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ENHANCEMENT OF THE DISSOLUTION RATE AND BIOAVAILABILITY OF PIROXICAM FROM HARD GELATIN CAPSULES AND DIRECT COMPRESSED DISPERSIBLE TABLETS VIA SURFACE HYDROPHILIZATION

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ABSTRACT

The dissolution rate of piroxicam, a nonsteroidal anti-inflammatory drug (NSAID) was markedly increased by the surface hydrophilization technique using Tween 80, polyvinylpyrrolidine K-30 (PVP) and polyethylene glycol 4000 (PEG). The in- vitro release of hydrophilized piroxicam from hard gelatin capsules and directly compressed dispersible tablets was tested in 0.1N HCl (pH 1.2) and phosphate buffer (pH 7.4) and was compared with two commercially available formulations of piroxicam (Feldene 20 mg capsules and Feldene 20 mg dispersible tablets, Pfizer Inc., USA). The dissolution rate of hydrophilized piroxicam was higher for PVP and PEG 4000 as compared to Tween 80. Hydrophilized piroxicam tablets gave higher dissolution rates than capsules. The drug release was found to be affected by the pH of the dissolution medium and was higher in pH 7.4 than pH 1.2.

A two-way crossover design was performed to compare the bioavailability of piroxicam. After oral administration of the selected formulations to six healthy individuals, serial blood samples were collected over 24 hours. Piroxicam was determined in the plasma by using high-performance liquid chromatograhy (HPLC). The obtained pharmacokinetic data indicated shorter t_{max} and higher C_{max} for the hydrophilized piroxicam preparations using PVP as compared to the commercial formulations of piroxicam. These results cleary indicate the usefulness of the utilized surface hydrophilization technique for the enhancement of the dissolution rate and bioavailability of piroxicam.

INTRODUCTION

Currently, in the field of pharmaceutical technology, great efforts are being directed towards the refabrication of existing drug molecules in a fashion, capable of solving problems related to toxicity, poor water solubility, poor bioavailability, instability and dosing problems [1-3]. Various techniques [4-11], have been tried to enhance solubility of drugs whose gastrointestinal absorption is dissolution rate limited, and those which are poorly water soluble. But all those conventional methods, including micronization have their inherent disadvantages. A reduced dissolution rates after micronization have been reported [9-10].

Piroxicam (Feldene, Pfizer), an oxicam derivative, is a nonsteroidal anti-inflammatory drug (NSAID) widely used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthiritis, rheumatoid arthiritis, and juvenile rheumatoid arthiritis, in soft-tissue disorders and in acute gout [10-13].

Like other NSAIDS, the most frequent side effects of piroxicam are the gastrointestinal disorders [11,12]. Piroxicam betadex (piroxicam beta cyclodextrin complex) is used in some preparations for treatment of a variety of painful or inflammatory conditions. Such a complex may have more rapid onset of therapeutic effect due to its enhanced solubility [11,12]. This improves the rate of absorption of piroxicam, and possibly also reduces contact time with the mucosa of the upper gastrointestinal tract. Thus, formulations of piroxicam that limit the contact of the drug with the gastric mucosa may theoretically reduce the incidence of mucosal injury [11,12].

Piroxicam is practically insoluble in water and sparingly soluble in alcohol and most organic solvents [12,13]. Thus, dissolution could be rate limiting step in the gastrointestinal absorption of piroxicam from solid dosage forms [14-18]. In addition, the drug melts at relativelly high (200 °C) temperature [12,13,19]. Thus, the crystallization (micronization) technique or solid dispersion formation with hydrophilic carriers (through fusion and co-precipitation) can not be easily adopted to enhance the dissolution of piroxicam [14-18]. The preparation of solid dispersions of piroxicam by fusion or co-precipitation is considered a difficult, expensive and time consuming techniques because of the aforementioned inherent physical charateristics of the drug [12,13, 19]. Pan et al. [16] used temperature-regulated oil bath to prepare solid dispersions of piroxicam and polyvinylpyrrolidone K-30 (PVP) by the fusion method. On the other hand, preparation of solid dispersions by co-precipitation requires utilization of large amounts of organic solvents for solubilization of piroxicam [14-19].

Hydrophilic materials or surface active agents may be adsorbed on the surface of hydrophobic drug particles to increase its wettability and hence its dissolution rate. In this respect, De Jong [20] have described the surface hydrophilization technique. The technique has been fully discussed later on by Lerk et al.[21], for increasing the release rate of the hydrophobic hexobarbitone from hard capsules. This technique involves the conversion of hydrophobic surface of the drug to hydrophilic surface by the intensive mixing with small amount of a film forming polymer solution (hydroxyethylcellulose). The method appears similar to a conventional granulation technique and simply depends on improving the wettability and dissolution of hydrophobic drugs [21]. Felt et al. [22] found that the rate and extent of bioavailability of griseofulvin hydrophilized with 10% ethanolic solution of hydroxypropylcellulose were increased significantly when compared with the non-treated powder. Moreover, Finholt [23] reported that the dissolution of phenacetin

can be improved by granulating phenacetin powder with hydrophilic binder (gelatin). The use of surfactants to increase the dissolution of insoluble drugs through this technique was first described by Chiou et al[24]. The drug was dissolved in ethanol to form a saturated alcoholic solution . The drug was then precipitated by addition of aqueous surfactant solution [24]. Ebian and Abugella [25] have described two methods for preparing crystals of hydrophobic drug covered with surfactants, by soaking or shaking with aqueous surfactant solution for one hour. In addition, non-ionic surfactants are commonly used in tablet formulations for improving tablet disintegration and dissolution rates [26,27].

The surface hydrophilization technique has been utilized successfully to increase the dissolution rate of an insoluble, antituberculosis drug, thiacetazone [28,29].

The objective of this study was to investigate the dissolution rate of piroxicam from surface hydrophilized formulations (hard gelatin capsules and directly compressed dispersible tablets) prepared by using different hydrophilizing materials such as Tween 80, polyvinylpyrrolidone K-30 (PVP) and polyethylene glycol 4000 (PEG). In addition, preliminary bioavailability experiments were carried out on six healthy human volunteers to compare the t_{max} , C_{max} and AUC_{0-24h} of piroxicam following single oral administration of the hydrophilized formulations and the commercial products of piroxicam. Feldene 20 mg capsules and Feldene 20 mg dispersible tablets (Pfizer Inc. USA) were used as reference products.

EXPERIMENTAL

Materials:

Piroxicam (Pfizer, USA); Microcrystalline cellulose (Avicel PH 102), (FMC corporation, USA); Tween 80 (Atlas Chem. Ind., Wilmington, USA); polyvinylpyrrolidone K-30 (PVP) (Kollidon 30, BSF)), polyethylene glycol (PEG) 4000 (S.D. Fine Chem. Ltd). All organic solvents were of analytical or HPLC grade and were purchased from Lab-Scan-UK. All other chemicals were of pharmaceutical grades and were purchased from GCC-UK.

Commercial products:

Feldene 20 mg dispersible tablets (lot No. 712070902, Pfizer Inc., USA),Exp.Date: 2/2003. Feldene 20 mg capsules (lot No. 9000405, Pfizer Inc., USA) Exp.Date: 9/2002.

METHODS

1. Preparation of hydrophilized systems of piroxicam

Hydrophilized piroxicam systems were prepared as described in previous works [28,29]. Piroxicam powder was throughly mixed in a clean morter with a small, specified amount (5ml) of hydroalcoholic solution (absolute alcohol / water, 50 / 50 % V/V) of the selected hydrophilizing agent (Tween 80, PVP or PEG). The mixture was then dried at 40°C for 24 hours and sieved through 125 µm sieve. Hard gelatin capsules and directly compressed dispersible tablets were prepared using the hydrophilized piroxicam systems as shown below.

2. Preparation of piroxicam capsules

Hard gelatin capsule (No.2) were filled with the hydrophilized piroxicam systems (amount equivalent to 20 mg piroxicam). Capsule 1, (Tween 80), capsule 2 (PVP) and capsule 3 (PEG). The control capsules were prepared using untreated drug (Table 1).

3. Preparation of piroxicam dispersible tablets

Piroxicam dispersible tablets were prepared by direct compression using a single punch tablet machine (Erweka-AR 400 E, Germany). The composition of the prepared tablets are shown in Table 1. The hydrophilized piroxicam systems were accurately weighed and mixed (Turbula Mixer, Switzerland) with Avicel PH 102 for 5 minutes. Talc powder (lubricant) was then added and mixing continued for 2 minutes before compression.

4. Mechanical properties of tablets

The mechanical properties of the prepared tablets were determined according to USP/NF23. For tablet average weight (CV %) data came from 20 tablets, individually weighed (Mettler PC 4400, Switzerland). Tablet hardness (Erweka® GmbH, Heusenstamm, Germany) was carried out on 10 tablets and the mean (CV %) was reported. Friability was measured with an Erweka instrument (Erweka GmbH TAR 20, Germany). Ten tablets were weighed, then rotated for 5 minutes at 20 rpm, then reweighed to calculated the percent friability. Tablet disintegration time was measured using an Erweka disintegration apparatus (Erweka, Germany) in water at 37°C.

5. Dissolution studies

The dissolution of hydrophilized piroxicam from the prepared dispersible tablets and hard gelatin capsules as well as the commercial piroxicam products was performed according to the USP type II paddle apparatus (Hanson Research Co. USA). All data reported are the mean of three determinations. The dissolution was carried out in both 0.1N HCl (pH 1.2) and phosphate buffer (pH 7.4) over a period of 4 hours. The dissolution medium (900 ml) was stirred at 50 rpm and maintained at 37±0.5°C. The concentration of piroxicam in withdrawn samples (5 ml) was determined spectrophotometrically (Shimadzu, UV/vis, Japan) after measuring the absorbances at 335 nm.

6. Relative dissolution rate (R.D.R.)

The relative dissolution rate was calculated by dividing the percent piroxicam released from the experimental formulations at any particular time by the percent released from the control (untreated) piroxicam formulation at that time.

7. Dissolution half-life ($T_{50\%}$)

Time for 50% drug release of any tested formulation is taken as the half-life of dissolution.

8 Dissolution enhancing factor(D.E.F.)

The Dissolution enhancing factor (D.E.F.) was calculated by dividing the dissolution rate constant (K) of any formulation by that of the control (untreated) piroxicam formulation.

9. Bioavailability studies

Two-way crossover study design (Tables 2a and 2b) were carried out to compare the preliminary oral bioavailability of piroxicam from the selected hydrophilized piroxicam preparations (capsule 2 and tablet 2) with two commercially available reference formulations of piroxicam (Feldene 20 mg capsules and Feldene 20 mg dispersible tablets) after single oral administration to six informed healthy male volunteers 25.2±2.6 years of age, 160.7±5.1 cm height, and 70.5±6.7 kg weight. The volunteers were screened for normal physical and physiological functions and were fasted for 12 hr prior to drug administration.

10. Blood sampling

Venous blood samples (5 ml) for determination of piroxicam were collected in heparinzed tubes pre-dose (0 hr) and at 1, 2, 4, 6, 12, 18 and 24 hr after drug administration. Plasma was separated immediately by centrifugation and directly analyzed for piroxicam using HPLC [30].

11. HPLC method and chromatographic conditions

The HPLC apparatus was composed of a Hitachi pump (Model L-6200A), operated at a flow rate of 2.5 ml/min, a variable UV detector (L-400A) set at 330 nm. The separation was performed at 40°C on a stainless-steel column (25 cm x 4.5 mm I.D.) packed with Spherisorb 5 µm (C_{18} reversed-phase, Perkin-Elmer, Norwalk, CT, USA). A stainless-steel pre column (100 mm x 20 mm I.D.) packed with pellicular reversed-phase material (Spherisorb) was used as a guard column. The samples were injected onto the column using a 100-µl loop valve (Rheodyne, Cotani, CA, USA). The mobile phase was acetonitrile 0.1M acetate buffer (33/67, v/v) with a final pH of 3.3 which was adjusted by the dropwise addition of glacial acetic acid [30].

12. Sample preparation

Plasma samples were prepared by the addition of 200 µl trichloroacetic acid, 100 µl naproxen (internal standard, 15 µg/ml) and 0.7 ml methanol to 1 ml heparinized plasma and a 100 µl aliquot of the extracted supernatant was injected onto the HPLC column. The retention times were 2.6 and 3.2 min for piroxicam and naproxen, respectively.

13. Pharmacokinetic data and statistical analysis

The pharmacokinetic parameters (C_{max} ,t_{max}, and AUC_{0-24h}) of piroxicam were estimated from the individual's plasma concentration versus time profiles following oral administration of the tested formulations. The maximum concentration was calculated from the individual's plasma concentration versus time profiles (C_{max}) and the time to reach the maximum concentration (t_{max}). The area under the plasma concentration versus time curve (AUC) was calculated by the trapezoidal rule [31]. Data reported as means ± SD (n = 6).

A two-way statistical analysis of variance (ANOVA) of the plasma concentrations and pharmacokinetic parameters was performed at a 5 % significance level ($p<0.05$) . When significance was observed, pair-wise comparison were made by the paired t-test [32].

14. Relative bioavailability (F_R)

The relative bioavailability (F_R) was calculated by dividing the AUC_{0-24h} obtained for tested formulation by that obtained for the commercial product.

RESULTS AND DISCUSSION

Piroxicam, is a poorly water soluble NSAID which produces severe adverse effects on the gastrointestinal tract (G.I.T.) after oral administ- ration [12]. However, formulations of piroxicam that limit the contact time of the drug with the gastric mucosa may theoretically reduce the incidence of mucosal injury [32-34].

Table (1): Composition (mg) of the prepared hydrophilized formulations of piroxicam.

Ingredients	Capsules				Tablets			
	Control capsule*	Capsule 1	Capsule 2	Capsule 3	Control tablet**	Tablet 1	Tablet 2	Tablet 3
Piroxicam	20	20	20	20	20	20	20	20
Tween 80	-	1	-	-	-	1	-	-
PVP	-	-	1	-	-	-	1	-
PEG	-	-	-	1	-	-	-	1
Avicel PH 102	-	-	-	-	175	175	175	175
Talc	-	-	-	-	4	4	4	4
Total weight (mg)	20	21	21	21	200	200	200	200

*Control capsule contains 20 mg piroxicam (untreated or without hydrophilization).
**Control tablet contains untreated piroxicam (without hydrophilization), Avicel PH 102 and talc.

Molecular complexation of piroxicam with β-cyclodextrin improves its dissolution rate. This increases its solubility by approximately 5 times and would, therefore, be expected to enhance its absorption. This would be of clinical importance in terms of gastrointestinal tolerability [12,49-54].

Table (2-A) : Bioavailability study design (capsule formulations)

Phase*	Treatment	
	A	B
I	1, 2, 3	4, 5, 6
II	4, 5, 6	1, 2, 3
Total number of volunters	6	6

*The two phases were separated by a two weeks washout period.

Treatment A: Given Feldene 20 mg capsule (reference product).

Treatment B: Given Hydrophilized piroxicam capsule 2 (PVP).

Table (2-B) : Bioavailability study design (tablet formulations).

Phase*	Treatment	
	A	B
I	1, 2, 3	4, 5, 6
II	4, 5, 6	1, 2, 3
Total number of volunters	6	6

* The two phases were separated by a two week washout period.

Treatment A: Given Feldene 20 mg dispersable tablets (reference product).

Treatment B: Given hydrophilized piroxicam dispersible tablets (tablet 2 formulation).

In this study, we used a surface hydrophilization technique as an alternative process to increase the solubility and dissolution rate of piroxicam. Surface hydrophilization is defined as the conversion of the hydrophobic surface of the insoluble drug to a hydrophilic surface by utilizing a small, specified amount of a hydrophilizing agent or surfactant [26-28]. This hydrophilized surface will be easily wetted by the dissolution medium and hence the dissolution rate could be increased to a degree comparable to the dissolution rates of products generated using the β-cyclodextrin complexation processes [12,51-54].

The composition of the prepared hard gelatin capsules and directly compressed dispersible tablets of hydrophilized piroxicam are shown in Table 1. All the prepared tablets of hydrophilized piroxicam fulfilled the USP/NF23 requirements for weight uniformity, drug content and friability (Table 3). These tablets also exhibited acceptable hardness and uniformity of diameter. The prepared dispersible tablets of piroxicam were characterized by lower weight and hardness and shorter disintegration time as compared to the commercial, Feldene 20 mg dispersible tablets (Table 3).

The dissolution of piroxicam from the hydrophilized formulations was markedly faster in 0.1 N HCl (pH 1.2) as compared to the contol (untreated) drug or the commercial formulations (Figures 1 and 2). In addition, higher dissolution rates were observed for the tablet formulations (Figure 2) as compared to the capsule formulations (Figure 1). The same observations were obtained for dissolution in phosphate buffer (pH 7.4), (Figures 3 and 4). The relative dissolution rate (R.D.R.) of piroxicam from the prepared hydrophilized preparations (capsules and dispersible tablets) using different hydrophilizing agents (Tween 80, PVP and PEG) are illustrated in Table 4. In 0.1N HCl (pH 1.2) the dissolution rate of piroxicam from every hydrophilized system was markedly higher than the control piroxicam preparation (untreated-drug) where the relative dissolution rate (R.D.R.) was always higher than one (>1). Capsule 3 (PEG) gave the highest dissolution rate as compared to other capsule formulations [capsule 1 (Tween 80) and capsule 2 (PVP)] or Feldene capsules (Table 4). After 0.5 h, the relative dissolution rate (R.D.R.) of piroxicam was 4.96 for capsule 3 (PEG) as compared to 3.96, 3.25 and 2.55 for capsule 1 (Tween 80), capsule 2 (PVP) and Feldene 20 mg capsules respectively (Table 4). Thus, the effect of hydrophilized systems using PVP and PEG in increasing the dissolution rate of piroxicam is supported by these results.

In 0.1N HCl (pH 1.2) the dissolution rate of piroxicam from tablets was markedly higher than capsules (Table 4). This could be attributed to the hard gelatin shell in acidic conditions, which decreases the diffusion of piroxicam to the dissolution medium (Table 4).

In phosphate buffer (pH 7.4), the the relative dissolution rate (R.D.R.) of piroxicam is shown in Table 4 . The dissolution of piroxicam from the prepared hydrophilized formulations (capsules and tablets) in phosphate buffer (pH 7.4) was higher than the acidic medium (pH 1.2). This difference in dissolution profiles could be attributed to the acidic nature of piroxicam (pK_a 6.3). At 0.5 hr in phosphate buffer (pH 7.4), capsule 2 (PVP) gave the highest R.D.R. (17.39) compared to 15.52, 12.05, 11.05 for capsule 3 (PEG), capsule 1 (Tween 80) and Feldene capsule respectively (Table 4). Comparatively, the R.D.R. for tablet 2 (PVP) at 0.5 hr was 15.76 compared to 12.49, 11.90 and 7.08 for tablet 1(Tween 80), tablet 3 (PEG) and Feldene tablets respectively (Table 4).

These data indicate the usefulness of surface hydrophilization in increasing the dissolution rate of piroxicam as compared to the control preparations or the commercial products (Table 4).

The dissolution kinetics (first order) of piroxicam from the prepared hydrophilized formulations and commercial piroxicam formulations are shown in (Table 5) The dissolution rate constant (k), the dissolution half-life ($T_{50\%}$) and the dissolution enhancing factors (D.E.F.) are shown in Table 5. The high values of

dissolution enhancing factor (D.E.F > 1) provide a good comparison of the enhancement of the dissolution rate of piroxicam from the prepared hydrophilized preparations (capsules and tablets) to the commercial piroxicam formulations (Table 5).

The faster dissolution rate of piroxicam from the hydrophilized formulations might be caused by the surface tension lowering effects of the hydrophilizing agents (Tween 80, PVP and PEG 4000). Also, the enhanced dissolution could be attributed to the interaction of piroxicam with the hydrophilizing agents. Tantishaigakul et al.(14) attributed the enhancement of dissolution of piroxicam from its soild dispersions with PVP K-30 to the increased drug wettability and also the interaction of the drug and PVP as indicated by FTIR analysis. Polyvinylpyrrolidone has been demonsterated to retard and inhibit the crystallization of drugs giving amorphous solid dispersions with increased drug dissolution rates and solubilities [33].

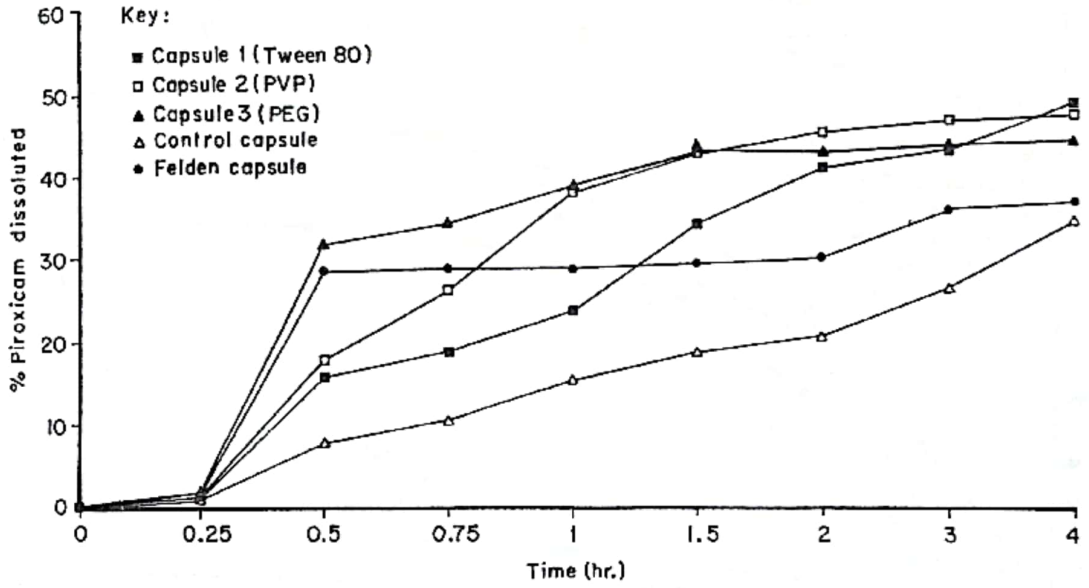

Fig. (1): dissolution of piroxicam (in 0.1 NHCl, pH 1.2) from capsules filled with different hydrophilized systems in comparison with commercial capsules of piroxicam (Feldene 20 mg capsules).

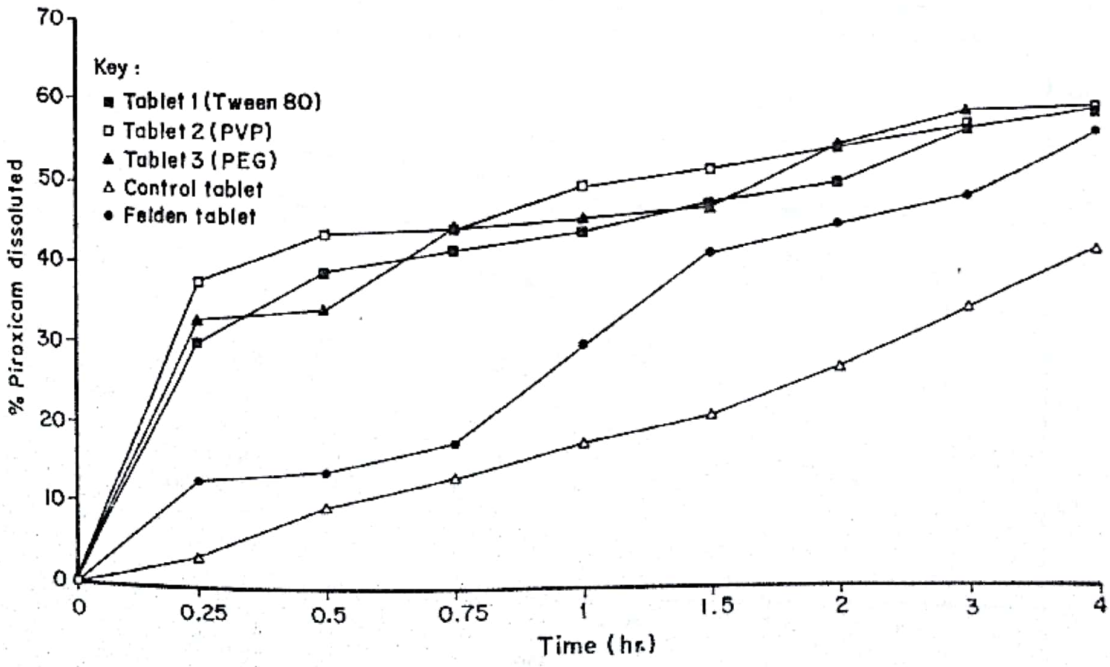

Fig. (2): Dissolution of piroxicam (in 0.1 NHCl, pH 1.2) from tablets prepared with different hydrophilized systems in comparison with commercial tablets of piroxicam (Felden 20 mg dispersible tablets).

Bioavailability studies.

The comparison of the mean plasma concentration versus time profiles for piroxicam after oral administration of the prepared hydrophilized preparations to those profiles of the Feldene 20 mg capsules and Feldene 20 mg dispersible tablets is shown in Figure 5. Rapid absorption was observed for the hydrophilized piroxicam tablets compared to that obtained using the hydrophilized capsule preparations (Figure 5). Feldene 20 mg capsules gave the slowest rate of absorption (Figure 5).

The pharmacokinetic parameters (C_{max}, t_{max} and AUC_{0-24hr}) piroxicam derived from the plasma piroxicam concentration - time plots are summarized in Table 6 . The prepared hydrophilized capsules, Capsule 2 (PVP) produced a significant ($P< 0.05$) reduction in t_{max} (5.50 ± 1.50 hr) and higher C_{max} (1.94 ± 0.80 µg/ml) as compared to the Feldene 20 mg capsules, t_{max} (12.00 ± 2.50 hr) and C_{max} (1.67 ± 0.40 µg/ml) (table 6). Also mg dispersible tablets, t_{max} (6.00 ± 1.80 hr) and C_{max} shorter t_{max} (4.00 ± 0.90 hr) and higher C_{max} (2.66 ± 0.70 µg/ml) values were obtained for hydrophilized tablets, Tablet 2 (PVP) as compared to Feldene 20 (2.20 ± 0.40 µg/ml) (Table 6).

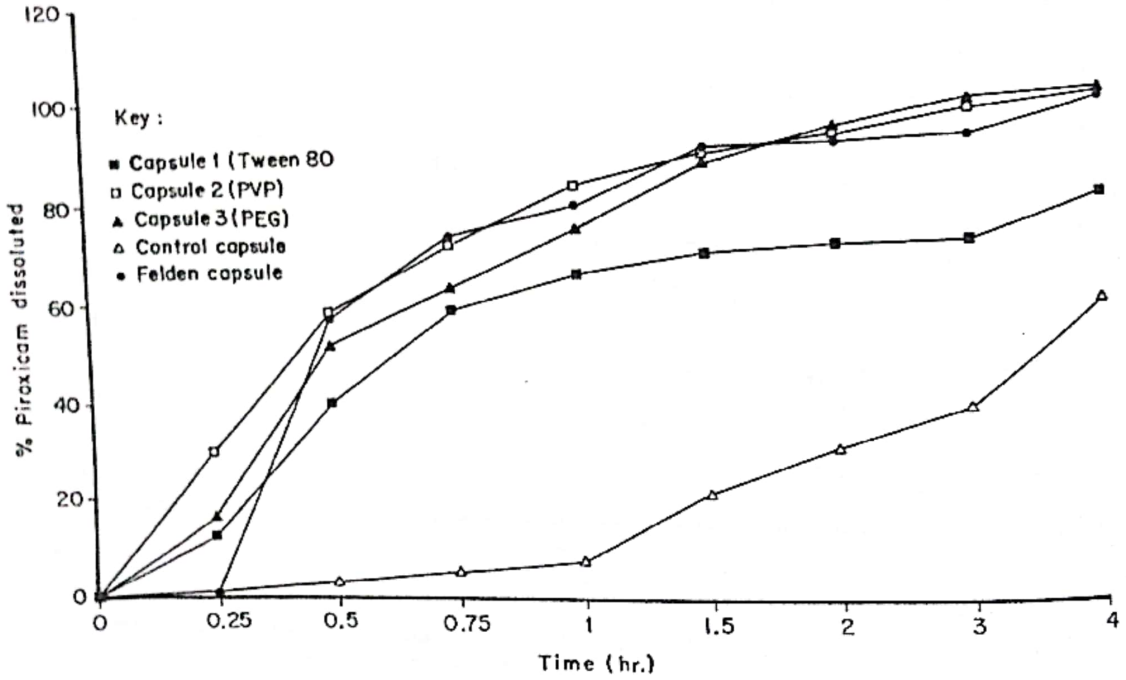

Fig. (3): Dissolution of piroxicam (in phosphate buffer, pH 7.4) from capsules filled with different hydrophilized systems in comparison with commercial capsules of piroxicam (Feldene 20 mg capsules)

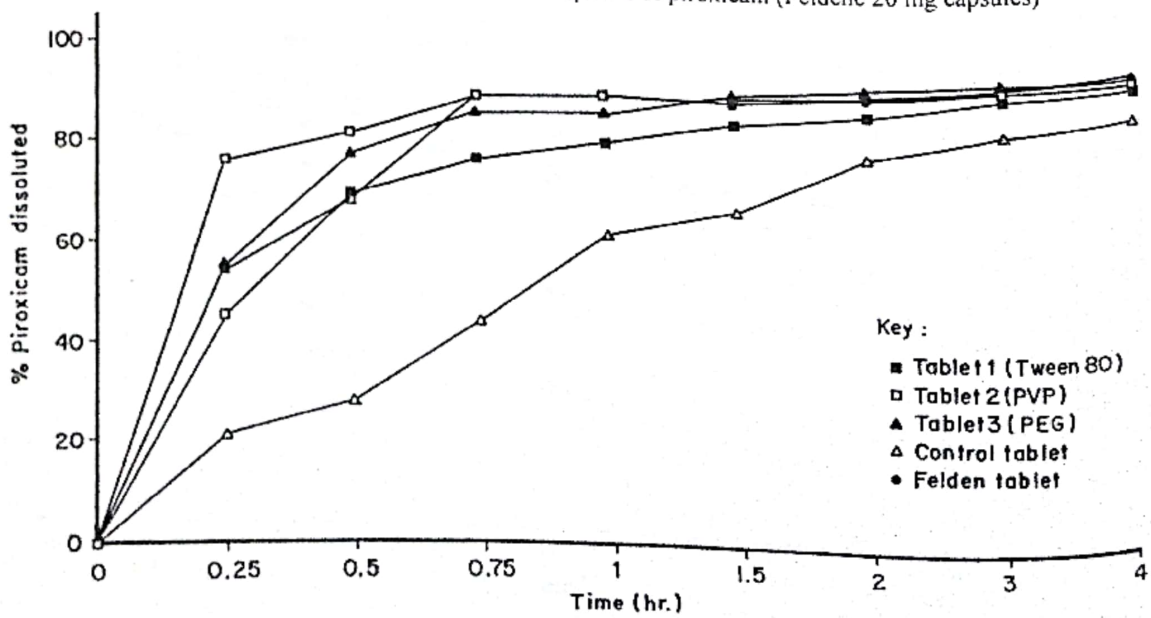

Fig. (4): Dissolution of piroxicam (in phosphate buffer, pH 7.4) from dispersible tablets prepared with different hydrophilized systems in comparison with commercial tablets of prioxicam (Feldene 20 mg dispersible tablets).

The relative bioavailabilies of piroxicam (F_R) were 1.10 ± 0.04 and 0.93 ± 0.06 for the prepared Capsule 2 (PVP) and Tablet 2 (PVP) respectively as compared to the commercial products (Table 6). These results cleary indicate the usefulness of the utilized surface hydrophilization technique for the enhancement of the dissolution rate and bioavailability of piroxicam from solid dosage forms.

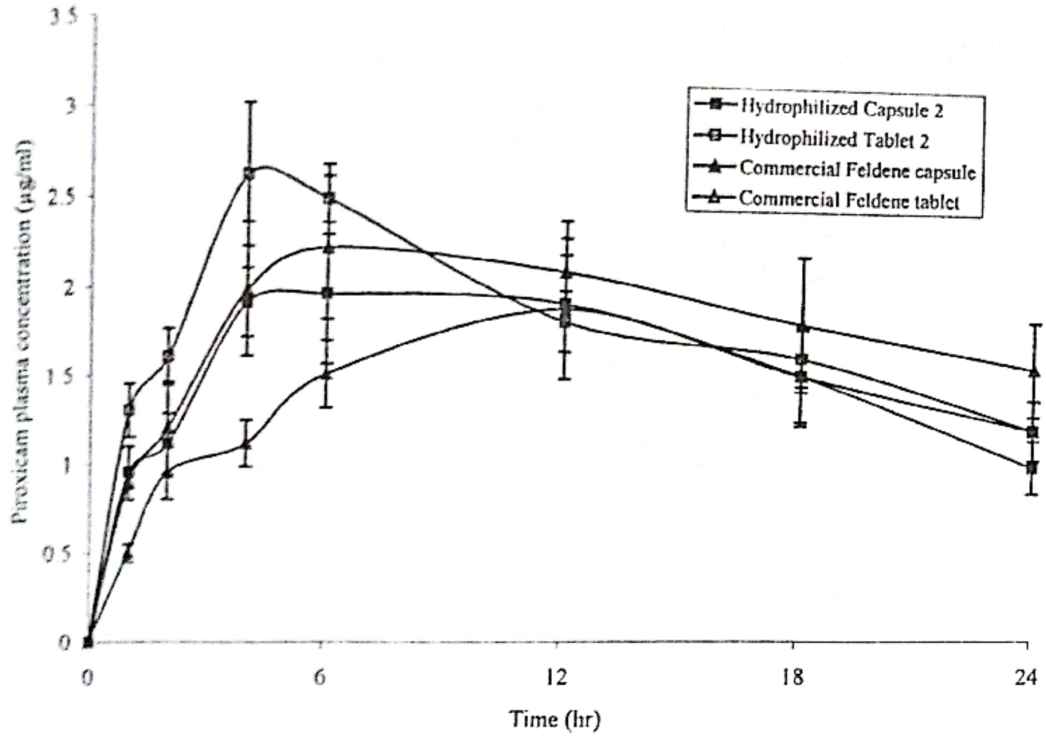

Fig.(5): Plasma concentration- time profiles of piroxicam after oral administration of hydrophilized systems and commercial formulations of piroxicam (Feldene 20 mg capsules and Feldene 20 mg dispersible tablets).

Table (3) : Mean physical characteristics (CV%) of the prepared hydrophilized piroxicam dispersible tablets.

Formulation Code	Weight (mg)	Drug content (mg)	Hardness (N)	Diameter (mm)	Friability %	Disintegration time (min.)
Tablet 1 (Tween 80)	201.50 (3.71)	20.11 (5.21)	47 (3.50)	12.01 (0.20)	0.523	1.5 (6.15)
Tablet 2 (PVP)	198.11 (2.19)	19.40 (4.80)	46 (2.40)	12.09 (0.25)	0.450	1.5 (6.15)
Tablet 3 (PEG)	198.30 (2.91)	19.71 (4.50)	72 (5.11)	12. 08 (0.30)	0.425	2 (5.25)
Control tablet*	201.31 (1.99)	20.05 (6.10)	80 (5.50)	12.08 (0.25)	0.650	2.5 (7.71)
Feldene tablets**	350 ± (5.60)	19.78 (5.13)	121 (6.70)	12.06 (0.30)	0.560	3.0 (6.20)

*Control tablet contains piroxicam, avicel pH 102 and talc (without hydrophilization).

**Feldene 20 mg dispersable tablet (reference tablets, Pfizer, USA).

Table (4) : Comparison of the dissolution parameters obtained from the prepared hydrophilized piroxicam formulations and the control (untreated) and commercial formulations.

Medium pH	Formulation code	Relative Dissolution Rate (R.D.R)				
		0.25 h	0.5 h	1 h	2 h	4 h
0.1N HCl (pH 1.2)	Capsule 1 (Tween 80)	3.16	3.96	2.53	1.97	1.41
	Capsule 2 (PVP)	3.39	3.25	2.45	2.18	2.37
	Capsule 3 (PEG)	4.91	4.96	2.51	2.07	2.29
	Feldene capsule	2.86	2.55	1.86	1.45	1.06
	Tablet 1 (Tween 80)	7.99	5.92	2.45	2.82	1.41
	Tablet 2 (PVP)	9.97	5.39	3.77	2.98	1.40
	Tablet 3 (PEG)	8.74	5.50	3.54	2.99	2.42
	Feldene tablet	3.37	3.40	2.68	1.64	2.34
Phosphate Buffer (pH 7.4)	Capsule 1 (Tween 80)	11.54	12.05	8.36	5.30	1.34
	Capsule 2 (PVP)	17.11	17.39	10.57	4.97	3.66
	Capsule 3 (PEG)	12.16	15.52	9.50	4.03	2.68
	Feldene capsule	7.20	11.05	8.08	3.93	2.65
	Tablet 1 (Tween 80)	12.12	12.49	5.28	4.10	2.06
	Tablet 2 (PVP)	17.56	11.90	7.43	5.15	3.08
	Tablet 3 (PEG)	15.58	15.76	8.38	3.16	2.09
	Feldene tablet	8.53	7.08	6.43	4.14	1.99

Table (5) : Dissolution characteristics of piroxicam from the prepared hydrophilized systems (capsules and tablets) in comparison with commercial formulations of piroxicam.

Medium pH	Formulation code	First-order Kinetics				
		Slope (B)X10^{-2}	Linear correlation coefficient (r)	K (h^{-1})	$T_{50\%}$ (h)	D.E.F
0.1N HCl (pH 1.2)	Capsule 1 (Tween 80)	-6.25	-0.962	0.143	4.81	1.211
	Capsule 2 (PVP)	-6.92	-0.927	0.159	4.35	1.35
	Capsule 3 (PEG)	-5.54	-0.936	0.127	5.45	1.10
	Control capsule	-5.13	-0.996	0.118	5.85	-
	Feldene capsule	-7.66	-0.941	0.176	3.93	1.49
	Tablet 1 (Tween 80)	-7.21	-0.945	0.166	4.17	1.91
	Tablet 2 (PVP)	-9.23	-0.901	0.212	3.25	2.43
	Tablet 3 (PEG)	-9.72	-0.944	0.223	3.10	2.56
	Control tablet	-3.81	-0.978	0.087	7.96	-
	Feldene tablet	-5.88	-0.959	0.135	5.11	1.55
Phosphate Buffer (pH 7.4)	Capsule 1 (Tween 80)	-19.70	-0.909	0.453	1.53	2.43
	Capsule 2 (PVP)	-12.00	-0.901	0.278	1.43	1.50
	Capsule 3 (PEG)	-42.0	-0.930	0.969	0.715	5.21
	Control capsule	-8.10	-0.950	0.186	3.71	-
	Feldene capsule	-0.183	-0.910	0.421	2.49	2.26
	Tablet 1 (Tween 80)	-19.90	-0.05	0.458	1.51	2.86
	Tablet 2 (PVP)	-41.70	-0.983	0.961	0.72	6.01
	Tablet 3 (PEG)	-58.82	-0.999	1.35	0.511	8.43
	Control tablet	-6.95	-0.982	0.160	4.33	-
	Feldene tablet	-34.94	-0.979	0.805	0.861	5.03

Table (6) : Pharmacokinetic parameters (mean ± SD) of piroxicam after oral administration of hydrophilized piroxicam preparations (capsules and tablets) and reference formulations of piroxicam (Feldene) to six healthy volunteers.

Pharmacokinetic parameters	Tested formulations			
	Capsules Formulations		Tablet formulations	
	Capsule 2 (PVP)	Feldene 20 mg Capsules	Tablet 2 (PVP)	Feldene 20 mg Tablets
C_{max} (µg/ml)	1.94*±0.80	1.67±0.40	2.66*±0.70	2.20±0.40
t_{max} (hr)	5.50*±1.50	12.00±2.50	4.00*±0.90	6.00±1.80
AUC_{0-24} (µg hr/ml)	37.50*±6.30	33.96±5.91	46.50±5.30	45.39±7.30
F_r	1.10 ± 0.04	----	0.93 ± 0.06	----

C_{max} maximum plasma concentration
t_{max} time to reach the maximum concentration
AUC_{0-24} area under the plasma concentration-time curve (from zero time to 24 hours)
F_r the relative bioavailability
*indicates statistically significant difference between the results obtained from the hydrophilized formulations compared to commercial reference products of piroxicam.

CONCLUSION

1- The prepared hydrophilized piroxicam formulations (hard gelatin capsules and directly compressed dispersible tablets) markedly increased the rate of dissolution of piroxicam as compared to untreated drug or the commercial piroxicam products, Feldene 20 mg capsules and Feldene 20 mg dispersible tablets.

2- Hydrophilized piroxicam tablets produced dissolution rates higher than those obtained with hydrophilized capsules.

3- The dissolution rate of piroxicam was higher in phosphate buffer (pH 7.4) compared to 0.1N HCl (pH 1.2) for all the tested formulations.

4- The bioavailability studies indicated shorter t_{max} and higher C_{max} for the prepared hydrophilized piroxicam formulations (capsules and tablets) as compared to the corresponding commercial formulations of piroxicam (Feldene 20 mg capsules and Feldene 20 mg dispersible tablets). This could be of clinical importance in reducing the contact time of the drugs in gastrointestinal tract (G.I.T.) and thus reduces the main side effects of piroxicam [32,34].

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زيادة معدل الاذابة والاتاحة الحيوية لعقار البيروكسكام من صيغ كبسولات الجيلاتين الصلبه واقراص سريعة الذوبان وذلك بإستخدام طريقة زيادة القابلية السطحية للماء

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قســـم الصيدلانيات–كليـــــــة الصيدلـــــــــة – جامعة أســـيوط– أسيوط – مصر

من المعروف أن عقار البيروكسكام المستخدم فى علاج الالتهاب لا يذوب فى الماء وشـــحيح الذوبان فى الكحول ومعظم المذيبات العضوية كما أنه ينصهر عند درجة حرارة عالية حوالـــى ٢٠٠ درجة مئوية . لذلك فإن العديد من الطرق المستخدمة فى زيادة ذوبان الادوية شحيحة الذوبـــان فـــى الماء لايمكن إستخدامها بسهولة مع عقار البيروكسكام.

يتناول البحث إستخدام طريقة زيادة القابلية السطحية للماء لزيادة معدل ذوبان البيروكسكام فـــى الماء وذلك بأستخدام : توين ٨٠ ، عديد الفينيل بيروليدون عديد الايثيلين الجليكول ٤٠٠٠ وقـــد تـــم دراسة معدل الذوبان للعقار بعد صياغته فى شكل كبسولات وأقراص سريعة الذوبان وقد تم مقارنـــة معدل الذوبان للعقار من الصيغ المحضرة مع الصيغ التجارية تحتوى على ٢٠ ملجم بيروكســـكام (فلدين كبسولات وفلدين أقراص سريعة الذوبان) .

وقد وجد أن للصيغ المحضرة سرعة ذوبان أعلى من المستحضرات التجارية . كما وجـــد أن معـــدل الذوبان من جميع الصيغ يتأثر بالأس الهيدروجينى للوسط المستخدم فى تجارب سرعة الذوبان.

وقد تم مقارنة الاتاحة الحيوية للكبسولات والاقراص المحضرة بأستخدام مادة عديـــد الفينيـــل البيروليدون ك – ٣٠ مع المستحضرات التجارية بعد تعاطيها عن طريق الفم لعدد ستة من المتطوعين الاصحاء .وقد أستخدمت طريقة التحليل الكروماتوجرافى ذات الضغط العالى فى تعيين تركيز العقـــار فى بلازما الدم . وقد وجد أن للاقراص المصاغة معدل امتصاص أعلى وكذلك أقصى تركـــيز فـــى بلازما الدم . وتدل النتائج التى تم الحصول عليها من هذا البحث على أهمية إستخدام طريقـــة زيـــادة القابلية السطحية للماء لزيادة معدل ذوبان وإمتصاص العقار داخل الجسم .