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Ketoprofen sustained-release suppositories containing hydroxypropylmethylcellulose phthalate in polyethylene glycol bases

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Abstract

In this study, conventional and sustained-release suppositories of ketoprofen (KP) were prepared and the effects of suppository bases and the inert matrix material (hydroxypropylmethylcellulose phthalate, HP 55) on in vitro release of ketoprofen suppositories were investigated. Suppositories containing 100 mg ketoprofen were prepared by the fusion method. Witepsol H15, Massa Estarinum B, and polyethylene glycols (PEG) were used as examples of hydrophobic and hydrophilic bases, respectively. Sustained-release suppositories of KP were prepared by using HP 55. Weight variation, content uniformity, breaking (hardness) and melting range tests were then conducted on these formulations. In vitro release and diffusion rate tests were also carried out according to the USP XXII basket method and the Muranishi method, respectively. The results show that the rate of release of KP is very slow for Witepsol H15 and Massa Estarinum B bases. However, KP was released very rapidly from the PEG bases in the conventional suppositories. On the other hand, HP 55 might be useful as a vehicle for sustained release preparations of ketoprofen in suppository form. It was shown from the kinetic assessment of release data that the best fit was achieved with zero-order kinetics.

Keywords: Ketoprofen; Sustained-release suppository; Solid dispersion; Hydroxypropylmethylcellulose phthalate

1. Introduction

Ketoprofen, which is a highly potent and safe nonsteroidal drug of the propionic acid derivative group, has anti-inflammatory and analgesic effects in treatment (Thomas and Kantor, 1986). Since KP produces gastro-intestinal side effects, its administration rectally is considered as a serious alternative to the oral route. Besides the conventional form, sustained-release suppositories can be prepared to in order to achieve sustained-action medication clinically, alleviation of pain during sleep being often helpful in reducing anxiety.

In this study, we have attempted to enhance the bioavailability and also to formulate sustained-release dosage forms of KP by using the

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solid dispersion technique. The suppository bases were prepared in matrix form by using different PEG mixtures as a water-soluble carrier and HP 55 as a poorly soluble carrier. In addition, in conventional suppository formulations, different PEG mixtures were used as suppository bases.

An official dissolution method is not as yet available to test for drug release of rectal dosage systems in vitro. However, it is apparent from the literature that many research groups have been examining different techniques and their applicabilities (Bornschein et al., 1985). Such techniques are based on different principles depending mainly on how close they are aimed at simulating in vivo conditions (Tukker and De Blaey, 1983; Von Dibbern and Wirbitzki, 1983; Koch et al., 1987).

2. Materials and methods

2.1. Materials

Ketoprofen was supplied by Drifen Pharm. Co. (Turkey), Witepsol H15 was purchased from Dynamit-Nobel, Massa Estarinum B from Ciba-Geigy, and PEGs and HP 55 from Merck. Other reagents used were of analytical grade.

2.2. Preparation of suppositories

(1) Conventional suppositories (F1, F2, F3, F4, F5-W15, F6-ME): these suppositories were prepared by the fusion method at either 38°C (F5-W15 and F6-ME) or 48°C (PEG mixtures) depending on the base used.

(2) Matrix suppositories (F1-HP-12, F2-HP-12, F3-HP-12, F4-HP-12, F1-HP-13, F2-HP-13, F3-HP-13, F4-HP-13): the matrix suppositories were prepared by the fusion method as follows. Physical mixtures of specified proportions of HP 55 and PEG mixture were prepared. These mixtures were heated at 120°C in a thermostated oven with occasional stirring until clear homogeneous fused mixtures were formed. Then KP (100 mg) was melted in the HP 55-PEG fused mixtures, and these were quickly poured into steel moulds and allowed to solidify at room temperature.

HP 55 was added to the bases in two different ratios. The compositions of the formulations in this work are listed in Table 1 (the commercial suppository product designated F7-P was also examined).

The content of KP in all suppositories was 100 mg. After preparation, they were wrapped in aluminium foil and stored in a desiccator in the refrigerator at + 4°C until use.

Table 1
Code and constituents of suppositories

Code	Substances (mg)										
	KP	Witepsol H15	Massa Estrinum B	PEG-400	PEG-1000	PEG-1540	PEG-2000	PEG-4000	PEG-6000	Water	HP-55
F1	0.100	–	–	–	2.184	–	–	0.0446	–	–	–
F2	0.100	–	–	0.166	2.149	–	–	0.0462	–	–	–
F3	0.100	–	–	–	–	0.939	–	–	1.056	0.352	–
F4	0.100	–	–	–	–	–	2.292	–	–	–	–
F5-W15	0.100	1.874	–	–	–	–	–	–	–	–	–
F6-ME	0.100	–	1.863	–	–	–	–	–	–	–	–
F1-HP-12	0.100	–	–	–	1.988	–	–	0.0406	–	–	0.200
F2-HP-12	0.100	–	–	0.100	1.861	–	–	0.0400	–	–	0.200
F3-HP-12	0.100	–	–	–	–	0.859	–	–	0.966	0.322	0.200
F4-HP-12	0.100	–	–	–	–	–	2.093	–	–	–	0.200
F1-HP-13	0.100	–	–	–	1.89	–	–	0.0386	–	–	0.300
F2-HP-13	0.100	–	–	0.951	1.768	–	–	0.038	–	–	0.300
F3-HP-13	0.100	–	–	–	–	0.819	–	–	0.921	0.307	0.300
F4-HP-13	0.100	–	–	–	–	–	1.993	–	–	–	0.300

2.3. Evaluation of physical properties of suppositories

The prepared suppositories were evaluated for uniformity of weight according to the BP 1988 and content uniformity. The mechanical strength test was carried out on an Erweka breaking strength tester.

2.4. Release of ketoprofen from suppositories

In vitro release and diffusion rate tests were carried out according to the USP XXII basket method and the Muranishi method, respectively.

USP XXII basket method: the USP rotating basket dissolution apparatus was used for the determination of release rates of KP from the various suppository bases. Each suppository was placed in the basket and lowered into a flask containing 500 ml of phosphate buffer solution (pH 7.2). The basket was rotated at 50 rpm at a constant temperature (37 ± 0.5°C). 2 ml samples were withdrawn at appropriate time intervals and assayed to obtain a dissolution profile. 2 ml phosphate buffer was immediately added to the dissolution medium to compensate for sampling. Released KP was assayed spectrophotometrically at 258 nm with (Pye-Unicam SP 1025 spectrophotometer) the test solution flowing continuously through the microflow cell. The results were the mean of three determinations ($n = 3$).

Muranishi method: the diffusion rate tests were carried out according to our modification of the method of Muranishi et al. (1979). A schematic diagram of the apparatus used in the study is shown in Fig. 1. The apparatus is a cylindrical cell. A suppository was placed in 3 ml of the test solution (pH 7.2 buffer solution) in the cell equipped with a Millipore filter (pore size 3.0 mm) and stirred with a rod at 25 rpm. The cell was connected with a glass vessel containing 300 ml of the test solution which was agitated using a magnetic stirrer at 250 rpm. The release of the drug across the membrane to the test medium was determined spectrophotometrically at 258 nm ($n = 3$). The diffusion data obtained for sustained-release suppositories were evaluated kinetically using a computer program written for this purpose (Agabeyoglu, 1983).

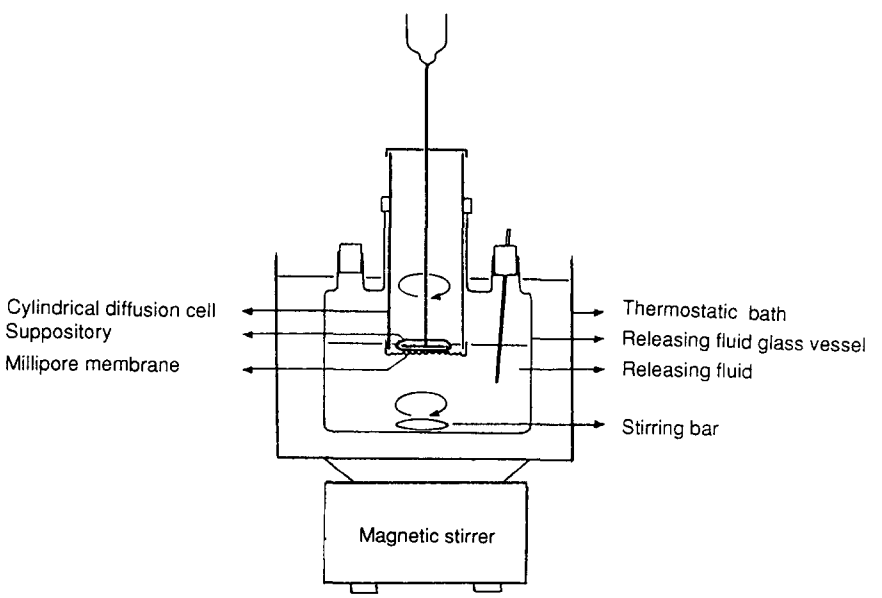

Fig. 1. Cross-sectional diagram of the in vitro release and diffusion rate apparatus.

3. Results and discussion

3.1. Physical characteristics of suppositories

All suppositories were found to satisfy the BP 1988 and USP XII requirements for weight uniformity and content uniformity, respectively. The results are given in Table 2.

The suppositories prepared with Witepsol H15 were found to be the strongest, among the conventional suppositories we prepared, against breaking forces followed by those prepared with Massa Estarinum B and PEG 2000. Since a matrix structure is formed in sustained-release suppositories prepared with HP 55, they have much higher resistance to breaking forces.

3.2. Release of KP from suppositories in vitro

Fig. 2 and 3 show, respectively, the release profiles and diffusion rates of conventional suppositories prepared for the study. As can be seen, the Muranishi method gives considerably different diffusion rates in comparison with release profiles obtained by USP XXII basket method on the basis of percentage drug release for the same formulations. This is because, in the former method, the drug diffuses across a membrane having a constant surface area to the aqueous medium. In the USP XXII basket method, however, the drug is released directly to the aqueous medium from the surface of the suppository.

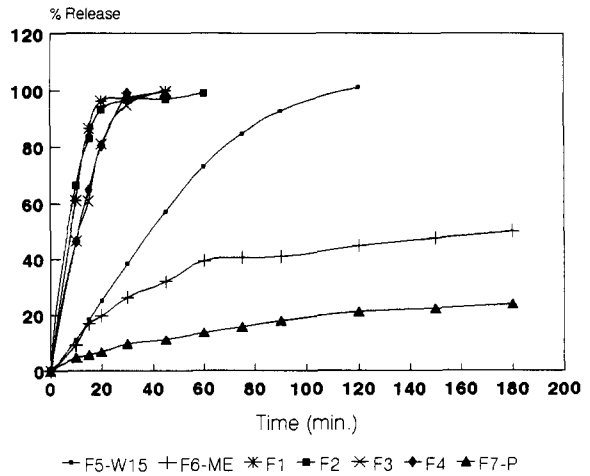

Fig. 2. Release profiles of ketoprofen from conventional suppositories.

Fig. 2 shows that complete drug release from all conventional suppositories with PEG mixtures takes place within 25–30 min with the USP XXII basket method. As can also be seen from Fig. 2, lipophilic bases for conventional suppositories led to much slower release than the hydrophilic bases. Similar results were obtained with the Muranishi method for the same conventional suppositories as shown in Fig 3. Although F1 and F2 coded conventional suppositories prepared with PEG

Table 2
Weight variation, content uniformity and breaking values of suppositories

Code	Weight variation (g)		Content uniformity (mg)		Breaking values (kg)	
	$\bar{X}$	±SD	$\bar{X}$	±SD	$\bar{X}$	±SD
F1	2.40	0.0281	99.9	2.05	0.96	0.134
F2	2.42	0.0157	98.1	1.88	1.40	1.013
F3	2.19	0.0461	99.7	3.12	1.72	0.415
F4	2.36	0.0466	97.5	0.985	3.33	0.096
F5-W15	1.97	0.0518	98.3	2.44	4.58	0.167
F6-ME	1.96	0.0411	96.7	1.78	3.72	0.200
F1-HP-12	2.45	0.0141	99.32	1.10	1.70	1.010
F2-HP-12	2.44	0.0242	102.86	1.85	1.85	1.084
F3-HP-12	2.09	0.0272	100.51	2.88	3.94	0.261
F4-HP-12	2.43	0.0211	99.96	3.57	> 5.40	–
F1-HP-13	2.40	0.0246	97.99	1.84	> 5.40	–
F2-HP-13	2.43	0.0263	95.77	1.07	> 5.40	–
F3-HP-13	2.23	0.0224	98.63	3.11	> 5.40	–
F4-HP-13	2.41	0.0313	96.81	0.95	> 5.40	–

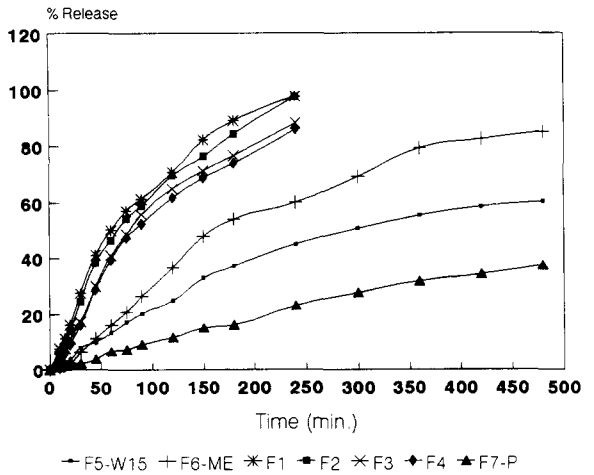

Fig. 3. In vitro diffusion rate profiles of ketoprofen from conventional suppositories.

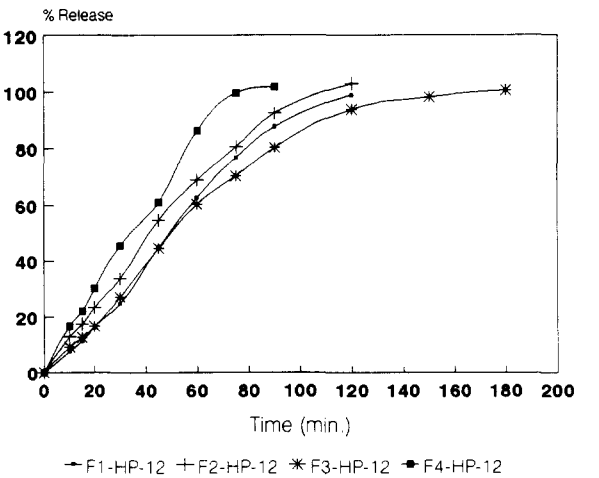

Fig. 4. Release profiles of ketoprofen suppositories prepared with HP55 (1:2).

mixtures give rise to complete diffusion within about 3.5 h, only 80 and 60% of the drug diffuse in 8 h time from F6-ME and F5-W15 coded suppositories, respectively. The amount of drug diffused from the commercial suppository was found to be very low (37.5% in 8 h) even when formulated as a conventional suppository.

The results obtained by both methods have shown that lipophilic bases are not suitable for sustained-release suppository formulations. However, PEG mixtures as hydrophilic bases are shown to be in suitable the formulation of sustained-release suppositories of ketoprofen. Vidras et al. (1982) used both lipophilic (cacao butter and Witepsol H15) and hydrophilic (PEG 1000) bases in the formulation of indomethacin suppositories and showed that PEG 1000 is the most suitable basis for sustained-release suppositories. This is consistent with our present results. Published material on this subject usually deals only with hydrophilic bases used in the formulation of sustained-release suppositories (Ohnishi et al., 1987a,b, 1988).

In vitro release profiles of four different sustained-release suppository formulations with PEG mixture basis are demonstrated in Fig. 4 and 5. The release profiles in Fig. 4 and 5 were obtained for ketoprofen/HP 55 ratios of 1:2 and 1:3, respectively. Examination of these release profiles showed that increasing the ketoprofen/HP 55 ratio from 1:2 to 1:3 for each formulation yielded slower release and hence considerably prolonged the duration of complete drug release. The F3-HP-13 coded formulation resulted in complete drug release within 3.5 h while for F3-HP-12 only 1.5 h was required. However, the conventional suppositories prepared with the same basis and coded as F3 formulation gave complete drug release within only 45 min.

Diffusion rates for the same formulations are found to vary over an 8 h time period as shown in

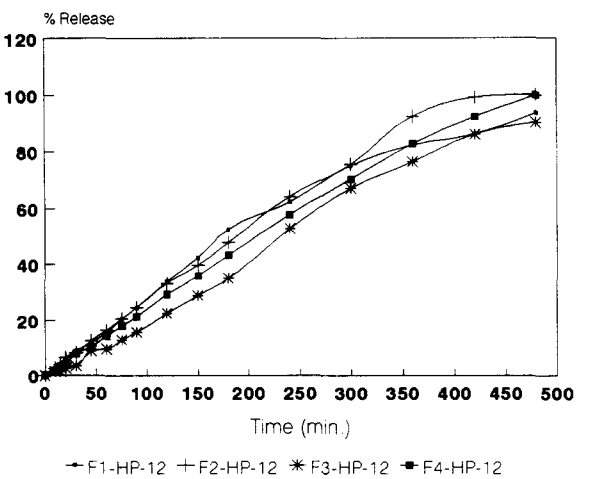

Fig. 5. In vitro diffusion rate profiles of ketoprofen suppositories prepared with HP55 (1:2).

Fig. 6 and 7. The sustained-release suppositories containing HP 55 in the ratio of 1:2 gave complete drug diffusion within 8 h while those containing HP 55 in a 1:3 ratio resulted in only 85% drug diffusion. For conventional suppositories, however, drug diffuses completely to the aqueous medium in a much shorter time (3–3.5 h). The above results demonstrate that the formulations described in this paper ensure the continuity of drug diffusion for a duration of 8 h.

This indicates that HP 55 is a suitable polymer (inert matrix material) in the formulation of sustained-release suppositories when PEG is used as the base material. In the literature, similar conclusions have been drawn for the sustained-release effect of HP 55 as a polymer (inert matrix material) in the formulation of sustained-release

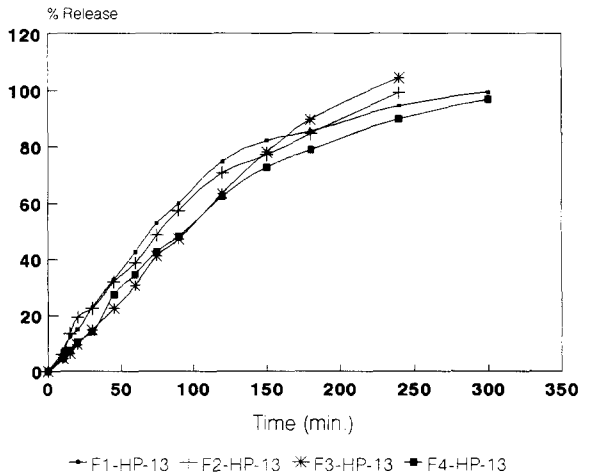

Fig. 6. Release profiles of ketoprofen suppositories prepared with HP55 (1:3).

Table 3
Kinetic assesment of release data

Kinetics		F1-HP-12	F2-HP-12	F3-HP-12	F4-HP-12
Zero order	k_0	13.3	13.6	12.7	13.1
	r^2	0.978	0.983	0.995	0.994
	SSD	5.41×10^{-2}	4.27	1.04×10^{-2}	1.24×10^{-2}
	SWSD	-3.55×10^{-2}	-5.60×10^{-2}	2.17	-4.75×10^{-2}
First order	k_1	0.569	0.821	0.330	0.563
	r^2	0.806	0.740	0.903	0.703
	SSD	0.806	1.59	0.462	1.05
	SWSD	3.79	13.6	1.10	5.28
$Q \rightarrow t$	k	0.721	0.738	0.519	0.634
	r^2	0.986	0.979	0.959	0.976
	SSD	0.204	0.232	0.303	0.238
	SWSD	0.506	0.626	0.618	0.572
		F1-HP-13	F2-HP-13	F3-HP-13	F4-HP-13
Zero order	k_0	12.3	11.2	11.7	11.7
	r^2	0.987	0.973	0.993	0.991
	SSD	2.10×10^{-2}	3.97×10^{-2}	1.30×10^{-2}	1.48×10^{-2}
	SWSD	1.83	0.164	7.40×10^{-2}	5.73×10^{-2}
First order	k_1	0.291	0.225	0.242	0.254
	r^2	0.966	0.993	0.967	0.946
	SSD	0.194	5.77×10^{-2}	0.219	0.276
	SWSD	0.410	9.05×10^{-2}	0.392	0.553
$Q \rightarrow t$	k	0.556	0.493	0.437	0.443
	r^2	0.980	0.982	0.957	0.943
	SSD	0.211	0.165	0.267	0.272
	SWSD	0.425	0.280	0.480	0.522

k_0, zero-order release rate constant; k_1, first-order rate constant; k, the rate constant from the slope of the linear regression of cumulative amount release per unit area vs square root of time; SSD, sum of the square deviations; SWSD, sum of the weighted square deviations.

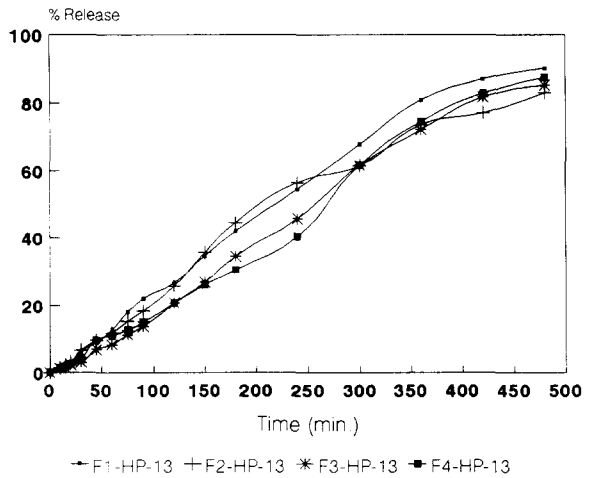

Fig. 7. In vitro diffusion rate profiles of ketoprofen suppositories with HP55 (1:3).

suppositories containing different drugs (Ohnishi et al., 1986, 1987a,b; Tarimci et al., 1990).

The results of the kinetic assessment of the diffusion data obtained for sustained-release suppositories are listed in Table 3. The results show that the best fit is obtained for a zero-order kinetic process. This is because HP 55 has an inert matrix structure and hence forms a cage on the surface and in the suppositories, thus preventing the release of the drug from the suppository to the aqueous medium. The superficial erosion of HP 55 proceeds very slowly in aqueous medium. As this occurs, PEG-entrapped drug is released from the suppository in a controlled manner and the rate of release is independent of drug concentration. This phenomenon continues until the suppository is completely dissolved.

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