulations F2, F3, F4, F5, F6, F7, F8, F9, F10, F12 and F13 were found to follow the first order equation, zero order equation, Higuchi equation, Hixon Crowell's equation and power law. As shown, majority of the formulations (F2, F3, F4, F5, F6, F7, F8, F9, F10, F12 and F13) have diffusional exponent value "n" between 0.469 and 0.855, and it is the indication that these formulations follow non-Fickian anomalous release mechanism (n value between 0.45 and 0.89) this means that the drug released pure diffusion controlled mechanism coupled with swelling and erosion mechanisms, while the remaining formulations showed n value less than 0.45. This smaller value, may be due to partially drug diffusion through swollen matrix and water filled pores in the formulations (Roshan et al., 2008). As shown in the same table (Table 3), the formulation containing Ethocel® standard FP7 premium (F2) showed better release kinetics as compared to other formulations containing different grades of ethylcellulose polymer and formulations containing co-excipients.

Conclusion

It is concluded that Ethocel® standard FP premium polymers are more efficient than conventional Ethocel standard premium polymers in extending and controlling the release rates of ibuprofen. Our results revealed that Ethocel standard 7 FP premium showed more effective role in controlling the release of drug. The co-excipients, such HPMC K100M, starch and CMC showed increase drug release. It is also concluded that controlled release matrix tablets of ibuprofen can be prepared using Ethocel® standard FP 7 premium without any unwanted interaction.

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