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Improvement of Dissolution Rate and Bioavailability of Piroxicam with Pregelatinized Starch

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Piroxicam (PPX) dispersions in pregelatinized starch (PGS) were prepared in different drug and carrier ratios and were characterized by X-ray diffractograms (XRD), differential scanning calorimetry (DSC), differential thermal analysis (DTA) and dissolution studies. Bioavailability studies were conducted on PRX-PGS dispersions and PRX pure drug in healthy human subjects as per cross over randomized block design (RBD). From Time Vs blood concentration data C_{max}, T_{max}, K_a, AUC and $T_{1/2}$, were calculated. Higher dissolution rates were noted with dispersions when compared to piroxicam as such. PRX-PGS dispersions also gave fast absorption and higher blood levels of piroxicam when compared to pure drug. All the absorption parameters namely C_{max}, percent absorbed in 1 and 2 h, Ka, AUC were higher indicating faster absorption of PRX from dispersions.

Pregelatinized starch (PGS) is a modified starch prepared from potato starch and characterized as described elsewhere[1]. PGS has been evaluated as carrier for nimodipine and nifedipine dispersions[2,3]. In the present study piroxicam (PRX), a non-steroidal antiinflammatory agent of benzothiazine family was used. It is highly crystalline, practically insoluble in aqueous fluids and its prolonged use is associated with side effects like gastric bleeding and mucosal damage[4]. Because of the limited aqueous solubility it exhibits poor dissolution characteristics and its oral absorption is dissolution rate limited. In our earlier papers we tried to improve *in vitro* bioavailability of nifedipine and nimodipine from PGS dispersions[2,3]. PGS is an easily dispersible modified starch, which exhibits higher swelling capacity. It is suggested that the dissolution rate of the drug can be improved by combination of disintegration and solvent deposition effects. Hence to improve dissolution rate and bioavailability of piroxicam, dispersions of piroxicam in pregelatinized starch were prepared and evaluated.

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METHODS

Piroxicam U.S.P., was obtained from M/s S.G. Pharmaceuticals, Vadodara, pregelatinized starch was prepared from potato starch in our laboratory[1]. Methanol (Merck), hydrochloric acid (Ranbaxy), acetonitrile (Qualigens) and perchloric acid (Ranbaxy) were purchased from commercial sources, mentioned in parentheses.

Preparation of PRX-PGS dispersions:

PRX-PGS dispersions were prepared by solvent evaporation method. The required quantity of drug after passing through mesh no. 120 was dissolved in methanol to get a clear solution. PGS was then added to the clear solution and dispersed. The solvent was then removed by evaporation at 40° under vacuum. The mass obtained was crushed, pulverized and sifted through mesh no. 120. Different proportions of drug: carrier such as 1:1, 1:3 and 1:9 were used to prepare the dispersions after passing through mesh no. 120. XRD, DTA and DSC studies were carried out to evaluate the physicochemical characteristics of dispersions.

Dissolution rate study:

The dissolution rate of PRX, PRX-PGS dispersions were studied using a USP XXI Dissolution Rate Test Apparatus which employs a paddle stirrer. In 900 ml of dissolution medium (0.1 N HCl), a sample equivalent to 20 mg of piroxicam, a speed of 100 rpm and a temperature of 37±1° were employed in each test. At appropriate time intervals, 5 ml sample was withdrawn and replaced by fresh dissolution medium. The sample was suitably diluted and assayed spectrophotometrically at 333 nm for piroxicam. Dissolution efficiency values were calculated from the dissolution data as suggested by Khan[5].

Bioavailability studies:

In vivo bioavailability studies were conducted on (i) pure piroxicam and (ii) PRX-PGS (1:9) dispersion in healthy male human subjects as per cross over RBD. Six healthy human subjects of age range between 24-28 y (average weight was 58.5±4.5 kg) were included in the study. All the subjects admitted to the study received oral and written explanations about the purpose of the trial and the properties of the administered drug. Each subject gave a written consent, confirming that the participation was voluntary. They were instructed to refrain from taking any medication during the study. The approval of an ethics committee was obtained before starting the study. Each subject was administered one product once a month. PRX products were administered at a dose of 20 mg of piroxicam in a hard gelatin capsule shell of 0 size. They were taken orally in the morning following overnight fasting. No food or liquid other than water was permitted until 4 h following administration of the product. After collecting the zero-hour blood sample (blank), the product in the study was administered orally with 200 ml of water. Two milliliters of blood samples were collected at 0.5, 1.0, 2.0, 3.0, 4.0, 8.0, 12.0, 24.0, 30.0, 36.0 and 48.0 h after administration. All the samples were stored under refrigerated conditions prior to assay. Blood concentrations of PRX were determined by a known spectrophotometric method which was described below[6]. The spectrophotometric method was revalidated, the relative standard deviation (RSD) in the estimated values was found to be 1.2%.

One milliliter of blood was pipetted into a glass stoppered centrifuge tube. Five milliliters of acetonitrile was added and mixed for 10 min. The contents of the tube were then centrifuged at 2500 rpm for 15 min. After centrifuging 4 ml of supernatant fluid was transferred into a test tube containing 0.2 ml of 1.47M aq. $HClO_4$ solution and mixed. The absorbance of the solution was measured at 330 nm against a blank prepared in the same manner using 0 h drug free blood sample. From the time Vs blood concentration curves peak blood concentration (C_{max}),time at which peak occurred (T_{max}) and area under the curve (AUC) were recorded. Absorption rate constant (Ka) was calculated by applying Wagner-Nelson's method to time Vs concentration data.

RESULTS AND DISCUSSION

Pregelatinized starch, employed in this study fulfilled official identification tests (USP XXIII). The PGS prepared was easily dispersible in purified water. Dispersions of PRX in PGS have low coefficient of variation values (<2%) in the per cent drug content ensured uniformity of drug content in each batch of dispersion prepared.

X-ray diffractograms of PRX exhibited characteristic diffraction patterns. Whereas in the case of diffractograms (fig. 1) of PRX-PGS (1:9) dispersion the sharp diffraction peaks disappeared. The absence of sharp peaks indicates that majority of drug is present in amorphous form.

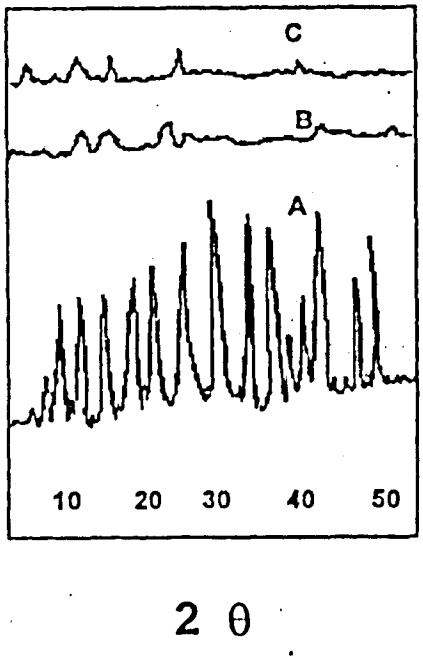

Fig. 1: X-ray diffractograms of piroxicam and piroxicam-pregelatinized starch dispersions

X-ray diffractograms of A-Piroxicam, B-Pregelatinized starch and C-Piroxicam-Pregelatinized starch dispersion (1:9)

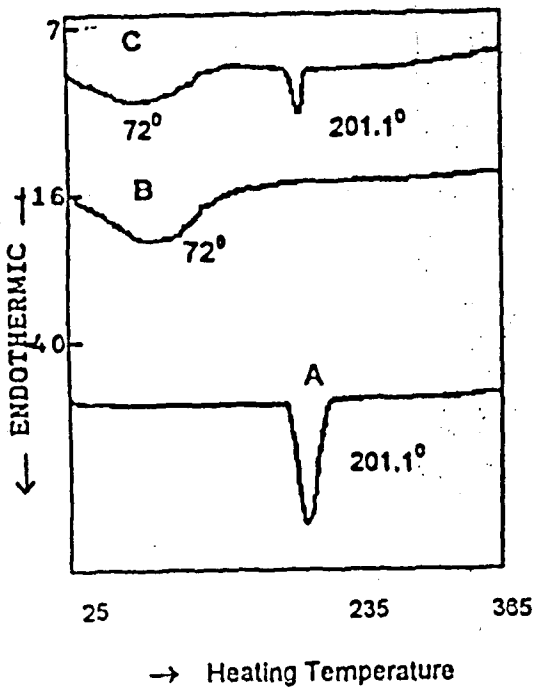

Fig. 2: Differential Scanning thermograms of piroxicam and piroxicam-pregelatinized starch dispersions

Differential Scanning thermograms of A-Piroxicam, B-Pregelatinized starch and C-Piroxicam-Pregelatinized starch dispersion (1:9)

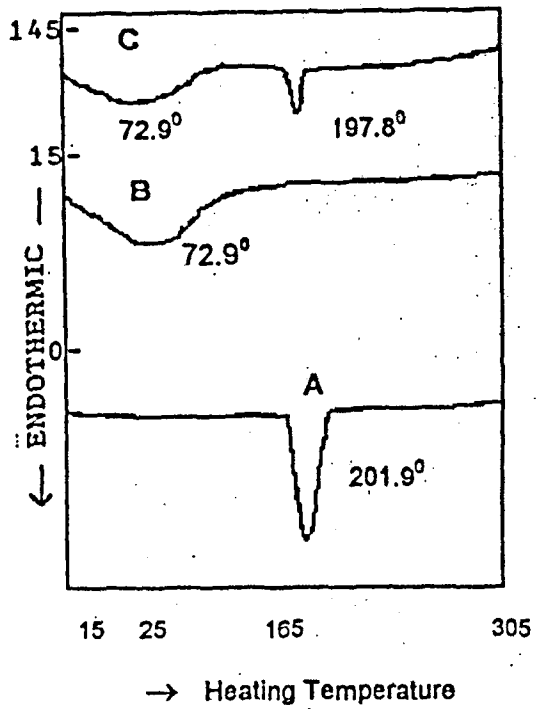

Fig. 3: Differential Scanning thermograms of piroxicam and piroxicam-pregelatinized starch dispersions

Differential Scanning thermograms of A-Piroxicam, B-Pregelatinized starch and C-Piroxicam-Pregelatinized starch dispersion (1:9)

The DSC thermograms of PRX, PGS and PRX-PGS (1:9) dispersion are shown in fig. 2. The DSC thermogram of dispersion showed two endothermic peaks, a sharp peak at 201.1 corresponding to PRX and a broad peak at 72 corresponding to PGS. The sharp endothermic peak at 201.1 (corresponding to PRX) in the DSC thermogram of dispersion indicates that, PRX is present in amorphous form in the dispersions.

The DTA thermograms of PRX, PGS and PRX-PGS dispersion (1:9) are shown in fig. 3. PRX exhibited an endothermic peak at 201.9°. PGS exhibited a broad endothermic peak at 72.9°. The DTA thermograms of the prepared dispersions showed peaks at 197.8° corresponding to the melting point of PRX and 72.9° corresponding to PGS respectively, indicating that there is no chemical interaction between PRX and PGS.

The dispersions gave faster dissolution of PRX when compared to pure drug. The increased dissolution rate of PRX from its dispersions is due to the presence of drug in amorphous form, since amorphous form is the highest energy form of a compound which produce faster dissolution[7]. Other factors such as possible reduction in particle size, the ease and rapid dispersibility of PGS might have also contributed to the increased dissolution rate of PRX from dispersions. The dissolution rate of PRX increased when the proportion of PGS in the dispersion increased. Thus the dissolution of piroxicam from dispersions followed first-order kinetics as shown in Table 1.

TABLE 1: DISSOLUTION PARAMETERS OF VARIOUS DISPERSIONS PREPARED

Dispersion	First-Order Dissolution Rate (min^{-1})10^3	Dissolution efficiency (%)
Piroxicam	8.28±1.36	28.58±4.37
PRX-PGS (1:1)	11.99±0.97	35.54±4.56
PRX-PGS (1:3)	21.85±4.73	50.67±6.12
PRX-PGS (1:9)	50.28±6.50	74.28±6.36

TABLE 2: PHARMACOKINETIC PARAMETERS OF ORAL PIROXICAM PRODUCTS 1 AND 2

Parameter	Product1	Product2	t-value	Result
C_{max} ($\mu g/ml$)	2.45 ±0.31	3.12 ±0.50	2.97	S
T_{max} (h)	6.0 ±2.31	2.75 ±0.96	2.96	S
K_{el} (h^{-1})	0.0205 ±0.0039	0.0209 ±0.0062	-	-
$t_{1/2}$ (h)	34.33 ±6.02	35.50 ±11.51	-	-
(AUC) (μg-h/ml)	115.35 ±10.55	164.23 ±21.89	4.02	S
K_a (h^{-1})	0.5078 ±0.1025	2.0333 ±0.0502	7.13	S
PER CENT ABSORBED				
1h	20.83 ±8.59	49.61 ±11.37	-	-
2h	45.66 ±10.96	91.68 ±15.59	-	-

Product 1: Piroxicam pure drug; Product 2: PRX-PGS dispersion (1:9); S: Significant at P≤0.05.

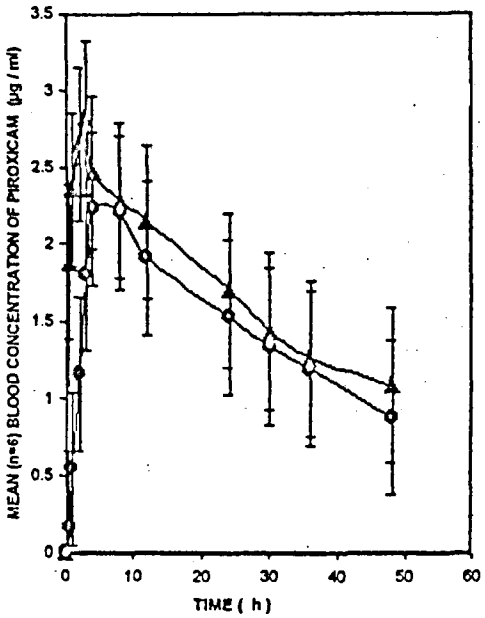

Fig. 4: Plasma concentration-time curves of piroxicam

Plasma levels of piroxicam at different time points after oral administrations of Product 1(-●-) and Product 2(-■-). Each point is a mean of (n=6)

The results of *in vivo* bioavailability studies (Table 2) indicated fast absorption and higher blood levels of PRX from dispersions in PGS when compared to piroxicam as such. Higher Cmax and lower Tmax values indicate (fig. 4) fast absorption of PRX from PRX-PGS dispersions. All the absorption parameters namely per cent absorbed in 1 and 2 h, Ka and AUC were also higher indicating rapid and higher absorption of piroxicam from PRX-PGS dispersions. The significance of the observed difference in various pharmacokinetic parameters such as C_{max}, T_{max}, K_a and AUC following the administration of piroxicam as such and as dispersion in PGS was tested by students t-test for determining significance. The results shown in Table 2 indicates that the observed difference in all the pharmacokinetic parameters tested was significant ($p<0.05$). As piroxicam is poorly water soluble, the observed increase in the absorption characteristics and bioavailability with PRX-PGS dispersion was attributed to the rapid dissolution of PRX from its dispersions. The biological half-life was found to be nearly the same with all the products indicating that the elimination characteristics of piroxicam remained unaltered. Thus the

dissolution rate and bioavailability of poorly water soluble drugs could be improved by dispersion in pregelatinized starch.

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