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A FACTORIAL STUDY ON THE ENHANCEMENT OF DISSOLUTION RATE OF KETOPROFEN BY SOLID DISPERSION IN COMBINED CARRIERS

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ABSTRACT

Ketoprofen, 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 it needs enhancement in the dissolution rate and bioavailability to derive its maximum therapeutic efficacy. The objective of the present study is to prepare and evaluate solid dispersions of ketoprofen in combined carriers, a water dispersible modified starch namely Starch 1500 and a water soluble polymer namely PVP K30 for enhancing the dissolution rate and dissolution efficiency of ketoprofen in a 2^2 factorial study. The individual and combined effects of Starch 1500 and PVP K30 in enhancing the dissolution rate and dissolution efficiency of ketoprofen were evaluated in a 2^2 factorial study. Solid dispersions of ketoprofen in Starch 1500 (a modified starch) and PVP K30 alone and in combination were prepared as per 2^2 factorial design by kneading method and were evaluated for dissolution rate and dissolution efficiency. The dissolution rate (K_1) and dissolution efficiency (DE_{30}) of ketoprofen could be significantly enhanced by solid dispersion in Starch 1500 and PVP K30. A 2.42, 1.32 and 1.60 fold increase in the dissolution rate (K_1) and a 1.67,1.31 and 1.63 fold increase in the dissolution efficiency (DE_{30}) was observed respectively with solid dispersions SD_a , SD_b and SD_{ab} when compared to F1 (ketoprofen pure drug). ANOVA indicated that the individual and combined effects of Starch 1500 (factor A) and PVP K30 (factor B) in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) are highly significant ($P < 0.01$). Solid dispersion of ketoprofen in Starch 1500 (SD_a) alone gave higher enhancement in the dissolution rate and efficiency of ketoprofen. Combination of Starch 1500 with PVP K30 has no additional advantage in enhancing the dissolution rate and dissolution efficiency of ketoprofen. Hence solid dispersion of ketoprofen in Starch 1500 alone is recommended to enhance the dissolution rate and dissolution efficiency of ketoprofen, a BCS class II drug.

Key words: Ketoprofen, Starch 1500, PVP K30, Factorial study, Solid dispersions

INTRODUCTION

About 95% of all new potential therapeutic drugs (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pH and consequent low dissolution rate. These drugs are classified as class II drugs under BCS with low solubility and high permeability characters and pose challenging problems in their pharmaceutical product development process. Ketoprofen, 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 it needs enhancement in the dissolution rate and bioavailability to derive its maximum therapeutic efficacy. 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 approaches, solid dispersion[2, 3] in water soluble

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and water dispersible excipients is a simple, industrially useful approach for enhancing the solubility, dissolution rate and bioavailability of poorly soluble drugs. In solid dispersions the poorly soluble drug is dispersed in an inert water-soluble carrier such as urea, polyethylene glycol, poly vinyl pyrrolidone and surfactants at solid state. In the case of solvent deposited dispersions the drug is deposited in minuscular form on an inert water insoluble excipient such as silica gel, starch and modified starches at solid state.

Starch is a naturally occurring polysaccharide and it is one of the most widely used excipients in the manufacture of solid dosage forms and can be used as filler, a disintegrant or a binder. Starches are modified to alter one or more of its key physical or chemical properties. Starch 1500 is a physically modified starch used as diluents and directly compressible vehicle in tablet formulations.

Polyvinylpyrrolidone (PVP), also commonly called Polyvidone or Povidone, is a water-soluble polymer made from the monomer *N*-vinylpyrrolidone. Use of poly vinyl pyrrolidone (PVP K30) is also reported[4-6] for solubilization and to enhance the dissolution rate of poorly soluble drugs.

Though modified starches and surfactant, PVP K30 have been used individually as carriers in solvent deposition and solid dispersion systems respectively, no reports are available on their combined use in enhancing the dissolution rate of poorly soluble drugs. The objective of the present study is to prepare and evaluate solid dispersions of ketoprofen in combined carriers, a water dispersible modified starch (Starch 1500) and a water soluble surfactant (PVP K30) for enhancing the dissolution rate and dissolution efficiency of ketoprofen in a 2^2 factorial study. The individual and combined effects of the two carriers, Starch 1500 and PVP K30 in enhancing the dissolution rate and dissolution efficiency of ketoprofen were evaluated in a 2^2 factorial study.

EXPERIMENTAL

Materials:

Ketoprofen was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. PVP K30, Starch 1500 and methanol (Qualigens) were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Estimation of Ketoprofen:

An UV Spectrophotometric method based on the measurement of absorbance at 258 nm in phosphate buffer of pH 7.4 was used for the estimation of ketoprofen. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 1-10 µg/ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.95% and 1.02% respectively. No interference by the excipients used in the study was observed.

Preparation of Solid Dispersions in Combined Carriers:

Solid dispersions of ketoprofen in Starch 1500 and PVP K30 as per 2^2 factorial design were prepared by kneading method. The required quantities of drug and PVP K30 were dissolved in the solvent methanol to get a clear solution in a dry mortar. Starch 1500 powder (100 mesh) was added to the drug- surfactant solution in the motor and mixed. The mixture was kneaded for 30 min by continuous trituration. Small volume of the solvent was added to maintain the mixture as thick slurry during kneading process. Trituration was continued until a dry mass was obtained. The mass obtained was further dried at 45°C for 1 hour in a hot air oven. The dried product was powdered and passed through mesh no. 100 in each case.

Estimation of Drug Content of Solid Dispersions:

From each batch four samples of solid dispersion equivalent to 20 mg of the medicament was taken into a 100 ml conical flask and extracted with 3 x 10 ml quantities of methanol. The methanolic extracts were filtered and collected into 50 ml volumetric flask and the volume was made up to 50 ml with methanol. The solution was subsequently diluted with phosphate buffer of pH 7.4 and assayed for the ketoprofen content at 258 nm.

Dissolution Rate Study:

Dissolution rate of Ketoprofen from various solid dispersions prepared was studied in water (900 ml) employing USP 8 station Dissolution Rate Test Apparatus (M/s Lab India Disso 8000) with a paddle stirrer at 50 rpm. A

temperature of 37±1°C was maintained throughout the study. Ketoprofen or its solid dispersion equivalent to 50 mg of ketoprofen was used in the test. Samples of dissolution fluid (5 ml) were withdrawn through a filter (0.45 µm) at different intervals of time, suitably diluted and assayed for ketoprofen at 258 nm. The dissolution fluid withdrawn at each sampling time was replaced with fresh dissolution fluid and suitable correction is made in calculating the amount of drug dissolved. All dissolution rate experiments were conducted in triplicate (n=3).

RESULTS AND DISCUSSION

In the present study solid dispersions of ketoprofen in Starch 1500 (a modified starch) and PVP K30 (surfactant) were prepared as per 2^2 factorial design by kneading method with a view to enhance the dissolution rate and dissolution efficiency of ketoprofen. The individual main effects and combined (interaction) effects of Starch 1500 (factor A) and PVP K30 (factor B) on the dissolution rate and dissolution efficiency (DE_{30}) of ketoprofen were evaluated in a 2^2 factorial study. For this purpose two levels of Starch 1500 (0 and 1:1 ratio of drug: carrier) and two levels of PVP K30 (0 and 2%) were selected and the corresponding four treatments involved in the 2^2 factorial study were ketoprofen pure drug (1); ketoprofen- Starch 1500 (1:1) solid dispersion (SD_a); ketoprofen – PVP K30 (2%) solid dispersion (SD_b) and ketoprofen – Starch 1500 (1:1) – PVP K30 (2%) solid dispersion (SD_{ab}). The above mentioned solid dispersions were prepared by kneading method.

All the solid dispersions prepared were found to be fine and free flowing powders. Low C.V (< 1.0%) in the percent drug content indicated uniformity of drug content in each batch of solid dispersions prepared. The dissolution of ketoprofen as such and from various solid dispersions was studied in water to evaluate the individual and combined effects of the two factors involved. The dissolution profiles of various solid dispersions prepared are shown in Fig.1.The dissolution parameters of ketoprofen and its solid dispersions prepared are given in Table 1.

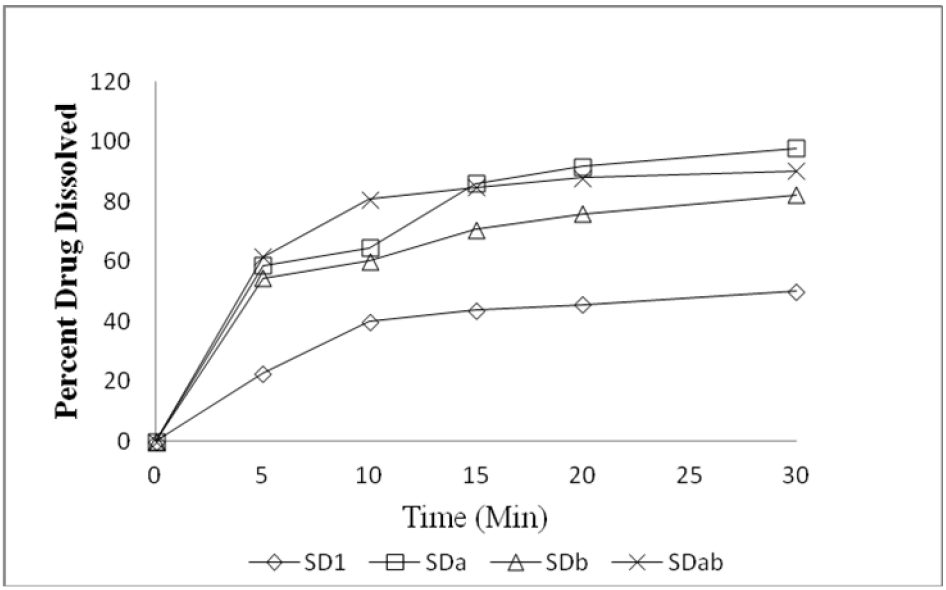

Fig. 1: Dissolution Profiles of Ketoprofen and its Solid Dispersions in Starch 1500 and PVP K30 as per 2^2 – Factorial Study

All solid dispersions prepared gave rapid and higher dissolution of ketoprofen when compared to ketoprofen pure drug. The dissolution data were analyzed as per zero order and first order kinetics in each case. The correlation coefficient (r) values were higher in the first order model than in zero order model indicating that the dissolution of ketoprofen as such and from its solid dispersions followed first order kinetics.

The correlation coefficient (r) values in the first order model were found to be in the

range 0.912 – 0.961. The corresponding dissolution rate (K_1) values of various products were estimated. Dissolution Efficiency (DE_{30}) values were calculated as described by Khan[7].The dissolution parameters are summarized in Table 1.

Table 1: Dissolution Parameters of Ketoprofen Solid Dispersions in Starch 1500 and PVP K30 Prepared as per 2^2 Factorial Studies.

Formulation	PD_{10} (%)	DE_{30} (%)	Increase in DE_{30} (no. of folds)	K_1 (min^{-1})	Increase in $K_1 x 10^3$ (no. of folds)
SD_1	40.00	45.83	-	0.04	-
SD_a	74.72	76.85	1.67	0.097	2.42
SD_b	62.18	60.35	1.31	0.053	1.32
SD_{ab}	71.13	75.16	1.63	0.064	1.60

All the dissolution parameters namely PD_{10}, DE_{30} and K_1 indicated rapid dissolution of ketoprofen from the solid dispersions prepared employing Starch 1500 and PVP K30 as carriers alone and in combination.

A 2.42, 1.32 and 1.60 fold increase in the dissolution rate (K_1) and a 1.67, 1.31 and 1.63 fold increase in the dissolution efficiency (DE_{30}) was observed respectively with solid dispersions SD_a, SD_b and SD_{ab} when compared to F1 (ketoprofen pure drug). Solid dispersion of ketoprofen in Starch 1500 (SD_a) alone gave higher enhancement in the dissolution rate and efficiency of ketoprofen. Combination of Starch 1500 with PVP K30 has no additional advantage in enhancing the dissolution rate and dissolution efficiency of ketoprofen. Hence solid dispersion of ketoprofen in Starch 1500 alone is recommended to enhance its dissolution rate.

Table 2: ANOVA of dissolution Rate (K_1) Values

Source of Variation	D.F	S.S	MSS	F- ratio
Total	11	63.70	5.79	-
Treatment	3	48.96	16.32	8.86
Error	8	14.74	1.84	-
Factor A (Starch 1500)	1	31.10	31.10	16.90
Factor B (PVP K30)	1	3.94	3.94	3.14
Factor AB	1	13.91	13.91	7.55

Table 3: ANOVA of Dissolution Efficiency (DE_{30}) values

Source of variation	D.F	S.S	MSS	F- ratio
Total	11	2274.82	206.8	-
Treatment	3	2128.94	709.64	38.94
Error	8	145.83	18.22	-
Factor A	1	1441.45	1441.45	79.08
Factor B	1	4468.92	4468.92	20.43
Factor AB	1	3782.25	3782.25	17.29

$F_{0.05}(3, 8) = 4.07$; $F_{0.05}(1, 8) = 5.32$; $F_{0.01}(3, 8) = 7.59$; $F_{0.01}(1, 8) = 11.3$

The dissolution parameters, K_1 and DE_{30} were subjected to Analysis of Variance (ANOVA) to find out the significance of the individual and combined (interaction) effects of Starch 1500 (factor A) and PVP K30 (factor B) in enhancing the dissolution rate and dissolution efficiency of ketoprofen.

The results of ANOVA are given in Tables 2-3. ANOVA indicated that the individual and combined effects of Starch 1500 (factor A) and PVP K30 (factor B) in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) are highly significant ($P < 0.01$).

CONCLUSION

The dissolution rate (K_1) and dissolution efficiency (DE_{30}) of ketoprofen could be significantly enhanced by solid dispersion in Starch 1500 (a water dispersible modified starch) and PVP K30. A 2.42, 1.32 and 1.60 fold increase in the dissolution rate ($K1_)$ and a 1.67, 1.31 and 1.63 fold increase in the dissolution efficiency (DE_{30}) was observed respectively with solid dispersions SD_a, SD_b and SD_{ab} when compared to F1 (ketoprofen pure drug). ANOVA indicated that the individual and combined effects of Starch 1500 (factor A) and PVP K30 (factor B) in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) are highly significant ($P < 0.01$). Solid dispersion of ketoprofen in Starch 1500 (SD_a) alone gave higher enhancement in the dissolution rate and efficiency of ketoprofen. Combination of Starch 1500 with PVP K30 has no additional advantage in enhancing the dissolution rate and dissolution efficiency of ketoprofen. Hence solid dispersion of ketoprofen in Starch 1500 alone is recommended to enhance the dissolution rate and dissolution efficiency of ketoprofen, a BCS class II drug.

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