Faculty of Pharmacy[1], Gomal, University, D.I. Khan, N.W.F.P; Department of Pharmacy[2], Islamia, University, Bahawal Pur; Department of Pharmaceutics[3], Faculty of Pharmacy, University of Karachi, Pakistan

Formulation and evaluation of controlled release matrices of ketoprofen and influence of different co-excipients on the release mechanism

A. WAHAB[1], G. M. KHAN[1], M. AKHLAQ[1], N. R. KHAN[1], A. HUSSAIN[1], M. F. KHAN[1], H. KHAN[1]

Received February 13, 2011, accepted April 8, 2011

Dr. Abdul Wahab, Faculty of Pharmacy, Gomal, University, Dera Ismail Khan, 28000 Pakistan
wahabscholar@yahoo.com

Pharmazie 66: 677–683 (2011) *doi: 10.1691/ph.2011.1040*

The present work reports the study of different controlled release formulations of ketoprofen, which is a non-steroidal anti-inflammatory drug (NSAID) and like other NSAIDs requires large and frequent daily doses, resulting in severe side effects and non-compliance. To avoid these problems, controlled release matrices were developed using different grades of ethylcellulose polymer with a drug-polymer ratio of 10:3 by the direct compression method. The effect on drug release of partial replacement of lactose by different co-excipients, HPMC K100 M, starch and CMC, was also studied. The tablets were tested for their drug content, weight variation, friability, hardness, thickness and diameter, all these physical properties being within the USP range. The release profile of all formulations containing polymer and co-excipients was compared with a formulation developed without polymer and co-excipients. After a 24-hour release study, it was concluded that formulations containing different grades of ethylcellulose polymer showed prolonged release for 6–18 hours, but the formulation containing the polymer Ethocel® standard FP 7 Premium without co-excipient showed controlled release for 24 hours. DSC and FT-IR studies were performed to investigate any incompatibility between drug, polymer and co-excipient but no interaction was found. Different kinetic models were used, such as first order equation, zero order equation, Higuachi equation, Hixon Crowel's equation and Korsmeyer-Peppas to study the release mechanism. The formulations containing co-excipients showed an enhanced release rate.

1. Introduction

Ketoprofen [2-(3-benzoylphenyl)propionic acid] is a 2-alrylpropionic acid derivative belonging to the non-steroidal antiinflamatory (NSAID) group of analgesics, used for rheumatoid arthritis, osteoarthritis and post-operative pain, and for reduction of fever and inflammation (Montoya et al. 2004). It is poorly soluble in water, and thus eliminated from the gastrointestinal tract (GIT) after administration before being completely absorbed and dissolved in the systemic circulation, resulting in slower onset of action and failure to achieve the desired therapeutic level (Shekunov and York 2000; Liversidge and Cundy 1995; Merisko-Liversidge et al. 2003). Due to the dosage frequency, its short half life, some GIT irritation and its poor water solubility ketoprofen is a suitable subject for the preparation of controlled release formulations. Controlled release formulations reduce side effects and allow the desired concentration of drug at the desired delivery rate to reach the site of action, maintaining the plasma concentration of the drug within the therapeutic range (Rajan et al. 2002; Brabander et al. 2003). Controlled release formulations facilitate better patient compliance and the safety level of controlled release formulations of potent drugs is higher (Kar et al. 2009). In the present study a matrix system was selected because it is easy to manufacture and popular on a commercial scale in industry (Kar et al. 2009). Incorporation of a drug within a matrix offers a better means of controlling the release of the drug, and controlled release matrices are also cost effective (Muhammad et al. 2010). For the preparation of the controlled release matrices, the direct compression method was used, because this method is becoming popular for the manufacture of controlled release tablets and, compared with wet granulation, the method is not complicated. In this process, tablets are compressed directly from a 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 than with wet granulation (Yasmeen et al. 2005). Direct compression offers higher efficacy as compared with wet granulation. The direct compression method is preferable to the wet granulation method because the unnecessary contact of any drug with heat and moisture is undesirable (Shangraw 1998).

In this study of the preparation of controlled release matrices, hydrophobic ethyl cellulose polymer derivatives were used because ethyl cellulose polymer shows sustained release properties when the tablets are formulated by the direct compression method (Brabander et al. 2003). And for extended release formulations it is mostly used as a controlling agent (Scott et al. 2008). The hydrophilic polymer, hydroxypropyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (CMC) and starch were used as co-excipients to show the effect on drug release from hydrophobic matrices.

Table 1: Composition of ketoprofen matrix tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F16	F17	F18	F19	F20	F21	F22	F23	F24	F25
Ketoprofen	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 Preimuim	–	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	–	–	–	–	–	3	–	–	–	–	30
HPMC K100M	–	–	–	–	–	–	–	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
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	11	1	1
Na-CMC	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	20.7	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

2. Investigations, results and discussion

2.1. Preparation and physical characteristics of ketoprofen matrices

Matrix tablets were developed using different grades of ethylcellulose polymer with different drug-polymer ratios as shown in Table 1. While different methods are used to formulate matrix tablets, in this study the direct compression method was used because it is not time consuming, is economical, requires no preliminary treatment and is easy to handle. The formulated matrices were evaluated physically as shown in Table 2. These properties were studied by determining the drug content, average weight, hardness, friability, thickness and diameter of the prepared matrices. The evaluation of ketoprofen matrix tablets containing different polymers and co-excipients showed that the drug content of all the formulations ranged from $98.041 \pm 2.813\%$ to $100.042 \pm 2.153\%$, indicating a uniform amount of drug in all the formulations. All these formulations provided satisfactory weight variation, and the hardness ranged from 6.97 ± 0.048 to 7.995 ± 0.022, within the USP range, while other characteristics such as thickness and diameter gave results as shown in Table 2, which also fall in the USP range. The matrices also passed the friability test ($F < 1\%$), indicating that all formulations are within the USP25 limits (Guyot and Fawaz 2000).

2.2. Differential scanning calorimetry (DSC) studies

Differential scanning calorimetry studies were performed to investigate possible drug-polymer and drug-excipient interactions. The DSC thermograms are shown in Fig. 1. The thermal

Table 2: Physical properties of ketoprofen matrix tablets

Batch code	Dug content (%)	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^3)	Friablity (%)
F1	99.02 ± 2.123	199.5 ± 0.51	3.495 ± 0.022	7.995 ± 0.022	7.01 ± 0.05	0.25
F2	98.09 ± 2.823	200.05 ± 0.605	3.5 ± 0.032	7.995 ± 0.022	6.97 ± 0.048	0.124
F3	99.07 ± 2.034	200.1 ± 0.447	3.505 ± 0.039	7.995 ± 0.022	6.98 ± 0.042	0.124
F4	98.22 ± 1.322	199.9 ± 0.553	3.495 ± 0.022	7.995 ± 0.022	7 ± 0.082	0.25
F5	99.211 ± 2.037	199.9 ± 0.308	3.5 ± 0.032	7.99 ± 0.031	6.97 ± 0.048	0.15
F6	99.321 ± 1.994	200.01 ± 0.512	3.49 ± 0.031	7.995 ± 0.022	7 ± 0.082	0.134
F7	98.08 ± 2.327	199.9 ± 0.553	3.5 ± 0.032	7.99 ± 0.031	7 ± 0.082	0.15
F8	100.01 ± 2.193	200.15 ± 0.587	3.49 ± 0.031	7.99 ± 0.031	6.98 ± 0.042	0.099
F9	99.05 ± 1.334	200.05 ± 0.51	3.49 ± 0.031	7.99 ± 0.031	7.01 ± 0.074	0.161
F10	100.02 ± 1.163	199.9 ± 0.553	3.5 ± 0.034	7.99 ± 0.031	7 ± 0.082	0.2
F11	99.024 ± 2.172	200.05 ± 0.394	3.5 ± 0.032	7.99 ± 0.031	6.97 ± 0.048	0.149
F12	98.041 ± 2.813	200.1 ± 0.447	3.49 ± 0.031	7.985 ± 0.037	7.03 ± 0.095	0.149
F13	99.221 ± 2.163	199.95 ± 0.51	3.505 ± 0.022	7.995 ± 0.022	6.98 ± 0.042	0.255
F14	99.07 ± 2.201	200.1 ± 0.447	3.51 ± 0.31	7.995 ± 0.022	6.99 ± 0.032	0.125
F15	98.012 ± 3.103	200 ± 0.459	3.505 ± 0.022	7.995 ± 0.022	6.98 ± 0.042	0.22
F16	99.04 ± 2.136	200.05 ± 0.394	3.495 ± 0.039	7.985 ± 0.037	7.03 ± 0.095	0.27
F17	99.312 ± 3.121	199.85 ± 0.489	3.5 ± 0.032	7.99 ± 0.031	7 ± 0.082	0.15
F18	99.03 ± 2.356	200 ± 0.459	3.51 ± 0.031	7.995 ± 0.022	7.01 ± 0.074	0.1
F19	100.03 ± 2.113	200.1 ± 0.447	3.5 ± 0.032	7.985 ± 0.037	6.98 ± 0.042	0.299
F20	99.09 ± 2.213	199.95 ± 0.394	3.5 ± 0.032	7.985 ± 0.037	6.98 ± 0.042	0.175
F21	99.012 ± 2.135	200.05 ± 0.394	3.495 ± 0.022	7.99 ± 0.031	6.99 ± 0.08	0.274
F22	98.231 ± 2.211	199.95 ± 0.51	3.5 ± 0.032	7.99 ± 0.031	7.01 ± 0.074	0.2
F23	99.032 ± 2.523	200.05 ± 051	3.495 ± 0.039	7.985 ± 0.037	6.98 ± 0.042	0.199
F24	99.122 ± 3.183	199.85 ± 0.489	3.49 ± 0.31	7.995 ± 0.022	7.03 ± 0.095	0.21
F25	100.042 ± 2.153	200.05 ± 0.394	3.5 ± 0.032	7.99 ± 0.031	6.99 ± 0.088	0.27

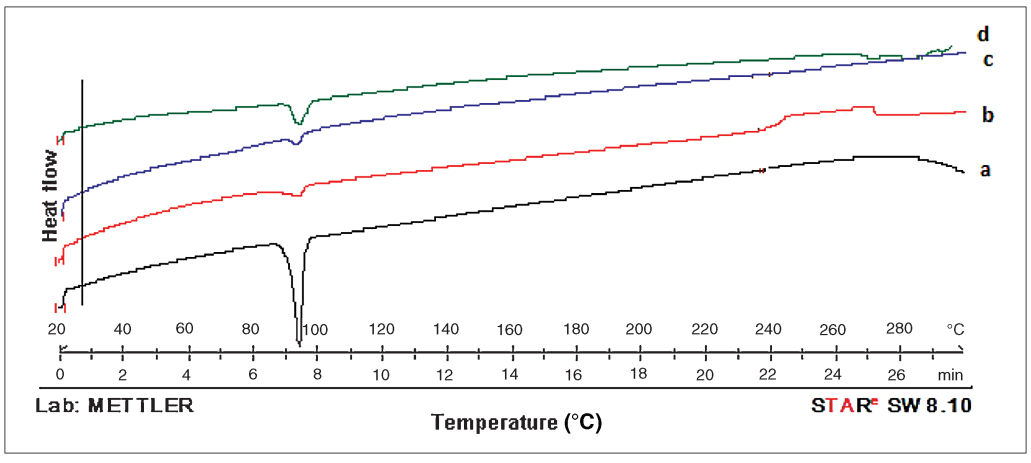

Fig. 1: DSC Thermogram of (a) pure ketoprofen, (b) physical mixture of ketoprofen with ethylcellulose polymer, magnesium stearate, lactose and HPMC, (c) physical mixture of ketoprofen with ethylcellulose polymer, magnesium stearate, lactose and starch, (d) physical mixture of ketoprofen with ethylcellulose polymer, magnesium stearate, lactose and CMC.

curve of ketoprofen (Fig. 1 a) showed a single endothermic peak at 94 °C, corresponding to the melting point of ketoprofen (Mudit et al. 2010). As shown in Fig. 1, a-d the endothermic peaks of ketoprofen in the physical mixture of ethylcellulose polymer and different excipients such as lactose, magnesium sterate, hydroxypropylmethylcellulose (HPMC), starch and carboxymethylcellulose (CMC) were found at the same temperatures as with pure ketoprofen, indicating that no possible chemical interaction was found between ketoprofen and the polymer or the different excipients.

2.3. *Fourier transform infrared (FT-IR) studies*

For further analysis, FT-IR spectra were also taken to assure the compatibility between pure drug and its physical mixtures with ethylcellulose polymer and the different excipients such as lactose, magnesium stearate, hydroxypropylmethylcellulose (HPMC), starch and carboxymethylcellulose (CMC). The FT-IR spectra of pure ketoprofen (Fig. 2a) showed characteristic symmetric carbonyl peaks at 1693.8 cm^{-1} and 1654.0 cm^{-1} due to dimeric carboxylic and ketonic group stretching vibrations, respectively (Sancin et al. 1999; Mura et al. 1998). The characteristic acid carbonyl stretching band of ketoprofen was unchanged in formulations with ethylcellulose polymer and different excipients such as lactose, magnesium stearate, hydroxypropylmethylcellulose (HPMC), starch and carboxymethylcellulose (CMC) as shown (Fig. 2 a-d). These

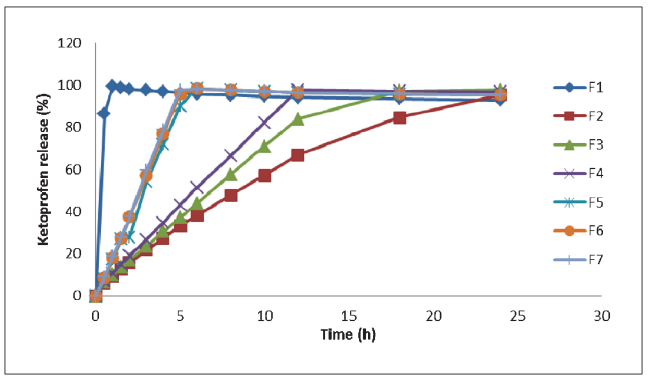

Fig. 3: Drug release profiles for ketoprofen from different grades of ethylcellulose polymer.

studies confirm the lack of a possible interaction between the drug, the polymer and the different excipients.

2.4. *In vitro release analysis of ketoprofen from matrices*

Figures 3, 4, 5, and 6 show the percentage release profile of ketoprofen from matrix tablets containing different grades of ethylcellulose polymer and co-excipients. As shown in Fig. 3, formulation F1 containing ketoprofen and lactose without polymer and co-excipient released all of the drug after 0.5 h because

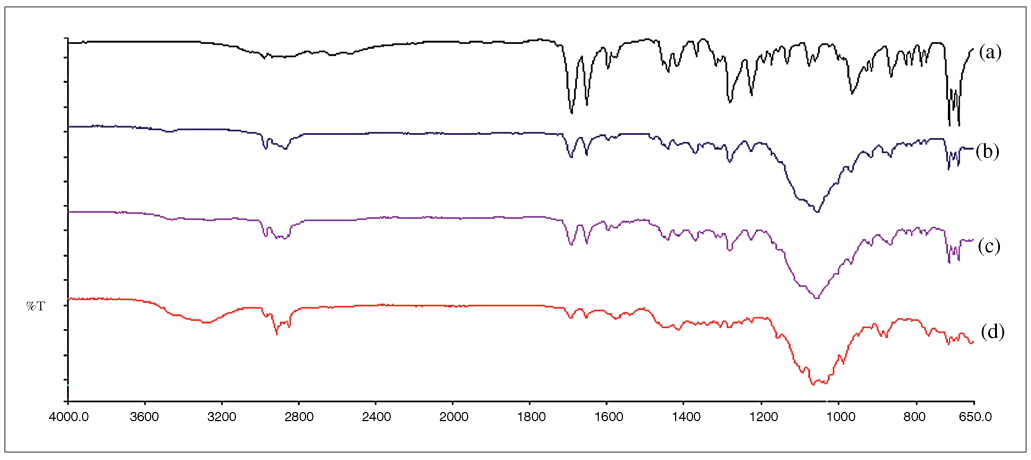

Fig. 2: FT-IR Spectra of (a) pure ketoprofen, (b) physical mixture of ketoprofen with ethylcellulose polymer, magnesium stearate, lactose and HPMC, (c) physical mixture of ketoprofen with ethylcellulose polymer, magnesium stearate, lactose and starch, (d) physical mixture of ketoprofen with ethylcellulose polymer, magnesium stearate, lactose and CMC.

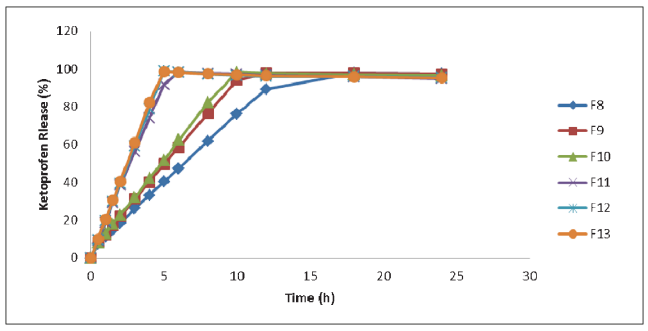

Fig. 4: Drug release profile for ketoprofen from different grades of ethylcellulose polymer in presence of co-excipient K100 M HPMC.

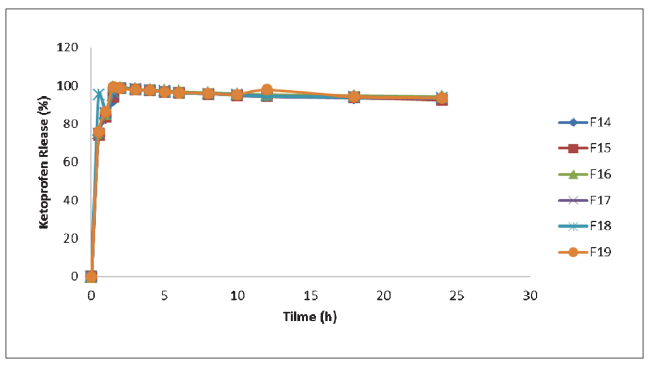

Fig. 5: Drug release profile for ketoprofen from different grades of ethylcellulose polymer in presence of co-excipient starch.

no polymer was used to retard the release of the drug but, as shown in the same figure, slow release of ketoprofen was observed from formulations such as F2, F3, F4, F5, F6 and F7, containing different grades of ethylcellulose polymer. As shown, all the drug was released from F3, F4, F5, F6 and F7 after 24 hours but release from formulation F2 was only 95.5% even after 24 h because in this formulation Ethocel® standard FP 7 Premium polymer was used. This extended release effect with Ethocel® standard FP 7 Premium polymer is due to the small particle size of the polymer as compared with 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 because all these grades have a larger particle size as compared with Ethocel® standard FP 7 Premium. The same findings were observed by Khan and Meidan (2007) so, these results conform their findings. Similarly, Figures 4, 5 and 6 show the release of ketoprofen from different grades of ethylcellulose polymer in the presence of co-excipients such as HPMC, starch and CMC. The release of drug from the formulation containing HPMC K100 M was extended compared with formulations containing starch and CMC, because 90% of the drug was released in 5–12 hours from formulation F8-F13, but, compared with the release from formulation F2 containing Ethocel® standard FP 7 Premium without co-excipient, the release from these formulations was fast, and the more extended release as compared with starch and CMC may be due to the lower hydration capacity of HPMC K100 M (Luana et al. 2004), while the higher release compared with the formulation containing Ethocel® standard FP 7 Premium without co-excipient may be due to the development of osmotic pressure because HPMC creates osmotic forces following penetration of water within the matrices. These results confirm the findings of Alderman (1984), Ford et al. (1987), Khan and Zhu (1998a, b) and Gohal et al. (2003), that HPMC in small quantities may act as a channeling agent and can increase the release rate, but note the results shown in Fig. 5 for the release of ketoprofen from formulations containing starch as co-excipient. As shown, more than 90% of the drug is released within 2–3 h. This is because starch is insoluble in water and due to the insoluble nature of starch it may cause non-uniformity of the polymeric material around the drug and due mostly to this property imperfections in the membranes occur, which causes the quick release of the drug from tablets, and it may be due to the swellable nature of starch in water that the same findings were observed by Khan and Zhu (1998b) for the enhancement of drug release from formulations containing starch. This is attributed to the water-swellable properties of starch because due to this property it might cause the polymeric membrane to be ruptured, causing the enhancement of the drug release rate. The same findings were observed when CMC was used as co-excipient as shown in Fig. 6 because all the drug was released from the formulations containing CMC within 2 h. These results might be attributed to the relatively lower viscosity of CMC leading to low swellability and rapid dilution and erosion of the diffusion gel layer (Alderman 1984; Hamdy et al. 2007). The disintegrating properties of CMC (Khan and Rhodes 1975; Shah and Jarwoski 1981) might also contribute to this effect. Furthermore, this rapid release may be due to the solubility of CMC in water, because it has also been observed by Khan and Zhu (1998b) that a water-soluble co-excipient may break up the polymeric membrane due to the creation of osmotic forces within matrices, causing a higher drug release rate.

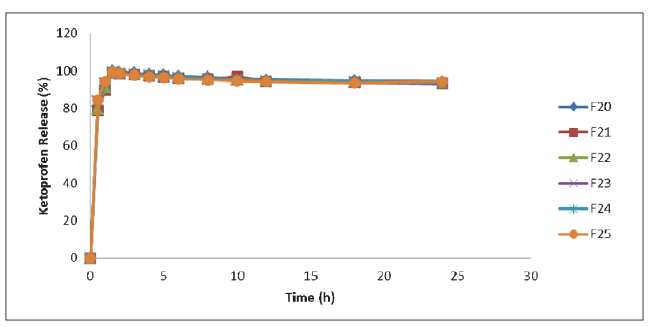

Fig. 6: Drug release profile for ketoprofen from different grades of ethylcellulose polymer in presence of co-excipient CMC.

2.5. Drug release kinetics

The experimental data were fitted to Eqs. (1) – (5) to interpret the release rate of the drug from matrix tablets. The rate constants, r^2 for zero order, first order, Higuichi and Hixon Crowel's equations and "n" values for the power law, of the formulated matrix tablets are given in Table 3. Considering the r^2 values obtained from different kinetic equations, ketoprofen release from most of the formulations, such as F2, F3, F, F5, F6, F7, F8, F9, F10, F12 and F13, was found to follow the first order equation, zero order equation, Higuichi equation, Hixon Crowel's equation and power law. As shown, the majority of the formulations (F2, F3, F, F5, F6, F7, F8, F9, F10, F12 and F13) have a diffusional exponent
value "n" between 0.596 and 0.784, indicating that these formulations follow a non-Fickian anomalous release mechanism (n value between 0.45 and 0.89); this means that the drug is released by a 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 drug diffusion occurring partially through the swollen matrix and water filled pores in the formulation (Roshan et al. 2008). The formulation containing Ethocel® standard FP 7 Premium (F2) showed better release kinetics compared with other formulations containing different grades of ethylcellulose

Table 3: Different kinetic models applied to determine release profile of ketoprofen from different formulations consisting of ethylcellulose polymer of different viscosity grades and co-excipients HPMC K100 M, starch, CMC and formulation consisting of lactose only without polymer and co-excipients (mean ± SD of three determinations)

Formulation KTF:Ethocel	$W = k1t$		$(100-W) = \ln 100 - k2t$		$(100-W)^{1/3} = 100^{1/3} - k_3 t$		$W = k_4 t^{1/2}$		$M_t/M_\infty = k_5 t^n$		
	$k_1 \pm SD$	r_1	$k_2 \pm SD$	r_2	$k_3 \pm SD$	r_3	$k_{4\pm SD}$	r_4	$k_5 \pm SD$	r5	n
F1	1.645 ± 7.541	0.0262	1.403 ± 1.587	0.2427	1.269 ± 1.436	0.1611	1.030 ± 5.372	0.0262		0.3809	-0.000
F2	4.793 ± 1.454	0.9923	0.093 ± 0.017	0.9204	0.128 ± 0.022	0.967	5.669 ± 1.063	0.9923	0.167 ± 0.343	0.9879	0.784
F3	5.882 ± 2.271	0.957	0.118 ± 0.032	0.7279	0.153 ± .022	0.8335	6.325 ± 2.561	0.957	0.126 ± 0.265	0.9882	0.776
F4	6.643 ± 3.153	0.9619	0.144 ± 0.058	0.7783	0.177 ± 0.037	0.8632	6.832 ± 3.806	0.9619	0.088 ± 0.188	0.9853	0.771
F5	9.0766 ± 10.1347	0.8343	0.296 ± 0.160	0.7633	0.323 ± 0.126	0.8211	8.056 ± 9.443	0.8343	0.024 ± 0.071	0.933	0.662
F6	7.79 ± 10.043	0.8142	0.322 ± 0.174	0.7452	0.347 ± 0.140	0.7961	8.327 ± 8.901	0.8142	0.020 ± 0.059	0.9719	0.633
F7	9.7 ± 10.275	0.8031	0.336 ± 0.192	0.7069	0.358 ± 0.149	0.7717	8.263 ± 9.222	0.0831	0.015 ± 0.046	0.9747	0.619
F8	6.09 ± 2.564	0.9636	0.131 ± 0.036	0.7615	0.168 ± 0.028	0.8585	6.446 ± 2.946	0.9636	0.073 ± 0.151	0.9914	0.745
F9	6.977 ± 3.900	0.9625	0.171 ± 0.063	0.8324	0.206 ± 0.043	0.8956	6.968 ± 3.825	0.9625	0.044 ± 0.097	0.9924	0.730
F10	7.172 ± 4.483	0.9536	0.185 ± 0.082	0.8004	0.218 ± 0.053	0.8773	7.049 ± 4.901	0.9536	0.037 ± 0.081	0.9867	0.723
F11	9.750 ± 9.438	0.813	0.311 ± 0.152	0.7634	0.343 ± 0.124	0.8183	8.263 ± 8.167	0.8313	0.014 ± 0.042	0.6979	0.612
F12	9.705 ± 10.472	0.7998	0.346 ± 0.214	0.6451	0.366 ± 0.157	0.7442	8.221 ± 9.301	0.7998	0.011 ± 0.033	0.9702	0.596
F13	7.172 ± 4.483	0.9536	0.185 ± 0.082	0.8004	0.218 ± 0.053	0.8773	7.049 ± 4.901	0.9536	0.037 ± 0.081	0.9861	0.723
F14	3.315 ± 5.322	0.321	2.109 ± 0.973	0.5012	2.321 ± 0.977	0.109	3.098 ± 7.04	0.321	0.0001 ± 0.001	0.9321	0.0432
F15	3.714 ± 7.890	0.209	1.011 ± 0.864	0.038	1.030 ± 0.986	0.0915	2.471 ± 5.668	0.209	0.000 ± 0.000	0.8693	0.039
F16	3.731 ± 9.086	0.1718	1.167 ± 1.077	0.2007	1.102 ± 1.058	0.0286	2.516 ± 6.990	0.1718	0.000 ± 0.000	0.7664	0.037
F17	3.688 ± 8.171	0.1953	1.041 ± 0.890	0.0313	1.050 ± 1.005	0.0815	2.474 ± 5.853	0.1953	0.000 ± 0.000	0.8373	0.037
F18	0.253 ± 9.270	0.0052	1.306 ± 1.632	0.026	1.246 ± 1.584	0.0074	0.048 ± 6.565	0.0052	0.000 ± 0.000	0.2768	0.004
F19	3.614 ± 9.330	0.1767	1.144 ± 1.054	0.0056	1.098 ± 1.068	0.047	2.443 ± 6.679	0.1767	0.000 ± 0.000	0.7529	0.035
F20	2.785 ± 7.541	0.0869	1.375 ± 1.410	0.0453	1.199 ± 1.212	0.0009	1.836 ± 5.394	0.869	0.000 ± 0.000	0.734	0.021
F21	2.94 ± 7.975	0.0972	1.159 ± 1.090	0.0007	1.125 ± 1.137	0.0102	1.947 ± 5.722	0.0972	0.000 ± 0.000	0.7183	0.023
F22	2.892 ± 7.912	0.0731	1.219 ± 1.162	0.0147	1.154 ± 1.169	0.0004	1.909 ± 5.656	0.0731	0.000 ± 0.000	0.7023	0.020
F23	2.148 ± 6.306	0.0174	1.223 ± 1.215	0.0382	1.176 ± 1.254	0.0078	1.383 ± 4.519	0.0174	0.000 ± 0.000	0.6721	0.010
F24	2.156 ± 6.344	0.0201	1.261 ± 1.247	0.0411	1.194 ± 1.268	0.008	1.393 ± 4.544	0.0201	0.000 ± 0.000	0.6637	0.012
F25	2.061 ± 6.182	0.0083	1.251 ± 1.269	0.0566	1.194 ± 1.290	0.0182	1.313 ± 4.428	0.0083	0.000 ± 0.000	0.6201	0.001

polymer and formulations containing co-excipients as shown in Table 3.

2.6. Conclusion

Controlled release matrix tablets of ketoprofen were prepared using different grades of ethylcellulose polymer by a direct compression method. All the physical tests performed, such as hardness, weight variation, thickness and diameter, gave results within acceptable limits. The formulations containing different grades of ethylcellulose polymer showed prolonged release up 12 h compared with the formulation without polymer, but drug release from the formulation containing Ethocel® standard FP 7 Premium polymer was prolonged and controlled over 24 h. All the co-excipients used in this study, such as HPMC K100 M, starch and CMC, produced an enhancement in the drug release rate. However, HPMC K100 M showed a slower drug release rate compared with starch and CMC. No possible interactions of the drug with different grades of ethylcellulose polymer and excipients were observed in this investigation, as confirmed by the DSC and FT-IR studies. It is concluded that controlled release matrices of ketoprofen can be prepared without risk of possible interactions using Ethocel® standard FP 7 Premium polymer to avoid the side effects of ketoprofen and improve patient compliance due to reduced dosage frequency.

3. Experimental

3.1. Materials

Ketoprofen (donated by Drug Testing Laboratory, Peshawar, Pakistan), Ethocel Standard Premium 7, 10, 100, and Ethocel Standard FP Premium 7, 10, 100 (Dow Chemical Company), monobasic potassium phosphate (Merck,), NaOH (Merck), HPMC K100 M PE (Dow Chemical Company), Na-CMC, starch, deionised water, Pharma Test dissolution apparatus PTWS-11/P, TPT (Germany), UV/Visible double beam spectrophotometer (UV1601,Shimadzu, Japan), Friabilator (Erweka, Germany), hardness tester (Erweka, Germany), vernier callipers (Germany), analytical balance (AX-200, Shimadzu,Japan), micropipette, pH-meter (Denver, USA), syringes (Otsuka, Pakistan), single punch tablet compression machine (AR 400, Erweka, Germany), beakers, volumetric flasks, test tubes, (Pyrex, Japan).

3.2. Methods

3.2.1. Formulation of matrix tablets containing ketoprofen

Matrix ketoprofen tablets were prepared using Ethocel standard premium and Ethocel standard FP premium polymer of different viscosity grades; HPMC K100 M, Na-CMC, starch and lactose were used as co-excipients to determine their influence on the release mechanism of ketoprofen from polymers and magnesium stearate was used as a lubricant. The direct compression method was used to prepare the matrix tablets and the drug:polymer ratio was kept at 10:3. All ingredients except magnesium stearate were mixed according to the dilution principle of powders and then a polybag was used for further mixing. After this for thorough mixing the powder mixture was passed through a No 30-mesh size screen and then the required amount of magnesium stearate 0.5% was added as lubricant and mixed well and then each resultant mixture was passed twice through the same mesh screen and then each mixture was directly compressed using a single punch machine (Erweka, Germany) equipped with an 8 mm punch and die set. The composition of the various formulations is given in Table 1.

3.2.2. Differential scanning calorimetry (DSC) studies

The differential scanning calorimetry (DSC) study was performed for the determination of drug interactions with polymers and excipients, using a DSC instrument (Mettler Toledo DSC 822e, Greifensee, Switzerland) equipped with the Star^e computer program. Approximately 3–6 mg of sample was weighed in an aluminum pan and then sealed with a punched lid. The temperature range was 20–300 °C, with a heating rate of 10 °C/min under nitrogen gas flow.

3.2.3. Fourier transform infrared (FT-IR) studies

The FT-IR spectra of pure ketoprofen and its mixture with polymers and different excipients were taken to observe drug-polymer and drug-excipient interactions, using an FT-IR SpectrumOne spectrophotometer (Perkin Elmer, UK) in the range of 650 to 4000 cm^{-1}. A sample of several milligrams was placed on the stage of the machine and then the handle of the machine was placed on the sample to generate enough pressure and sharp peaks with reasonable intensities were obtained. The spectra obtained were the result of 4 scans at 1 cm^{-1} resolution.

3.2.4. Physical evaluation of matrix tablets

As the basic aim of this study was to show the effect of different viscosity grades of ethyl cellulose derivative polymers and co-excipients on the release mechanism of ketoprofen from controlled release matrix tablets, the weight of the matrix tablets for all formulations was kept constant at 200 mg, hardness 7 kg/cm^2, thickness and diameter according to the punch and die set used, i.e 2.5 mm and 8 mm respectively

The following range of tests were applied for evaluation of physical characteristics:

For determine the uniformity of weight from each batch, 20 tablets were weighed individually and then the mean and standard deviation were calculated. The thickness and diameter of 20 tablets from each batch were measured using vernier callipers and then the mean and standard deviation were calculated. For this test 10 tablets from each batch were taken and their hardness was determined using a hardness tester (Erweka, Germany) and the mean and standard deviation were calculated. To determine the friability, 20 tablets from each formulation were used. For this test a Roche friabilator (Erweka, Germany) was used at a speed of 25 r.p.m for 4 min.

Drug content was analyzed by pulverizing 10 tablets from each batch using a pestle and mortar, then three samples of powder each containing 20 mg of ketoprofen were transferred to a 100 ml volumetric flask, a small volume of phosphate buffer (pH 7.4) was added to hydrate the samples and then the final volume was made up to the mark. The samples were then shaken for some time to dissolve the drug completely and then the samples were passed through filter paper and the absorbance of the standard and the samples was determined at λmax 258 nm using a double beam spectrophotometer (UV-1601, Shimadzu, Japan).

3.2.5. In vitro dissolution studies

In vitro dissolution studies to determine the release rate were carried out on all the designed formulations, for up to 24 h according to USP method 1 (basket method), using an eight-station dissolution apparatus (Pharma Test, PTWS-11/P, TPT, Hainburg, Germany), the rotation speed of the basket being 100 r.p.m. Each station or flask of the dissolution apparatus was filled with 900 ml of 0.2 M phosphate buffer (pH 7.4) used as dissolution medium to study the release rate and release pattern of drug from the tablet matrices for up to 24 h, while the temperature of the dissolution medium was kept at 37 ± 0.5 °C. Samples of 5 ml were withdrawn at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18 and 24 h with the help of syringes fitted with a 0.45 μm filter and after each sampling an equal volume of fresh dissolution medium was added to maintain the dissolution medium at a constant volume. Then after appropriate dilution the samples were analysed for ketoprofen using a double beam spectrophotometer (UV-1601, Shimadzu, Japan) at λ_{max} 258 nm and then the percentage release of ketoprofen was calculated by using a standard calibration curve for ketoprofen. The release studies for all formulations were conducted in triplicate.

3.2.6. Drug release kinetics

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

(i)Zero-order kinetics (Xu and Sunada 1995; Najib and Suleiman 1985)

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

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

$$\text{In} = (100 - W) = \text{In } 100 - k_2 t \quad (2)$$

(iii) Hixon Crowel's Equation (erosion model) (Costa et al. 2003).

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

(iv) Higuchi's Square of Time Equation (diffusion model) (Higuchi 1963; Korsmeyer et al. 1983)

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

(v) Power law equation or Korsmeyer- Peppas equation for mechanism of drug release (Brabander et al. 2003; Korsmeyer et al. 1983; Ritger 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. k1-k4 are release rate constants for equations used and these rate constants depend on the kinetic model used and k5 is the constant representing the structural and geometric characteristics of the device, W is the percentage 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 then 0.45 and less then 0.89 it indicates that it is non-Fickian or anomalous diffusion, while an n value of 0.89 indicates case II transport or typical zero order release (Siepmann and Peppas 2001) and n greater then 0.89 is super case II transport (Vueba et al. 2004)

Acknowledgement: This work was financially supported by the Higher Education Commession (HEC) of Pakistan.

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