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A FACTORIAL STUDY ON ENHANCEMENT OF DISSOLUTION RATE OF PIROXICAM BY SOLID DISPERSION TECHNIQUE EMPLOYING STARCH CITRATE, PVP K-30 AND PEG 4000

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ABSTRACT

Solid dispersion is a widely accepted technique for enhancing the dissolution rate of poorly soluble BCS class II drugs. In the present study starch citrate- a new modified starch, PVP and PEG 4000 were evaluated as a carriers in solid dispersions for enhancing the dissolution rate and efficiency of piroxicam, a BCS class II drug. Their individual and combined (interaction) effects in enhancing the dissolution rate and dissolution efficiency of piroxicam were evaluated in a 2^3- factorial study. Among the individual effects starch citrate gave highest enhancement in the dissolution rate of piroxicam (11.71 fold), followed by PVP (6.03 fold). Addition of PVP and PEG 4000 to the solid dispersions in starch citrate has further enhanced the dissolution rate upto 66.40 fold and dissolution efficiency upto 13.38 fold.

Key words: Solid dispersions, Piroxicam, Starch Citrate, PVP K-30, PEG 4000, Factorial Study.

INTRODUCTION

Piroxicam, a widely prescribed anti inflammatory and analgesic drug belong to Class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. Several techniques[1] such as micronization, cyclodextrin complexation, use of surfactants and solubilizers, solid dispersion in water soluble and dispersible carriers, use of salts, prodrugs and polymorphs which exhibit high solubility , microemulsions and self emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble drugs. Among the various approaches, solid dispersions in water dispersible excipients is a simple, industrially useful approach for enhancing the solubility, dissolution rate and bioavailability of poorly soluble drugs.

Wing[2] has reported reaction of starch with citric acid to yield starch citrate, a biodegradable product possessing high ion-exchange capacity. Wepner[3] have described a process for the synthesis of citrate derivatives of starch. Starch citrate is investigated as resistant starch in food industry. We have earlier reported[4,5] starch citrate, a new modified starch, as an efficient disintegrant and directly compressible vehicle in tablet formulations.

The objective of the present study is to evaluate starch citrate (a new chemically modified starch), PVP K-30 and PEG 4000 as a carriers in solid dispersions for enhancing the dissolution rate of piroxicam. Their individual and combined (interaction) effects in enhancing the dissolution rate and dissolution efficiency of piroxicam were evaluated in a 2^3- factorial study.

MATERIALS AND METHODS

Materials

Piroxicam was gift sample from M/s Dr. Reddys Laboratory, Hyderabad, starch citrate was prepared in the laboratory, Dichloromethane (Qualigens), potato starch (S.D Fine Chemicals), Methanol (S.D Fine Chemicals), were procured from commercial sources.

Methods

Preparation of Starch Citrate

Starch citrate was prepared based on the method of Klaushfer[6] with some modifications. Citric acid (20g) was dissolved in 20 ml of water, the pH of the solution was adjusted to 3.5 with 10 M sodium hydroxide and finally the volume was made upto 50 ml by adding water. The citric acid solution (50 ml) was mixed with 50g of potato starch in a stainless steel tray and conditioned for 16 h at room temperature (28^0C). The tray was then placed in forced air oven and dried at 60^0C for 6 h. The mixture obtained was ground and further dried in a forced air oven at 130^0C for 2 h. The dry mixture was

repeatedly washed with water to remove unreacted citric acid. The washed starch citrate was further dried at 50^{0}C to remove the water/moisture completely. The product obtained was ground and sized.

Estimation of Piroxicam

An UV spectrophotometric method based on the measurement of absorbance at 333 nm in 0.1N hydrochloric acid was used for estimation of piroxicam. The method obeyed Beer- Lambert's law in the concentration range of 0-10 µm/mL. When the standard drug solution was assayed repeatedly (n=6), the relative error (accuracy) and coefficient of variation (precision) were found to be 0.30% and 1.3% respectively. No interference from excipients used was observed.

Formulation of Piroxicam Solid Dispersions as per 2^3 Factorial Study

In the 2^3 factorial study, the three factors namely starch citrate (factor A), PVP K -30 (factor B) and PEG 4000 (factor C) each at two levels were investigated for their individual and combined effects on the dissolution rate of piroxicam solid dispersions. Starch citrate (factor A) was used as a carrier at a drug: carrier ratio of 1:2 and hence the two levels of starch phosphate (factor A) were 0 and 1:2 ratio of drug: carrier. PVP K -30 (factor B) and PEG 4000 (factor C) and were studied each at two levels i.e. 0% and 2% concentration.. A total of eight piroxicam solid dispersions were prepared employing selected combinations of the three factors.

Preparation of Solid Dispersions of Piroxicam in Starch Citrate

Solid dispersions of piroxicam in starch citrate were prepared employing selected combinations of the three factors by solvent evaporation method. Piroxicam was dissolved in dichloromethane (10 ml) in a dry mortar to get a clear solution. Starch citrate/PVP/PEG 4000 were then added and mixed. The thick slurry was triturated for 15 min for complete evaporation of dichloromethane and then dried at 55^{o}C until dry. The dried mass was pulverized and sieved through mesh no. 100.

Dissolution Rate Study

Dissolution rate of piroxicam as such and from its solid dispersions prepared was studied in 0.1N hydrochloric acid (900 ml) employing USP 8 station Dissolution Rate Test Apparatus (M/s Labindia Disso 8000) with a paddle stirrer at 50 rpm. Piroxicam or its solid dispersions equivalent of 20 mg of piroxicam was used in each test. A temperature 37$\pm$1^{o}C was maintained in each test. Samples of dissolution medium (5 ml) were withdrawn through a filter (0.45µ) at different time intervals and assayed for piroxicam at 333nm. All the dissolution experiments were replicated four times each (n=4).

RESULTS

Table.1.Dissolution Parameters of Piroxicam Solid Dispersions Prepared as per 2^3 Factorial Study

Solid Dispersion Formulation	Composition	Dissolution Rate $K_1(min^{-1}) \times 10^2$		Dissolution Efficiency DE_{30} (%)	
		($\bar{x}$±SD)	Increase in K_1 (no.of folds)	($\bar{x}$±SD)	Increase in DE_{30} (no.of folds)
F_1	Piroxicam	0.35±0.02	-	6.52±0.04	-
F_a	Piroxicam : Starch Citrate (1:2)	4.11±0.15	11.71	31.4±0.31	4.82
F_b	Piroxicam-PVP K-30 (2%)	2.20±0.08	6.031	29.1±0.34	4.45
F_{ab}	Piroxicam: Starch Citrate (1:2) –PVP K-30 (2%)	10.0±1.49	28.59	70.1±0.84	10.74
F_c	Piroxicam-PEG 4000 (2%)	1.90±0.07	5.409	34.3±0.48	5.26
F_{ac}	Piroxicam: Starch Citrate (1:2) -PEG 4000 (2%)	12.2±0.86	34.60	80.1±0.28	12.30
F_{bc}	Piroxicam- PVP K-30 (2%) – PEG 4000 (2%)	1.96±0.03	5.597	34.6±0.05	5.30
F_{abc}	Piroxicam: Starch Citrate (1:2) –PVP K-30 (2%)-PEG 4000(2%)	23.3±1.46	66.43	87.3±0.30	13.38

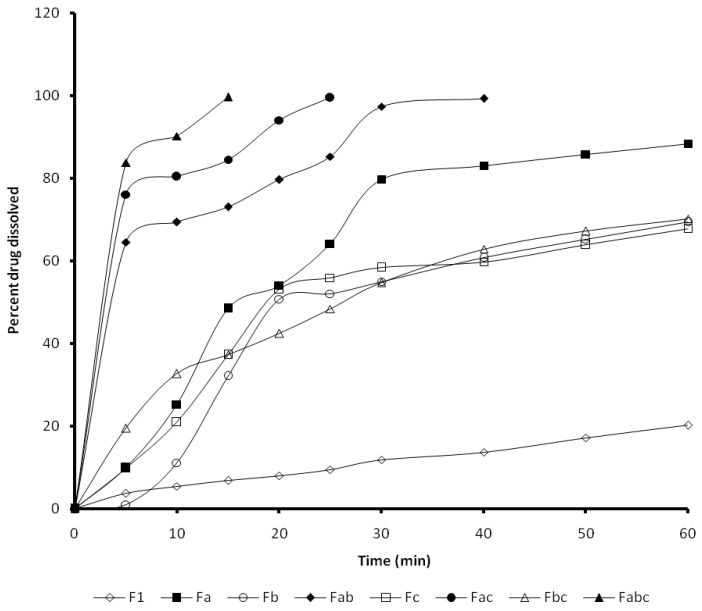

Fig.1.Dissolution Profiles of Piroxicam Solid Dispersions Prepared as per 2^3 Factorial Study

DISCUSSION

To evaluate the individual main and combined effects of starch citrate (factor A), PVP K-30 (factor B) and PEG 4000 (factor C) on the dissolution rate of piroxicam, solid dispersions of piroxicam were prepared employing selected combinations of the three factors as per 2^3 - factorial study. All the solid dispersions prepared were fine and free flowing powders. Drug content was uniform in each batch of solid dispersion prepared (c.v < 2%).

The dissolution of piroxicam from all the solid dispersions prepared was studied in 0.1N hydrochloric acid (n=4). The dissolution profiles of various solid dispersions prepared are shown in Fig.1. Dissolution data were analyzed as per zero order and first order kinetic models. The correlation coefficient 'r' values in the first order model were higher than those in the zero order model in all the cases indicating that the drug dissolution from all the solid dispersions prepared followed first order kinetics. Dissolution efficiency (DE_{30}) values were calculated as per Khan[7]. The first order dissolution rate constants (K_1) and dissolution efficiency (DE_{30}) values are given in Table 1. Much variations was observed in the dissolution rate (K_1) and DE_{30} values of the solid dispersions prepared as per 2^3 factorial study due to the effects of the factors involved. Dissolution parameters K_1 and DE_{30} were subjected to ANOVA to find out the significance of individual main and combined effects of the three factors involved.

ANOVA of K_1 values indicated that the individual as well as combined effects of the three factors in enhancing the K_1 are highly significant ($P<0.01$). ANOVA of DE_{30} values indicated that the individual effects of all the factors A, B and C were highly significant ($P<0.01$).

Solid dispersion F_1 contains piroxicam alone without the three factors (starch citrate, PVP K-30 and PEG 4000) and hence it is considered as control. All other solid dispersion formulations that contain selected combinations of the three factors gave rapid and higher dissolution when compared to control solid dispersion F1.

Among the individual effects starch citrate gave highest enhancement in the dissolution rate of piroxicam (11.71 fold), followed by PVP K-30 (6.03 fold). DE_{30} was also increased from 6.52% for piroxicam pure drug (F_1) to 34.4 %, 31.4 and 29.1 respectively with solid dispersions F_c, F_a and F_b. Addition of PVP and PEG 4000 to the solid dispersions in starch citrate has further enhanced the dissolution rate upto 66.40 fold and dissolution efficiency upto 13.38 fold. Solid dispersion formulations F_{ab}, F_{ac} and F_{abc} respectively gave 70.1, 80.2 and 87.3 fold increase in the dissolution rate of piroxicam when compared to piroxicam pure drug (control).

CONCLUSION

When the individual main and combined effects of the three factors namely starch citrate (factor A), PVP K- 30 (factor B) and PEG 4000 (factor C) in enhancing the dissolution rate and dissolution efficiency of piroxicam were evaluated in a 2^3- factorial study, starch citrate (F_a) gave highest enhancement in the dissolution rate of piroxicam (11.71 fold) followed by PVP K-30 (F_b) (6.03 fold) and PEG 4000 (F_c) (5.40 fold). Addition of PVP and PEG 4000 to the solid dispersions in starch citrate has further increased the dissolution rate upto 66.4 fold and dissolution efficiency upto 13.38 fold.

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