Formulation and Evaluation of Piroxicam Suppositories

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Abstract:
Pirolxicam is the first member of oxicam compounds of non-steroidal anti-inflammatory drugs (NSAIDs). It is a non-selective cox-1 and cox-2 inhibitor and is used widely in the management of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and pain following orthopedic and dental surgeries.

The major adverse effects of piroxicam, as all NSAIDs, are the damaging effects on mucosa resulting in erosions, ulcers and gastrointestinal bleeding.

Piroxicam is available in the market as capsules, dispersible tablets, fast-dissolving tablets, suppositories, topical gel, and intramuscular injections. A pharmacokinetic study of piroxicam revealed that it takes more than 2 hours to reach the maximum concentration, indicating the slow absorption rate after being administered orally.

To avoid many of piroxicam side effects, it was found that rectal administration carries a higher therapeutic index than oral administration and both the ulcerogenic effect and acute toxicity are appreciably less by the rectal route.

Piroxicam is practically insoluble in water, which hinders its formulation into aqueous solutions; also, this limits its dissolution prior to its absorption and, hence could limit its bioavailability upon administration.

In the present study,
1- Various techniques were applied to improve the solubility and the dissolution rate of piroxicam. These techniques include solid dispersion, melt granulation and lyophilization with certain water soluble carriers. Furthermore, the physicochemical characteristics of the prepared systems were investigated by IR-spectroscopy, DSC, X-ray diffraction and scanning electron microscope.
2- Rectal suppositories of piroxicam were prepared using different suppository bases to enhance in vitro release of piroxicam.
3- The anti-inflammatory activity of piroxicam in the selected formulae which gave the highest in vitro release and acceptable physical properties was determined using paw edema method in rats. Also, the bioavailability of piroxicam from the selected formula was investigated.

Thus, the thesis comprises three chapters:
Chapter I
Improvement of solubility and dissolution of piroxicam via solid dispersion, melt granulation & lyophilization techniques.

Chapter II
Formulation and evaluation of piroxicam suppositories.

Chapter III
Determination of the pharmacological effect and pharmacokinetic parameters of piroxicam from the prepared suppositories.

Chapter I
Improvement of Solubility and Dissolution Rate of Piroxicam via Solid Dispersion, Melt Granulation and Lyophilization Techniques

Based on biopharmaceutic classification system, piroxicam belongs to class II with a low solubility and high permeability. The work in this chapter was an attempt to improve the solubility and dissolution rate of piroxicam adopting three techniques namely; solid dispersion, melt granulation and lyophilization. Carriers such as PEG 4000, PEG 6000, pluronic F - 68 and pluronic F - 127 at different ratios (1:4, 2:3, 1:1, 3:2 and 4:1) of drug: carrier. Piroxicam solid dispersions were prepared by the solvent evaporation method & melt granules were prepared by the hot fusion method.
The prepared solid dispersion and melt granulation were evaluated for:

a) Solubility and dissolution rate studies:
Solubility results revealed a pronounced enhancement of piroxicam solubility in distilled water with solid dispersion and melt granules systems compared to the pure drug. The amount solubilized of the drug was increased by increasing the concentration of the carriers in the prepared systems. Polyethylene glycol 6000 (PEG 6000) exhibited the highest solubilizing effect in distilled water at drug: polymer ratio of (1:4). The same dispersion systems exhibited the higher dissolution rate compared to its corresponding physical mixture, at the same ratio, or untreated drug. Other carriers also showed increased solubility and dissolution of piroxicam. Accordingly, solid dispersion, melt granules and freeze dried solid dispersion and melt granules of piroxicam / carrier at the ratio 1:4 and the corresponding physical mixtures were selected for further investigations.

b) IR Studies:
IR spectra proved that no interaction has been occurred in the solid dispersion, melt granules and lyophilized solid dispersion, and melt granules of piroxicam with different carriers in ratio (1:4). The same result was observed with the corresponding physical mixtures.

c) Differential scanning calorimetry (DSC):
The DSC thermograms showed complete disappearance of the drug melting point either in the solid dispersions, melt granules and freeze dried solid dispersion, melt granules or the physical mixture with all carriers attributed to the conversion of piroxicam from a crystalline into amorphous form, on the other hand the absence of drug melting peak in the physical mixture may be due to the solubility of the drug in the molten carrier at higher carrier ratio.

d) X-ray diffractometry:
X-ray diffractometry showed that, the physical mixture of drug: PEG 6000 in weight ratio (1:4) still showing the characteristic drug peaks, while freeze dried solid dispersion and melt granules with the same ratio showed complete disappearance of drug characteristic peaks. This confirms the formation of the amorphous form of the drug when it was dispersed in PEG 6000.

e) Scanning electron microscopy:
The photomicrographs of PEG 6000, the drug and the piroxicam / PEG 6000 (1:4), freeze dried solid dispersion and melt granules showed the absence of crystalline structure of the drug, which confirm the transformation of piroxicam from the crystalline to the amorphous form.

From collected data, it can be concluded that the hydrophilic carrier PEG 6000 1:4 drug: polymer ratio exhibited the most remarkable enhancing effect on solubility and dissolution of piroxicam.

Chapter II
Formulation and Evaluation of Piroxicam Suppositories
The aim of work in this chapter was to formulate piroxicam suppository dosage forms using water soluble, emulsion and fatty suppository bases. The selected water soluble bases selected were blends of different polyethylene glycol suppository bases. The emulsion bases consists of witepsol E75, witepsol H15 or cocoa butter as the oily phase, while water and PEGs as the aqueous phase. Certain surfactants such as tween 20, tween 80 and span 60 used as emulsifying agents. Since the drug id hydrophobic, selection of fatty bases such as cocoa butter, witepsol H15, witepsol H37, AM and suppocire CM were just used to predict the release pattern of piroxicam from these lipophilic bases. Addition of tween (20, 40, 80), myrj 58 and brij 35 to suppocire AM and tween 80 and stearyl alcohol to cocoa butter enhanced the release of piroxicam from suppocire AM and cocoa butter bases.

I- Quality control testing of the prepared suppositories:
The physical properties of the prepared suppositories such as weight variation, hardness, disintegration time, melting range and content uniformity were studied. The
result revealed that, the prepared suppositories comply with the B.P. requirements with regard to content uniformity and weight variation. In addition, most of the suppository formulations exhibited suitable hardness and disintegration time.

II- In vitro drug release into phosphate buffer pH 7.4:
The in vitro release of piroxicam (20 mg) from the prepared suppositories was carried out using the dialysis method in phosphate buffer at pH 7.4. The obtained results revealed that,

a) Water-soluble suppository bases:
The release of piroxicam from the water soluble suppository bases was higher than those obtained from suppositories prepared with emulsion or fatty bases. All formulation prepared with PEG bases gave more or less identical release pattern, relatively the formula which composed of 20% PEG 6000, 40% PEG 1500 and 40% PEG 400 (F18) gave the highest release pattern.

b) Emulsion suppository bases:
The release rate from emulsion bases was variable depending on composition of the suppository formula. Formulations contained PEG 1500 with PEG 600 or with propylene glycol as the aqueous phase gave the higher release rate than other formulations. Among these formulations, formula contained mixture of PEG 1500 and propylene glycol (F20) as the aqueous phase exhibited the highest release rate.

c) Fatty suppository bases:
Being hyDROPhobic, piroxicam has a higher affinity to the lipophilic bases. As expected the release from such bases was very low and dependent on the melting behavior, chemical composition of the used base and partition coefficient of piroxicam between the fatty base and the buffer. Relatively, suppocire AM exhibited the highest release rate among fatty bases.

III- Kinetic analysis of release data:
The obtained results revealed that the release of piroxicam into phosphate buffer at pH 7.4 from water soluble, emulsion and fatty bases followed zero order kinetics.

Chapter III
Determination of the Pharmacological Effect and Bioavailability of Piroxicam Suppositories
The work in this chapter aimed to evaluate the anti-inflammatory effect and bioavailability of piroxicam suppositories compared to the marketed suppositories.

1- The pharmacological effects of piroxicam on carragenan-induced paw edema of healthy rats after rectal administration of the selected suppositories compared to the marketed suppository:
Two suppository formulations of piroxicam were selected: the water soluble base (F18) containing the freeze-dried solid dispersion and the water soluble base (F18) containing the freeze-dried melt granules. These formulations were selected on terms of their physical parameters and in vitro drug release.
The dose level of 0.36mg/200g of the drug corresponding