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FORMULATION AND IN VITRO - IN VIVO CHARACTERIZATION OF SOLID DISPERSIONS OF PIROXICAM

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ABSTRACT

The present work embodies studies performed with solid dispersions of the non-steroidal anti-inflammatory agent piroxicam, using biocompatible water soluble polymers polyethylene glycol (PEG) 4000 and 6000 alone, as well as in blends of various proportions. Different physicochemical properties and in vitro characterization were carried out. In vivo studies were performed to correlate with in vitro studies.

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, low biological half life, instability, dosing problems etc. (1,2,3). This trend of working has led to the development of new'drug delivery systems' (4-10). Various techniques (11-17), have been tried to enhance aqueous solubility of drugs whose gastrointestinal absorption is dissolution rate limited, and those which are poorly water soluble. But all these conventional methods, including micronization have their inherent disadvantages. Sekiguchi

and Obi (18) first introduced the concept of solid despersions as a new drug delivery system, with urea as the carrier and sulphathiazole as the poorly water soluble drug. Subsequent research (19-32) has utilized this technique for various drugs with good results.

For the present topic, piroxicam (33-35) was the chosen drug, for which literature reports indicate, it is practically water insoluble (36-37). Solid dispersions of piroxicam, prepared by the fusion technique were taken up for various studies, and described in the subsequent sections. This study comprised of comparison of the pharmacokinetic profile of this new dosage form with that of the powder piroxicam.

EXPERIMENTAL

Materials

Silica Gel G(E. Merck, Germany), silicagel HF (E. Merck, Germany), Piroxicam U.S.P. (courtesy : Cadila Antibiotics (P) Ltd.), PEG 4000 (S.D.Fine Chem. Ltd.), PEG 6000 (Loba Chemie), Acetonitrile (S.D.Fine Chem. Ltd.), Percholoric acid (S.D.Fine Chem. Ltd.), Toluene (S.D.Fine Chem. Ltd.), Acetic acid (E.Merck, India), Cyclohexane (E.Merck, India), Acetone (E.Merck, India), Dichloromethane (E. Merck, India), Ethanol (E. Merck, India), Chloroform (S.D.Fine Chem. Ltd.), Hydrochloric acid (S.D.Fine Chem. Ltd.). All reagents were of AR or GR grade and were used without further purification.

Equipments

Temperature controlled oil bath, Hitachi 200-20, UV - Vis spectrophotometer, Perkin-Elmer 298 I.R. spectrophotometer, gyratory shaker, centrifuge (Remi-Model).

Outline of the fusion method of preparation of solid dispersions

Required amount of different ratios of drug and carrier were weighed and made into a physical mixture in a glass pestle and mortar. Next, the physical mixture was heated in a tempera-

ture - regulated oil bath with constant stirring, till a homogeneous molten mass was obtained, noting the temperatures of onset and completion of melting. The molten mass was quickly congealed in an ice-bath under constant stirring. The congealed mass was stored in a vaccum dessicator for 24 hours for hardening, the hardened mass was crushed, pulverized, sieved through 60 mesh sieve and used for further studies.

Physicochemical characterizations of solid dispersions

Melting points of the solid dispersions, consisting of piroxicam with PEG 4000 and PEG 6000 singly and in blends, were determined and compared with that of the pure drug.

TLC characterizations : All the solid dispersions were subjected to TLC (the pure drug being spotted simultaneously with the dispersions) to determine the homogeneity and absence of drug degradation in the dispersions. Silicagel G and HF 254 were used as adsorbents, and different solvent systems used, namely - (a) Toluene-Acetic acid (95:5), (b) Cyclohexane-Acetone (10:5), (c) Dichloromethane-Ethanol (20:1), (d) Chloroform-Ethanol (10:1).

I.R. spectra characterizations : The dispersions were subjected to I.R. analysis, to determine any drug degradation, or interaction with carriers.

Solubility studies : For determination of solubility of the pure drug, physical mixtures and solid dispersions,the method outlined by Anastasiadon et al. (38) was adopted. All the solubility determinations were done at 32° - 34°C, the drug being estimated spectrophotometrically (39).

In vitro dissolution studies : For the dissolution rate profiles of pure drug and the dispersions, the rotating basket method of USP XXI (40) was used, using 500 ml of simulated Gastric Fluid (without pepsin) of pH 1.2 at 37 ± 1°C. 20 mg of pure drug and an equivalent amount of dispersions were used. Aliquots were assayed spectrophotometrically at 333 nm.

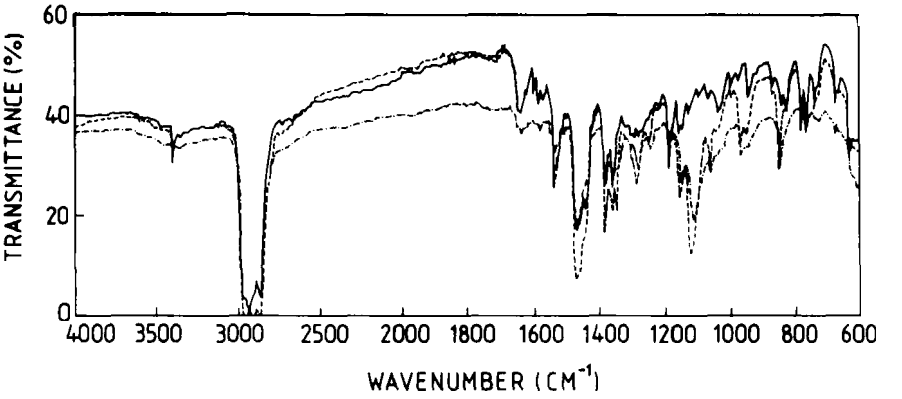

FIGURE 1

IR Spectra of Piroxicam (free drug), ~~~~; Drug:PEG 4000, 1:2 ——— ; Drug : PEG 6000, 1:7 ~~~~ .

Stability studies on solid dispersions : The dispersions were stored at 37°C for six months. Solubility and dissolution profiles were determined at intervals of one month. I.R. spectra was taken after 6 months.

In vivo bioavailability studies on rabbits : The studies were carried out on male rabbits, of appx. 1.5 kgs, fasted for 15 hrs. and allowing water ad libitum. An amount of piroxicam powder and 1:2 dispersion, equivalent to 20 mg of piroxicam, calculated on the basis of body weight of the animals were fed to the rabbits. Blood samples were withdrawn at predetermined intervals. The drug estimation was done after treatment of blood samples by the modified procedure (41) using spectrophotometric method, at 335 nm.

RESULTS AND DISCUSSION

From the various parameters studied, it was evident, that with increase in the carrier proportions, the melting point gradually decreases, which was expected. TLC studies confirmed the

absence of drug degradation in the dispersions. Stability studies (Fig.1) show that there is no change of the drug as such in the dispersions; solubility and stability studies also confirm the same. Solubility studies reveal, that with increment in carrier proportions, there is an increase in piroxicam solubility (Fig.2&3) upto the 1:2 ratio of drug : PEG 4000 dispersion, 1:7 ratio of drug : PEG 6000 dispersion and 1:2:2 ratio of drug : PEG 4000 : PEG 6000 dispersions and the corresponding physical mixtures. Beyond these proportions of drug and carriers, there is a marked decrease in drug solubility which confirms that these particular ratios are optimum for the maximum solubilization of piroxicam. The dissolution profiles prove the superiority of dispersions over the parent drug (Fig.3).

The mean plasma profiles following the administration of piroxicam are illustrated in figure 4. Absorption of the piroxicam (free drug) produced a mean peak piroxicam concentration of 2.4 mcg/ml at 5.0 hours. The solid dispersed dosage form demonstrated a rapid absorption, producing mean peak concentration of 3.5 mcg/ml at 4.0 hours. The values of areas under the plasma concentration time curves and other pharmacokinetic parameters are shown in table 1.

Based on these studies, it was noted that the 1:2 dispersions of drug and PEG 4000 gave the best results of enhanced solubility and dissolution characteristics(Fig.2&3). Thus it was chosen for further in vivo studies in rabbits. The table 1 summarizes the mean pharmacokinetic parameters estimated from the plasma concentrations versus time profiles, after administration of piroxicam and solid dispersions of piroxicam. A significant difference in the AUC values between pure piroxicam and the solid dispersed drug prepared with 1:2 ratio of drug and PEG 4000 was observed. The elimination data and the corresponding $t_{\frac{1}{2}}$ values are in agreement with the C_{max} values.

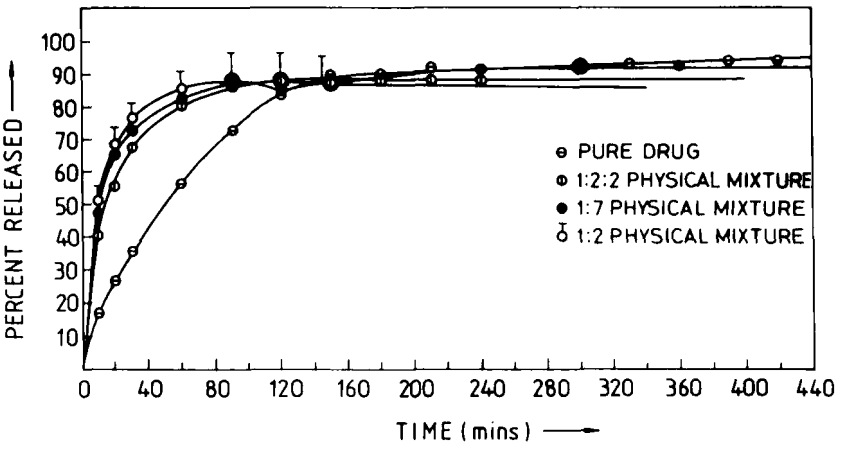

FIGURE 2

Comparative Dissolution Profile Depicting Percent Release For Pure Piroxicam and Physical Mixtures of Piroxicam and Different Carriers.

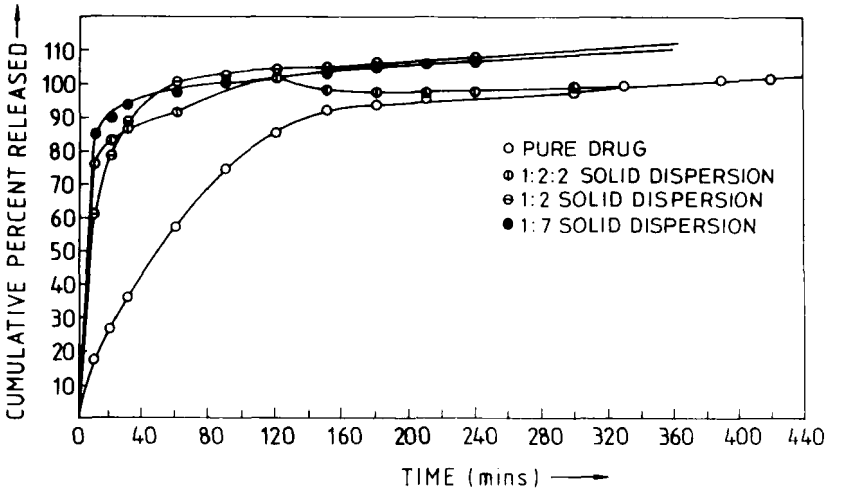

FIGURE 3

Comparative Dissolution Rate Profile Depicting Cumulative Percent Released For Pure Piroxicam And Various Solid Dispersions Of Piroxicam with Carriers.

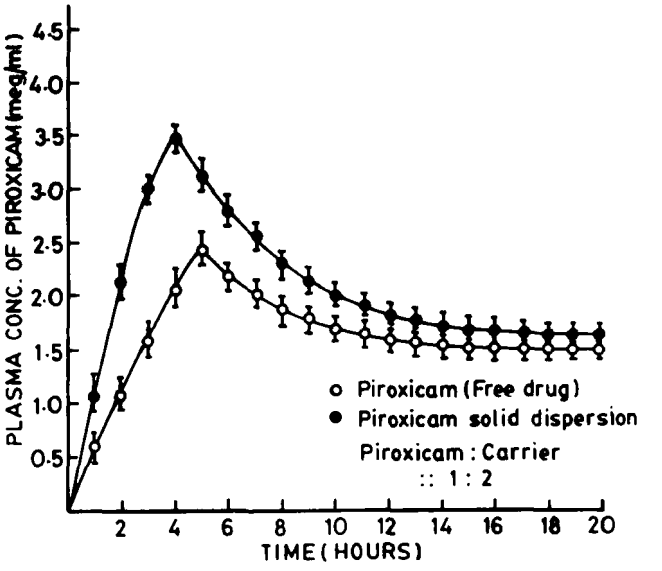

FIGURE 4

Plasma Level of Piroxicam following administration of Piroxicam (free drug) (0-0) and Solid Dispersed Dosage form (●-●), mean ± s.e.m., n=6.

TABLE 1

Pharmacokinetic parameters of piroxicam solid dispersion after oral administration in rabbits

Formulation	No.of rabbits	C_{max}^{b} (ug/ml)	t_{max}^{b} (hrs)	$AUC_{0-\infty}$ (ug.hr/ml)	K_{el}	$t_{1/2}$
Piroxicam (free drug)	6	2.4±0.10	5.0	167.71 ±8.33	0.033 ±0.002	21.0 ±0.85
1:2 solid dispersion of drug : PEG 4000	6	3.5±0.15*	4.0	216.71* ±7.12	0.04 ±0.004	17.32 ±1.02

Mean values (± SD) are shown. A significant difference from pure piroxicam, as determined by student "t" test is indicated by * $P<0.01$

[b] Observed peak concentration at time.

In vitro and in vivo dissolution and absorption profiles were subjected to linear regression analysis, and the correlation coefficient (r) was calculated. Plots of $t_{50\%}$, the time taken to release 50% of piroxicam in vitro versus C_{max}, gives a significant correlation between $t_{50\%}$ and C_{max} (r=0.996).

From all these studies, it is evident that solid dispersion can prove to be a superior mode of delivery of piroxicam in comparison to the conventional dosage forms, as shown by its enhanced bioavailability from the solid dispersions. It is possible, that a reduction in particle size of the drug crystallites, with concommitant increase in surface area, has led to the increased dissolution rates and bioavailability.

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