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PREPARATION AND EVALUATION OF MICRONIZED SUSPENSIONS OF PIROXICAM FOR ENHANCED DISSOLUTION RATE AND BIOAVAILABILITY

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ABSTRACT

Micronized suspensions of piroxicam were prepared by co-precipitation method employing three hydrophilic polymers namely hydroxy propyl methyl cellulose (HPMC), hydroxy ethyl cellulose (HEC) and polyethylene glycol 6000 (PEG) and were evaluated by *in vitro* and *in vivo* methods. The size of the dispersed drug particles was much reduced in the suspensions prepared by co-precipitation method. Suspensions formulated employing HPMC and PEG exhibited good suspendability and gave higher dissolution rate of piroxicam than those formulated employing piroxicam alone. Good linear relationship was observed between particle size and dissolution efficiency of the suspensions. The rate and extent of absorption of piroxicam was markedly higher in the case of formulation prepared with HPMC (F3) when compared to F1 (conventional). 2.17 and 2.31 fold increase respectively in K_a and $(AUC)_o^{2.5\ h}$ was observed with F3, when compared to F1.

Key words : Piroxicam, Dissolution rate, Bioavailability, Suspension, Co-precipitation method

INTRODUCTION

Micronization and nanosizing are efficient techniques[1,2] for enhancing the dissolution rate and bioavailability of hydrophobic and relatively insoluble drugs. Micro and nano sized drug particles can be dispensed in the form of tablets, capsules and suspensions. Physical stability, dissolution rate and bioavailability are parameters of importance in suspension formulation. Piroxicam, a widely prescribed antiinflammatory analgesic drug is poorly soluble in aqueous fluids and exhibits poor and variable oral bioavailability. The objective of the present study is to prepare and evaluate micronized suspensions of piroxicam by co-precipitation technique employing various hydrophilic polymers for enhancing physical stability, dissolution rate and bioavailability of piroxicam

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suspensions.

EXPERIMENTAL

Materials

Piroxicam, I. P., was a gift sample from M/s Micro Labs Ltd., Pondicherry. Hydroxy propyl methyl cellulose (HPMC, 50 cps), hydroxy ethyl cellulose (HEC, 20 cps), polyethylene glycol 6000 (PEG), sodium carboxymethyl cellulose (Sodium CMC, 1500-3000 cps), methyl cellulose (65 cps) and Tween - 80 (BDH) were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Methods

Preparation of piroxicam suspensions

Suspensions containing 20 mg of piroxicam in 5 mL were prepared as per the formulae given in Table 1.Piroxicam and the hydrophilic polymer (HPMC or HEC or PEG) were dissolved in a solvent blend of methanol–dichloromethane (2 : 1) in a mortar to get a clear solution. The solvent was removed by evaporation at room temperature (28 ±1 °C) while triturating the solution in the mortar until dry. The dried dispersion of drug and polymer was levigated with tween 80 solution. When a smooth paste has been formed, the mucilage of the suspending agent was added in divided portions while triturating the contents. Sucrose and sodium benzoate were then added as a solution in water and mixed. The suspensions were then blended in a mixer, adjusted to volume and transferred to measuring jars.

Table 1.Formulae of micronized suspensions of piroxicam prepared by co-precipitation method

Ingredient (g)	Formulation							
	F1	F2	F3	F4	F5	F6	F7	F8
Piroxicam	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
HPMC	-	-	0.1	0.1	-	-	-	-
HEC	-	-	-	-	0.1	0.1	-	-
PEG	-	-	-	-	-	-	0.1	0.1

Cont..

Ingredient (g)	Formulation							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Tween 80	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Sodium CMC	1.0	-	1.0	-	1.0	-	1.0	-
Methyl cellulose	-	1.0	-	1.0	-	1.0	-	1.0
Sodium benzoate	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Sucrose	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0
Purified water (mL) to	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Particle size measurement

Size of piroxicam particles in the suspensions was measured by microscopy. Average and standard deviation of 100 particles in each case were estimated.

Sedimentation study

The suspensions were transferred to stoppered measuring jars and were stored at room temperature (28 ± 1°C). The volume of sediment formed was noted at regular intervals of time. The sedimentation volume, ratio of ultimate height (Hu) of the sediment to the initial height (Ho) of the suspension (Hu/Ho) was calculated.

Estimation of piroxicam

An ultraviolet (UV) spectrophotometric method based on the measurement of absorbance at 333 nm in 0.1N hydrochloric acid was used for the estimation of piroxicam. The method obeyed Beer's law in the concentration range of 1-10 µg/mL. When a standard drug solution was assayed repeatedly (n = 6) the relative error (accuracy) and relative standard deviation (precision) were found to be 0.8 and 1.0 %, respectively.

Dissolution rate study

The dissolution rate of piroxicam from various suspensions was studied in 900 mL of water using USP XXIII – 3 station dissolution rate test apparatus (Model DR-3, Campbell Electronics) employing a paddle stirrer at 50 rpm and at 37 ± 1°C. A sample of suspension equivalent to 20 mg of piroxicam was used in each test. Samples of 5 mL each

were withdrawn at different time intervals and assayed at 333 nm for piroxicam using Schimadzu UV- 150 double beam UV spectrophotometer. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium. The dissolution rate experiments were conducted in triplicate.

In vivo evaluation

Pharmacokinetic evaluation was done on formulations F1 and F3 in healthy rabbits of either sex (n=4) weighing 1.5 - 2.2 kg as a cross over study. The *in vivo* study protocol was approved by Institutional Animal Ethics Committee. The products were tested at a dose equivalent to 0.5 mg/kg of piroxicam. After collecting the zero hour blood sample (blank) the product in the study was administered orally. Blood samples (2 mL) were collected at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0 and 12.0 h after drug administration. Plasma concentration of piroxicam was determined by the method described by Dhake et al.[3] as follows:

One mL blood was pipetted into glass centrifuge tube. Acetonitrile (5 mL) was added and mixed for 10 minutes. The contents of the tube were then centrifuged at 2, 500 rpm for 15 minutes. The supernatant fluid (4 mL) was transferred into a test tube containing 0.2 mL of 1.47 M $HClO_4$ solution and mixed. The absorbance of the solution was measured at 333 nm against blank prepared in the same way using zero hour drug free blood sample. From the time versus plasma concentration data, various pharmacokinetic parameters such as peak concentration (C_{max}), time at which peak occurred (T_{max}), AUC, elimination rate constant (K_{el}), biological half-life ($t_{1/2}$) and absorption rate constant (K_a) were calculated as per known standard methods.

RESULTS AND DISCUSSION

Suspensions F1 and F2 were formulated employing piroxicam as such and using sodium CMC and methyl cellulose as suspending agents, respectively, whereas suspensions F3 to F8 were formulated employing hydrophilic polymers and prepared by co-precipitation method. The average particle size was found to be 20.5 and 25.6 μ in formulations F1 and F2, respectively. The average particle size in the suspensions prepared by co-precipitation method was in the range 2.0 - 3.2 μ.The size of the dispersed particles was, thus, much reduced in the suspensions formulated by co-precipitation method (Table 2).

Table 2. Particle size, sedimentation volume and dissolution efficiency of micronized suspensions of piroxicam prepared by co-precipitation method

Formulation	Particle size (μ) $\bar{x}$ ± s.d.	Sedimentation volume (Hu/Ho)	Percent dissolved in			DE_{10} (%)
			2 min	5 min	10 min	
F1	20.5 ± 6.5	0.05	23.6	76.3	92.4	59.4
F2	25.6 ± 7.2	0.05	17.7	62.7	85.9	53
F3	2.0 ± 1.7	1.00	96.7	99.3	100	95.4
F4	2.3 ± 1.9	1.00	95.8	98.9	100	92.6
F5	2.7 ± 2.0	0.06	45.6	70.8	91.2	55.6
F6	3.2 ± 2.1	0.18	95.4	90.6	98.2	85.4
F7	2.9 ± 2.0	0.92	99.2	96.2	99.0	89.0
F8	3.0 ± 1.9	0.54	97.1	95.0	99.2	89.2

Table 3. Summary of pharmacokinetic parameters estimated following the oral administration of piroxicam suspension formulations

Formu-lation	C_{max} (μg/mL)	T_{max} (h)	$(AUC)_o^{2.5h}$ (μg-h/mL)	$(AUC)_o^{12h}$ (μg-h/mL)	$K_a(h^{-1})$	K_{el} (h^{-1})	$t_{1/2}$ (h)
F1	10.58 ± 0.3	4.0 ± 0.7	7.22 ± 6.5	55.58 ± 6.2	0.857 ± 0.12	0.172 ± 0.3	4.03
F3	14.2 ±1.2	2.5 ± 0.5	16.7 ± 3.4	58.2 ± 6.2	1.866 ± 0.20	0.184 ± 0.3	3.76

Settling of solids was rapid in suspensions F1 and F2 and in suspensions formulated employing HEC (F5 and F6). Suspensions formulated employing piroxicam-HPMC and piroxicam – PEG exhibited good suspendability of the dispersed phase without any sedimentation. These suspensions were also very smooth without any flocculation.

The dissolution rate of piroxicam from all the suspensions was studied in purified water to make a relative evaluation of the dissolution characters of the suspensions formulated. Dissolution efficiency (DE_{10}) values were calculated from the dissolution data as suggested by Khan[4]. Suspensions prepared by co-precipitation method gave relatively

higher dissolution than those formulated with piroxicam alone. Among all, suspensions formulated employing piroxicam - HPMC exhibited highest dissolution rate and dissolution efficiency. The dissolution efficiency was 59.4 and 53.0%, respectively in the case of formulations F1 and F2, whereas the dissolution efficiency was 95.4 and 92.6%, respectively in the case of formulations F3 and F4.The enhanced dissolution rate of piroxicam from the suspensions formulated employing hydrophilic polymers and prepared by co-precipitation method is due to smaller (micronized) particles present in these suspensions. Good linear relationship was observed between the particle size and dissolution efficiency of piroxicam from the suspensions (r = 0.988) (Fig. 1). Smaller particles gave higher dissolution rates and dissolution efficiency.

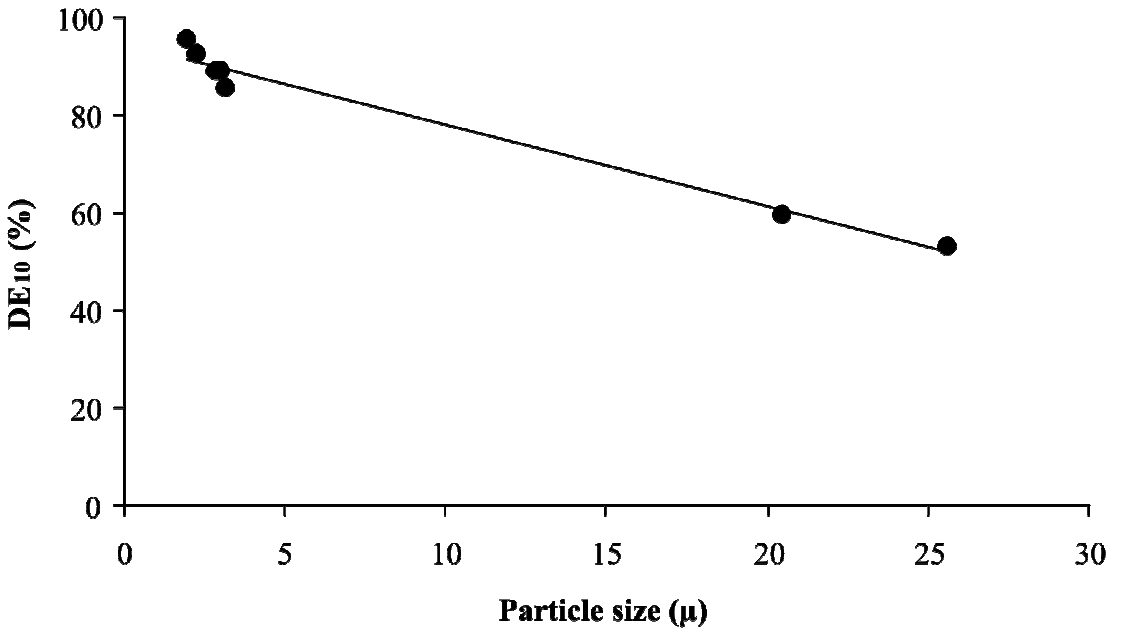

Fig. 1 : Relationship between particle size and dissolution efficiency of piroxicam suspensions.

The pharmacokinetic parameters (C_{max}, T_{max}, K_a) indicated rapid absorption of piroxicam from formulation F3. The C_{max} was higher and T_{max} was lower in case of F3 when compared to F1. Absorption rate (K_a) was increased from 0.857 ± 0.12 h^{-1} for formulation F1 to 1.866 ± 0.11 h^{-1} for formulation F3.

$(AUC)_o^{2.5\ h}$ was found to be 7.22 ± 6.5 µg h/mL in case of formulation F1 and 16.7 ± 3.4 µg h/mL in case of formulation F3.$(AUC)_o^{2.5\ h}$ values indicated higher

absorption of piroxicam from the formulation F3 during initial time periods after administration. However, $(AUC)_o^{12\ h}$ was nearly the same in both the cases indicating that the total extent of absorption was the same with both F1 and F3 formulations.

CONCLUSIONS

(i) The size of the dispersed drug particles was much reduced (micronized) in the suspensions prepared by co-precipitation method employing HPMC, HEC and PEG. These suspensions also exhibited good suspendability of solids and gave higher dissolution rate of piroxicam than those formulated employing piroxicam alone.

(ii) Suspensions formulated employing HPMC gave highest improvement in the dissolution rate and dissolution efficiency of piroxicam.

(iii) Good linear relationship was observed between particle size and dissolution efficiency of the suspensions.

(iv) The rate and extent of absorption of piroxicam were markedly higher in the case of formulation F3. 2.17 and 2.31 fold increase, respectively in K_a and $(AUC)_o^{2.5\ h}$ was observed with formulation F3, when compared to formulation F1.

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