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A Factorial Study on Formulation Development of Aceclofenac Tablets Employing Starch 1500 and PVP K 30

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ABSTRACT

Aceclofenac, a widely prescribed anti-inflammatory and analgesic drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Solid dispersion of aceclofenac in Starch 1500, a modified starch and polyvinyl pyrrolidone (PVP K 30) was investigated to enhance the dissolution rate and to develop aceclofenac tablets with fast dissolution characteristics. The individual and combined (interaction) effects of Starch 1500 and PVP K 30 on the dissolution rate of aceclofenac solid dispersions and tablets were evaluated in a series of 2^2 – factorial experiments. Solid dispersions and tablets of aceclofenac were formulated employing selected combinations of Starch 1500 and PVP K 30 as per 2^2 – Factorial design and were evaluated. The individual and combined effects of Starch 1500 and PVP on the dissolution rate of solid dispersions as well as tablets were highly significant ($P<0.01$).Solid dispersion of aceclofenac in Starch 1500 (a), PVP K 30 (b) and Starch 1500 – PVP K 30 (ab) enhanced the dissolution rate of aceclofenac by 4.89, 4.75 and 4.82 folds respectively when compared to aceclofenac pure drug. Tablets formulated employing solid dispersions of aceclofenac in Starch 1500 (Fa) and PVP K 30 (F_b) gave respectively 2.1 and 2.2 fold increase in the dissolution rate (K_1) of aceclofenac when compared to plain tablets (F_1). Aceclofenac tablets prepared employing solid dispersions in Starch 1500 – PVP K 30 (F_{ab}) gave highest enhancement (3.0 fold) in the dissolution rate of aceclofenac. Dissolution efficiency (DE_{15}) was also increased by 2.12 - 2.42 fold with tablets formulated employing solid dispersions in Starch 1500 (F_a), PVP K 30 (F_b) and Starch 1500 – PVP K 30 (F_{ab}) when compared to plain tablets (F_1). Aceclofenac tablets formulated employing all its solid dispersions in Starch 1500, PVP K 30 and Starch 1500 – PVP K 30 gave a very fast dissolution of aceclofenac, NLT 80% in 15 min. Thus, solid dispersions of aceclofenac in Starch 1500, PVP K 30 and Starch 1500 – PVP K 30 could be formulated in to tablets with fast dissolution characteristics.

Key words: Factorial Study, Solid Dispersions, Aceclofenac Tablets, Dissolution Rate, Starch 1500, PVP K 30

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INTRODUCTION

Aceclofenac, a widely prescribed anti-inflammatory and analgesic drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. As such the oral absorption of aceclofenac is dissolution rate limited and it requires enhancement in the 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, micro emulsions 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 techniques solid dispersion in water insoluble and dispersible excipients is a simple and industrially useful technique for enhancing the dissolution rate of poorly soluble drugs. In the present study solid dispersion of aceclofenac in Starch 1500, a modified starch and polyvinyl pyrrolidone (PVP K 30) was tried to enhance the dissolution rate and to develop aceclofenac tablets with fast dissolution characteristics. The individual and combined (interaction) effects of Starch 1500 (factor A) and PVP K 30 (factor B) on the dissolution rate of aceclofenac solid dispersions and tablets were evaluated in a series of 2 [2] factorial experiments. Aceclofenac solid dispersions and tablets were prepared employing the selected combinations of the two factors as per 2^2 factorial design and were evaluated.

MATERIALS AND METHODS

Materials:

Aceclofenac, Starch 1500 and croscarmellose sodium were gift samples from M/s Eisai Pharmatechnology and Manufacturing Pvt.Ltd; Visakhapatnam. Polyvinyl pyrrolidone (PVP K 30), lactose, acacia, dichloromethane (Qualigens), talc and magnesium sterate were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Estimation of Aceclofenac:

An UV spectrophotometric method based on the measurement of absorbance at 275 nm in phosphate buffer pH 6.8 was used for estimation of aceclofenac. The method obeyed Beer-Lamberts' law in the concentration range of 0-10 µg/ml. When the standard drug solution was analyzed repeatedly (n=6), the relative error (accuracy) and co-efficient of variation (precision) were found to be 0.9% and 1.2% respectively. No interference from the excipients used was observed.

Preparation of Solid Dispersions of Aceclofenac in Starch – 1500:

In the 2^2 factorial study, the two factors namely Starch 1500 (factor A) and PVP K 30 (factor B), each at two levels were investigated for their individual and combined effects on the dissolution rate of aceclofenac solid dispersions. Starch 1500 (factor A) was used as a carrier at

a drug: carrier of 1:2 and hence the two levels of Starch 1500 (factor A) was 0 and 1:2 ratio of drug: carrier. PVP K 30(factor B) was studied at two levels 0 and 2 % concentration. As such the four selected combinations as per 2^2 – factorial design are aceclofenac (1), aceclofenac – Starch 1500 (1:2) solid dispersion (a), aceclofenac-PVP K 30 (2%) solid dispersion (b) and aceclofenac-Starch 1500 (1:2) – PVP K 30 (2%) solid dispersion (ab).

The above mentioned solid dispersions were prepared by kneading method. Aceclofenac and PVP K 30 were dissolved in dichloromethane (20 ml) in a dry mortar to get a clear solution. Starch 1500 was added and mixed. The thick slurry formed was continuously triturated for 30 min. Additional quantities of dichloromethane were added to maintain the consistency of the mixture as thick slurry during the process of kneading. Kneading was continued for complete evaporation of dichloromethane and the product formed was dried at 55^0C until dry. The dried mass was powdered and sieved through mesh no: 100.

Preparation of Aceclofenac Tablets:

Tablets each containing 100 mg of aceclofenac were prepared by wet granulation method using selected combinations of Starch 1500 (factor A) and PVP K 30 (factor B) as per 2^2 factorial study. The two levels of Starch 1500 (factor A) is 0 and 1: 2 ratio of drug: Starch 1500. The two levels of PVP K 30 (factor B) are 0 and 2 % in the formula. Croscarmellose sodium (5%), acacia (2%), lactose (qs), talc (2%) and magnesium stearate (2%) were included in all the tablet formulations.

The required quantities of aceclofenac (or) aceclofenac – Starch 1500 (1:2) solid dispersion, diluent (lactose) and acacia were mixed thoroughly in a dry mortar by following geometric dilution technique. The granulating fluid water was added and mixed thoroughly to form a dough mass. The mass was passed through mesh no.12 to obtain wet granules. Wet granules were dried at 70^0C for 4 h. The dried granules were passed through mesh no.16 to break the aggregates. Croscarmellose sodium and the lubricants (talc and magnesium sterate) were passed through mesh no.80 on to the dry granules and blended in a closed polyethylene bag. The granules were compressed into tablets on a 10 station rotary tablet compression machine (Rimek) to a hardness of 6 kg/sq.cm using 9 mm round and flat punches.

Evaluation of Tablets:

All the tablets prepared were evaluated for content of active ingredient, hardness, friability, disintegration time, dissolution rate as per official (I.P) methods. Hardness of tablets was tested using Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Disintegration time was determined in a Labindia tablet disintegration test machine (Model: DT 1000) using water as test fluid.

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Dissolution Rate Study:

Dissolution rate of aceclofenac from the solid dispersions and tablets prepared was studied in phosphate buffer pH 6.8 (900 ml) employing USP 8 station dissolution rate test apparatus (M/s Labindia Disso 8000) with a paddle stirrer at 50 rpm. Solid dispersion (or) one tablet containing 100 mg of aceclofenac was used in each test. A temperature of 37 ± 1^0C was maintained throughout. Samples of dissolution medium (5 ml) were withdrawn through a filter (0.45µ) at different time intervals and analyzed for aceclofenac at 275 nm. The samples of dissolution fluid withdrawn at each time were replaced with fresh fluid. All the dissolution experiments were conducted in triplicate (n=3).

RESULTS AND DISCUSSION

To evaluate the individual and combined effects of Starch 1500 (factor A) and PVP K 30 (factor B) on the dissolution rate of aceclofenac, solid dispersions of aceclofenac were prepared employing selected combinations of the two factors as per 2^2 factorial study. All the solid dispersions prepared were fine and free flowing powders. Drug content was uniform in each batch of solid dispersion prepared (CV< 2 %). The dissolution of aceclofenac as such and from all the solid dispersions prepared was studied in phosphate buffer of pH 6.8. The 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_{15}) values were calculated as per Khan[2]. The first order dissolution rates (K_1) and dissolution efficiency (DE_{15}) values are given in Table 1. Much variations were observed in the dissolution rate (K_1) and DE_{15} values of the solid dispersions prepared due to the effects of the factors involved. Dissolution rate (K_1) and DE_{15} values were subjected to Analysis of Variance (ANOVA) to find out the significance of individual main and combined effects of the factors involved. ANOVA indicated that the individual and the combined effects of Starch 1500 and PVP K 30 in enhancing the dissolution rate and efficiency of aceclofenac solid dispersions were highly significant ($P<0.01$). Solid dispersion of aceclofenac in Starch 1500 enhanced the dissolution rate of aceclofenac by 4.89 fold. Drug – PVP K 30 solid dispersions also gave an enhancement of 4.75 folds in the dissolution rate of aceclofenac. No further enhancement in the dissolution rate (K_1) was observed when PVP K 30 was included in the solid dispersions of aceclofenac in Starch 1500. Solid dispersion of aceclofenac in Starch 1500-PVP K 30 (ab) also gave 4.82 fold increase in the dissolution rate (K_1) of aceclofenac.

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Table – 1: Dissolution Parameters of Aceclofenac Solid Dispersions Formulated as per 2^2 – Factorial Design

Solid Dispersion Formulation (Code as per 2^2 – Factorial Design)	Dissolution Rate ($K_1 \times 10^2$) (min^{-1})	Increase in Dissolution Rate (No. of Folds)	Dissolution Efficiency DE_{15} (%)	Increase in DE_{15} (No. of Folds)
1	1.97	-	20.10	-
a	9.63	4.89	50.66	2.52
b	9.37	4.75	64.33	3.20
ab	9.50	4.82	63.00	3.13

To evaluate the individual and combined effects of Starch 1500 and PVP K 30 on the dissolution rate of aceclofenac tablets, tablets each containing 100 mg of aceclofenac were prepared employing selected combinations of the two factors, Starch 1500 (factor A) and PVP K 30 (factor B) as per 2^2 factorial design. The tablets were prepared by wet granulation method as per the formulae given in Table 2. The hardness of the tablets prepared was in the range of 5-6 kg/sq.cm. Weight loss in the friability test was less than 0.8% in all the cases. Drug content was within 100 ± 2 % of the labeled claim. The disintegration time of the tablets was in the range 1-6 min. Thus all the tablets prepared were of good quality and fulfilled the official (I.P) specifications of uncoated tablets.

Table – 2: Formulae of Aceclofenac Tablets Prepared as per 2^2 Factorial Design

Ingredient (mg/tablet)	Formulation			
	F_1	Fa	F_b	F_{ab}
Aceclofenac	100	100	100	100
Starch 1500	-	200	-	200
PVP K 30	-	-	8	8
Lactose	268	68	260	60
Croscarmellose sodium	8	8	8	8
Acacia	8	8	8	8
Talc	8	8	8	8
Magnesium sterate	8	8	8	8
Total Weight (mg)	400	400	400	400

The dissolution rate of aceclofenac from all the tablets prepared was also studied in phosphate buffer pH 6.8. Dissolution of aceclofenac from the tablets prepared also followed first order kinetics. The dissolution rate (K_1) and DE_{15} values are given in Table-3. The dissolution rate (K_1) and DE_{15} values were subjected to ANOVA. ANOVA indicated that the individual and combined effects of the two factors in enhancing the dissolution rate and DE_{15} of aceclofenac tablets were also highly significant ($P<0.01\%$). Formulation F_1 contains aceclofenac alone without Starch 1500 and PVP K 30 and hence it is considered as plain (or) control tablets. Tablets formulated employing solid dispersions of aceclofenac in Starch 1500 (Fa) and PVP K 30 (F_b) gave respectively 2.1 and 2.2 fold increase in the dissolution rate (K_1) of aceclofenac when compared to plain tablets (F_1). Aceclofenac tablets prepared employing solid dispersions in

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Starch 1500 – PVP K 30 (F_{ab}) gave highest enhancement (3.0 fold) in the dissolution rate of aceclofenac. Dissolution efficiency (DE_{15}) was also increased by 2.12 - 2.42 fold with tablets formulated employing solid dispersions in Starch 1500 (F_a), PVP K 30 (F_b) and Starch 1500 – PVP K 30 (F_{ab}) when compared to plain tablets (F_1). Aceclofenac tablets formulated employing all its solid dispersions in Starch 1500, PVP K 30 and Starch 1500 – PVP K 30 gave a very fast dissolution of aceclofenac, NLT 80% in 15 min. Thus, aceclofenac tablets with fast dissolution characteristics could be designed employing its solid dispersions in Starch 1500, PVP K 30 and Starch 1500 – PVP K 30. These solid dispersions of aceclofenac could be formulated in to tablets with fast dissolution characteristics.

Table – 3: Dissolution Parameters of Aceclofenac Tablets Formulated as per 2^2 – Factorial Design

Formulation (Code asper 2^2–Factorial Design)	Dissolution Rate ($K_1 \times 0^2$) (min^{-1})	Increase in Dissolution Rate (No. of Folds)	Dissolution Efficiency DE_{15} (%)	Increase in DE_{15} (No. of Folds)
F_1	2.23	-	32.7	-
Fa	4.68	2.1	69.4	2.12
F_b	4.84	2.2	76.3	2.33
F_{ab}	6.76	3.0	79.2	2.42

CONCLUSIONS

1. The individual and the combined effects of Starch 1500 and PVP K 30 in enhancing the dissolution rate and efficiency of aceclofenac solid dispersions and their tablets were highly significant ($P<0.01$).

2. Solid dispersion of aceclofenac in Starch 1500 (a), PVP K 30 (b) and Starch 1500 – PVP K 30 (ab) enhanced the dissolution rate of aceclofenac by 4.89, 4.75 and 4.82 folds respectively when compared to aceclofenac pure drug.

3. Tablets formulated employing solid dispersions of aceclofenac in Starch 1500 (Fa) and PVP K 30 (F_b) gave respectively 2.1 and 2.2 fold increase in the dissolution rate (K_1) of aceclofenac when compared to plain tablets (F_1). Aceclofenac tablets prepared employing solid dispersions in Starch 1500 – PVP K 30 (F_{ab}) gave highest enhancement (3.0 fold) in the dissolution rate of aceclofenac.

4. Dissolution efficiency (DE_{15}) was also increased by 2.12 - 2.42 fold with tablets formulated employing solid dispersions in Starch 1500 (F_a), PVP K 30 (F_b) and Starch 1500 – PVP K 30 (F_{ab}) when compared to plain tablets (F_1).

5. Aceclofenac tablets formulated employing all its solid dispersions in Starch 1500, PVP K 30 and Starch 1500 – PVP K 30 gave a very fast dissolution of aceclofenac, NLT 80% in 15 min.

6. Thus, solid dispersions of aceclofenac in Starch 1500, PVP K 30 and Starch 1500 – PVP K 30 could be formulated in to tablets with fast dissolution characteristics.

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