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Research paper

Enhanced bioavailability of piroxicam using Gelucire 44/14 and Labrasol: in vitro and in vivo evaluation

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Abstract

Piroxicam is a non-steroidal anti-inflammatory drug that is characterized by low solubility and high permeability. The purpose of the study was to investigate the in vitro and in vivo performance of the semi-solid dispersion prepared with Gelucire 44/14 and Labrasol into hard gelatin capsules (GL) for enhancing the dissolution rate of the drug. The results were evaluated by comparing with pure piroxicam filled into hard gelatin capsules (PP) and a commercially available tablet dosage form containing a piroxicam:β-cyclodextrin complex (CD). The in vitro dissolution testing of the dosage forms was performed in different media (simulated gastric fluid, pH 1.2; phosphate buffers, pH 4.5 and 6.8; and water). Amongst the dosage forms, GL provided at least 85% piroxicam dissolution within 30 min in each of the media, behaving like a fast-dissolving immediate release drug product. Oral bioavailability of 20 mg piroxicam in GL, CD, and PP was compared after administration of a single dose to eight healthy volunteers. Three treatments were administered in crossover fashion, separated by a washout period of 2 weeks. Piroxicam was monitored in plasma by high-performance liquid chromatography. The apparent rate of absorption of piroxicam from GL (C_{max} = 2.64 μg/ml, t_{max} = 82.5 min) was significantly higher than that of the PP (C_{max} = 0.999 μg/ml, t_{max} = 144 min) ($P < 0.05$) and similar to that of CD (C_{max} = 2.44 μg/ml, t_{max} = 120 min) ($P > 0.05$). The relative bioavailability values as the ratios of mean total AUC for GL relative to PP and CD, were 221 and 98.6%. Piroxicam is characterized by a slow and gradual absorption via the oral route and this causes a delayed onset of therapeutic effect. Thus, plain piroxicam preparations are not indicated for analgesia. The results of the in vivo study revealed that the GL dosage form would be advantageous with regards to rapid onset of action, especially in various painful conditions where an acute analgesic effect is desired.

Keywords: Piroxicam; Gelucire 44/14; Labrasol; Semi-solid dispersion; Dissolution; Human; Bioavailability; Pharmacokinetics

1. Introduction

Piroxicam is a member of the oxicam group of non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are widely used for rheumatoid arthritis, osteoarthritis, and a variety of other acute and chronic musculoskeletal disorders, dysmenorrhea, and as ordinary analgesics [1,2]. According to the Biopharmaceutic Drug Classification System (BCS) proposed by Amidon et al. [3], piroxicam is a class 2 drug with low solubility and high permeability. Its pharmacokinetic pattern is characterized by slow and gradual absorption via the oral route and a long half-life of elimination, rendering a prolonged therapeutic action but also a delayed onset of anti-inflammatory and analgesic effect [4].

Recently, considerable attention has been focused on the improvement of bioavailability and clinical efficacy of poorly water-soluble, lipophilic drugs given orally. Numerous techniques have been used to improve the oral bioavailability of these drugs by enhancing their solubility in water and in biological fluids at physiological pH values. The most popular approaches are the incorporation of the drugs into inert lipidic vehicles such as oils, surfactant dispersions, self-emulsifying formulations [5–7] and the preparation of solid dispersions based on cyclodextrin inclusion complexes [8,9], polyvinylpyrrolidone [10], and polyethylene glycols 4000 and 6000 [11,12].

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Gelucire excipients have been used in the formulation of semi-solid dispersions [13–15]. They are solid waxy materials that are amphiphilic in character and identified by two values: their melting points and their HLB (hydrophilic–lipophilic balance) values. Gelucires are saturated polyglycolized glycerides consisting of mono-, di-, and tri-glycerides and of mono- and di-fatty acid esters of polyethylene glycol. The nature and proportion of each component are specific to a given grade of Gelucire. Gelucire 44/14 is a semi-solid excipient from this group. It has a nominal melting point of 44 °C and an HLB value of 14 [14,16]. Labrasol, of the same chemical nature as Gelucires, is a clear liquid surfactant with an HLB value of 14 [16].

In a preliminary study, the improvement of solubility of piroxicam by using Gelucires and Labrasol was investigated and semi-solid dispersions of the drug were prepared with Gelucire 44/14 and Labrasol. A semi-solid dispersion containing a mixture of 20% w/w Gelucire 44/14 and 80% w/w of Labrasol provided dissolution of not less than 85% of piroxicam within 30 min in each of the dissolution media (namely, acidic medium, pH 1.2 SGF; pH 4.5 buffer; pH 6.8 buffer; and water) like a rapidly dissolving immediate release drug product [17,18].

The purpose of the present work was to investigate the in vitro and in vivo performance of the semi-solid dispersion filled into hard gelatin capsules compared with pure piroxicam filled into hard gelatin capsules and with the commercially available tablet dosage form containing piroxicam:β-cyclodextrin inclusion complex.

2. Materials and methods

2.1. Materials

Piroxicam was obtained from Dipharma (Istanbul, Turkey). Gelucire 44/14 (lauroyl macrogolglycerides) and Labrasol (caprylocaproyl macrogolglycerides) were supplied by Gattefossé (Saint-Priest Cedex, France). Hard gelatin capsules were provided by Shionogi (Qualicaps SA, Madrid, Spain). The tablets containing piroxicam:β-cyclodextrin inclusion complex were provided by I.E. Ulagay (Istanbul, Turkey). Naproxen used as an internal standard was supplied by Abdi Ibrahim (Istanbul, Turkey). High-performance liquid chromatography (HPLC)-grade methanol and acetonitrile were obtained from Merck (Darmstadt, Germany). All other chemicals used were of analytical reagent grade. Double distilled water was used for preparing mobile phase solutions.

2.2. Preparation of semi-solid dispersions

Piroxicam was added to the molten base comprising Gelucire 44/14 and Labrasol at about 50 °C. The mixture was stirred and then poured into a plastic injector and volumetrically filled into hard gelatin capsules at the temperature close to the solidification point (about 30 °C) of the material to prevent the precipitation of the solid drug in the molten vehicle. The contents of the semi-solid dispersions filled into hard gelatin capsules and other dosage forms used for comparison, were as follows:

GL Semi-solid dispersion consisted of 20 mg of piroxicam, 76 mg of Gelucire 44/14, and 304 mg of Labrasol per capsule ($n = 10$, average weight of the content ± SE = 423.6 mg ± 3.171×10^{-3})

CD Commercially available tablet dosage form containing a 1:2.5 molecular complex of piroxicam:β-cyclodextrin equivalent to 20 mg of the drug ($n = 10$, average weight of the tablets ± SE = 415.6 mg ± 3.449×10^{-3})

PP Capsule containing 20 mg of pure piroxicam alone (capsules were filled manually by weighing one by one)

2.3. Dissolution testing

Dissolution studies of the semi-solid dispersions, the commercially available tablet dosage form containing piroxicam:β-cyclodextrin inclusion complex, and pure piroxicam in hard gelatin capsules were conducted using USP Apparatus 1 (rotating basket method) (Aymes D96D, Istanbul, Turkey) with three replicates, according to the USP monograph of the drug [19]. The dissolution media were 900 ml of phosphate buffers (pH 4.5 and pH 6.8), USP-simulated gastric fluid without pepsin (SGF) (pH 1.2), and water. The paddle rotation speed was kept at 50 rpm. In all experiments, 5 ml of dissolution sample was withdrawn at 5, 10, 20, 30, and 45 min and replaced with an equal volume of the fresh medium to maintain a constant total volume. Samples were assayed by UV spectrophotometry at 333 nm. Cumulative percentages of the drug dissolved from the preparations were calculated.

2.4. Volunteers

The in vivo study was carried out on eight healthy Caucasian volunteers. Table 1 lists the demographic data of the volunteers. The study protocol was approved by the Ethical Committee of Gülhane Military Medical Academy (Ankara, Turkey) and each volunteer signed an informed form of consent before starting the trial. All the volunteers were active, ambulatory adults with no negative past medical history and had not taken any medication at least 7 days before starting the trial. They were not in the habit of smoking or drinking alcoholic beverages.

2.5. Dosage schedule and blood sampling

The dosage forms containing 20 mg of piroxicam were administered in a single-dose, randomized, open, three-way crossover study.

Table 1
Demographic data of volunteers

Volunteer no.	Initials	Sex	Age (years)	Height (cm)	Weight (kg)
V1	Y.Ö.	M	40	180	80
V2	A.S.	M	39	180	85
V3	A.K.	F	42	163	53
V4	Ö.S.	M	29	163	57
V5	M.T.	F	24	168	53
V6	U.N.	F	25	168	53
V7	Ç.T.	M	32	175	80
V8	T.S.	F	25	155	50
Mean			32	169	63.9
SD			7.41	8.85	14.9
RSD%			23	5.24	23.4
Min.			24	155	50
Max.			42	180	85

The volunteers were served a low-fat content breakfast at 07:00 h and the dose was ingested with 200 ml of water at 09:00 h. Heparinized venous blood samples were drawn just before administration and at 30, 45, 60, 75, 90, 120, 150, 180, 210, and 240 min after administration. Plasma was separated and frozen prior to assay for piroxicam by HPLC. All volunteers fasted until 3 h after drug administration. A 15-day washout period was left between the dosing days.

2.6. HPLC assay of plasma samples

An HP1100 chromatographic apparatus (Agilent, Avondale, USA) consisting of a Model Agilent Series G-13158 detector and a Model Agilent 1100 Series G-1329 ALS auto sampler was used. Data were collected and processed with an Echrom Workstation. Chromatographic separation was performed on a reversed-phase Waters Spherisorb column (250 × 4.6 mm; 5 μm particle size) by an isocratic system. The mobile phase consisted of a mixture of acetonitrile/methanol/0.04 M KH_2PO_4, at a volume proportion of 40:10:50 with pH 3.8 and delivered at a flow rate of 0.9 ml/min. After precipitating the plasma proteins with $ZnSO_4$, $MgSO_4$, and acetonitrile/methanol (3:1) in plasma samples, piroxicam was detected at a wavelength of 330 nm. An injection volume of 20 μl was used. Naproxen was used as an internal standard. The linearity range of the method used was 0.025–5.0 μg/ml with an r (correlation coefficient) value of 0.999. Within-day precision was 0.49% and between-day precision was 0.98%. Detection and quantification limits of the method were 0.0016 and 0.054 μg/ml, respectively [20,21].

2.7. Calculation and statistical analysis

The dosage forms were evaluated through the following parameters:

- $AUC_{0\rightarrow tx}$ and $AUC_{0\rightarrow\infty}$: Trapezoidal area under the curve of plasma concentration vs. time, from time 0 to last sampling time (t_x) and from time 0 to infinity;
- C_{max}: Maximum plasma concentration;
- t_{max}: Time to C_{max}.

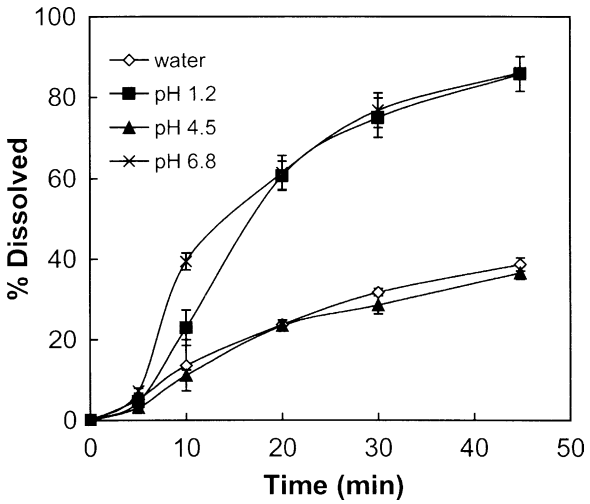

Fig. 1. Dissolution profiles of pure piroxicam (PP) in different dissolution media.

The parameters were obtained directly from the analytical data and compartment model independent analysis [22]. Parametric statistical evaluation of the data was performed by one-way variance analysis followed by Tukey multiple comparisons employing SPSS 8.0 for Windows (SPSS, Chicago, IL).

3. Results and discussion

3.1. In vitro dissolution

For low solubility–high permeability (class 2) drugs, the dissolution profile must be most clearly defined and

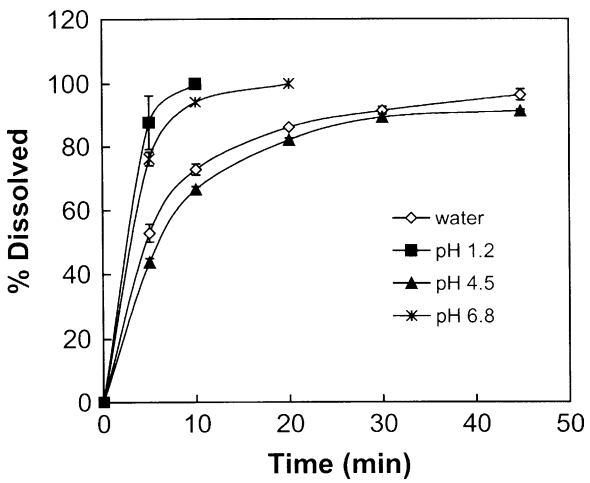

Fig. 2. Dissolution profiles of piroxicam from semi-solid dispersion (GL) in different dissolution media.

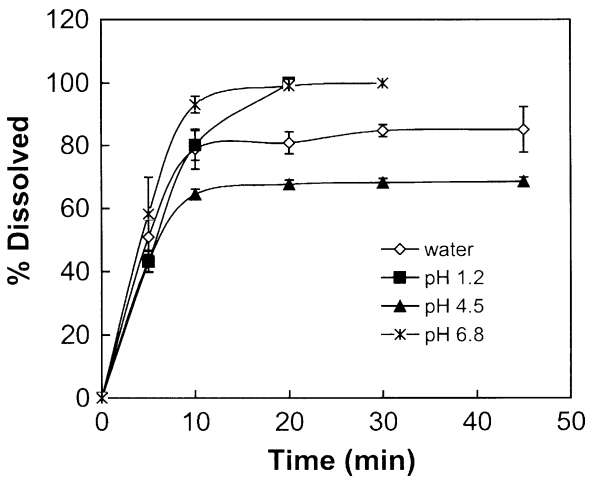

Fig. 3. Dissolution profiles of piroxicam from tablet dosage form (CD) containing piroxicam:β-cyclodextrin in different dissolution media.

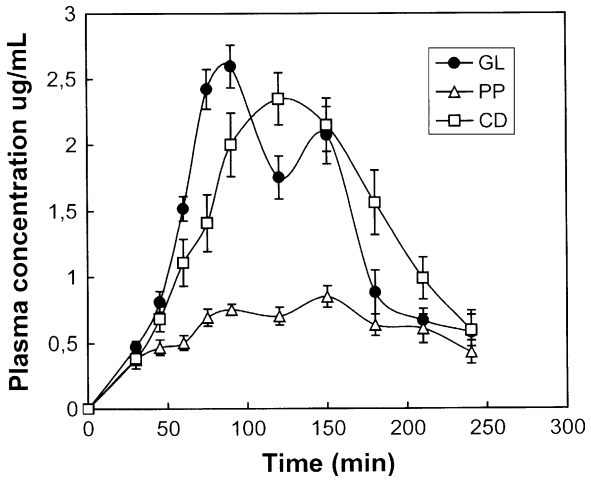

Fig. 4. Mean piroxicam plasma profiles from a single-dose, three-way, crossover bioavailability study comparing piroxicam dosage forms.

reproducible. Drug dissolution in vivo is the rate-controlling step in drug absorption. Although the stomach can secrete HCl at pH 1, the pH of the gastric contents is not always highly acidic. Gastric acid is buffered by food and the pH remains above 3 for at least 1 h after eating. Under fasting conditions, the pH may fluctuate between about 1 and 7, being low between meals and quite high for certain periods during sleep. Since the absorption of class 2 drugs will occur over an extended period of time, the drug will also reach the small intestine being exposed to high physiological pH in the range of 6.5–7.6 [3,23]. Therefore, the in vitro dissolution of piroxicam containing dosage forms was determined in media with different pH values.

As seen in Fig. 1, pure piroxicam (PP) shows a pH-dependent and incomplete dissolution behavior. Piroxicam dissolution at pH 4.5 and in water was lower than the dissolution at pH 1.2 and 6.8. At 15% w/v concentrations of Gelucire 44/14 and Labrasol in water at 37 °C the increase in the solubility of piroxicam was about 20- and 50-fold, respectively, compared to pure piroxicam [17]. Semi-solid dispersion formulation containing these excipients (GL) ensured at least 85% piroxicam dissolution within 30 min in each medium (Fig. 2).

The commercially available CD dosage form has been developed to increase the solubility of piroxicam by complexation with β-cyclodextrin. This improved solubility results in faster dissolution [8,9]. The CD dosage form provided complete dissolution of the drug in SGF pH 1.2 and in buffer 6.8 in 30 min while the dissolved amounts in buffer pH 4.5 and in water were 68.3 and 84.8%, respectively (Fig. 3).

3.2. In vivo evaluation

The in vivo evaluation of the different dosage forms of piroxicam was conducted in healthy volunteers. Fig. 4 shows the plot of plasma concentration of the drug vs. time for PP, GL, and CD. Double peaks exist in the plasma concentration-time curve of GL. Several hypotheses based on region-dependent variation in absorption, enterohepatic circulation, variable gastric emptying, intestinal transit rates, and intestinal bacterial reconversion of biliary metabolite have been proposed to account

Table 2
Comparison of the plasma concentrations of piroxicam at each sampling time point from the different formulations

Sampling time (min)	Mean plasma concentration, μg/ml (SE)			*P* value		
	PP	GL	CD	PP–GL	PP–CD	GL–CD
30	0.376 (0.0302)	0.476 (0.0396)	0.385 (0.0764)	0.386	0.992	0.452
45	0.469 (0.0582)	0.813 (0.0786)	0.684 (0.0944)	0.014*	0.154	0.487
60	0.504 (0.0551)	1.52 (0.0939)	1.11 (0.177)	0.000***	0.005**	0.062
75	0.693 (0.0651)	2.42 (0.150)	1.41 (0.215)	0.000***	0.010*	0.000***
90	0.753 (0.0417)	2.60 (0.163)	2.00 (0.241)	0.000***	0.000***	0.055
120	0.704 (0.0676)	1.75 (0.162)	2.35 (0.198)	0.000***	0.000***	0.030*
150	0.851 (0.0806)	2.07 (0.218)	2.15 (0.204)	0.001**	0.000***	0.949
180	0.636 (0.0812)	0.882 (0.167)	1.56 (0.246)	0.597	0.004**	0.034*
210	0.607 (0.108)	0.669 (0.0898)	0.988 (0.159)	0.932	0.095	0.181
240	0.430 (0.0879)	0.579 (0.164)	0.594 (0.0118)	0.690	0.640	0.996

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Table 3
Bioavailability comparison of piroxicam in different dosage forms

Vol.	C_{max} (μg/ml)			t_{max} (min)			$AUC_{0\rightarrow tx}$ (μg/ml/min)			$AUC_{0\rightarrow\infty}$ (μg/ml/min)[a]		
	PP	GL	CD	PP	GL	CD	PP	GL	CD	PP	GL	CD
V1	0.984	2.79	2.38	210	90	120	144.9	346.8	310.0	167.1	374.9	328.6
V2	1.08	2.45	2.48	210	75	150	162.2	270.2	311.3	-	-	347.8
V3	0.964	2.63	2.14	180	75	120	145.1	278.9	254.0	175.6	290.6	259.1
V4	1.11	3.54	1.91	150	90	120	140.1	416.1	253.6	154.1	492.6	–
V5	0.799	2.90	2.31	90	90	90	127.2	363.8	257.8	-	373.1	308.9
V6	0.997	2.21	2.09	90	90	120	120.6	257.0	355.7	142.8	285.3	–
V7	1.10	2.39	2.57	150	75	120	141.6	291.4	331.7	157.0	-	335.6
V8	0.904	2.20	3.61	75	75	120	21.5	232.0	480.2	136.3	248.9	513.9
Mean	0.991	2.64	2.44	144	82.5	120	137.9	306.9	319.3	155.5	344.2	349.0
SE[b]	0.0371	0.157	0.184	19.2	2.83	5.67	4.983	22.02	26.68	5.979	36.16	35.35
95% CI[c]												
LB[d]	0.903	2.27	2.00	98.9	75.8	106	126.1	254.8	256.2	140.1	251.3	258.1
UB[e]	1.08	3.01	2.87	189	89.2	133	149.7	359.0	382.4	170.8	437.2	439.8
Sig.[f]	PP-GL	PP-CD	GL-CD	PP-GL	PP-CD	GL-CD	PP-GL	PP-CD	GL-CD	PP-GL	PP-CD	GL-CD
P value	0.000***	0.000***	0.584	0.003**	0.322	0.083	0.000***	0.000***	0.902	0.001**	0.001**	0.993

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

[a] $AUC_{0\rightarrow\infty} = AUC_{0\rightarrow tx} + AUC_{tx\rightarrow\infty}$; when the residual area ($AUC_{tx\rightarrow\infty}$) is greater than 20% of the total area ($AUC_{0\rightarrow\infty}$), the values are not included in the table.

[b] Standard error.

[c] 95% confidence interval.

[d] Lower bound of CI.

[e] Upper bound of CI.

[f] Significance.

for these observations [24]. Piroxicam is eliminated to a large extent through the biliary route and has an elimination half-life of approximately 50 h. These may be consequences of enterohepatic circulation causing multiple peaking in plasma [1,23,25]. Complexation with β-cyclodextrin excluded the double peaks from the plasma concentration vs. time curve of piroxicam from CD dosage form. The difference between GL and CD regarding double peaks can be explained by the fact that for GL formulation, a higher amount of drug is available for absorption due to rapid dissolution of the drug. In this case, permeation rate, limited absorption has been reported to occur [26].

According to the statistical comparisons of mean plasma concentrations in Table 2, PP showed significantly lower plasma levels at 45–150 min when compared to the other dosage forms ($P < 0.05$). Plasma levels of GL were found to be significantly higher at 75 min and significantly lower at 120 and 180 min than those of the CD dosage form ($P < 0.05$). This result indicates that GL will provide a more rapid onset of pharmacological effect but a shorter duration of effect than CD. Mean plasma concentrations were not significantly different among all three dosage forms at 30, 210, and 240 min ($P > 0.05$).

The bioavailability parameters of the three piroxicam dosage forms are summarized in Table 3. The mean peak plasma concentration (C_{max}) for PP was found to be 0.999 μg/ml and the time to reach the peak concentration (t_{max}) was 144 min, indicating significantly slower apparent rate of absorption compared with the values for GL and CD ($P < 0.05$). Although the mean values of C_{max} and t_{max} were not statistically different between GL and CD, GL produced higher drug concentration (2.64 μg/ml) in a shorter time period (82.5 min) than did CD (2.44 μg/ml, 120 min). The peak plasma concentrations obtained from GL and CD agree well with the values for single 20 mg-dose which were given in references [1,22,25]. GL and CD had significantly higher values of both $AUC_{0\rightarrow tx}$ and $AUC_{0\rightarrow\infty}$ (total AUC) than PP ($P < 0.05$). No significant differences in AUC values were observed between GL and CD ($P > 0.05$). The relative bioavailability values as the ratios of mean total AUC for GL relative to PP and CD were 221 and 98.6%, respectively.

4. Conclusions

The results of the study demonstrate the importance of enhancing dissolution of class 2 drugs with high permeability-low solubility for increasing their in vivo absorption. The bioavailability of piroxicam could be improved by incorporation in Gelucire 44/14 and Labrasol (GL dosage form). Plain piroxicam preparations are indicated for osteoarthritis and rheumatoid arthritis but not for analgesia due to its delayed onset of pain relief [27]. However, a semi-solid dispersion of piroxicam, GL, would be advantageous with regard to a rapid onset of action, especially in various painful conditions where an acute analgesic effect is desired. Semi-solid – GL – dispersions of piroxicam into hard gelatin capsules also have the advantage of pH-independent rapid dissolution of the drug, ease of preparation, and use of edible and nontoxic excipients.

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