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A FACTORIAL STUDY ON FORMULATION AND EVALUATION OF SOLID DISPERSIONS OF NIMESULIDE EMPLOYING STARCH PHOSPHATE, PVP K-30 AND PEG 4000

K.P.R. Chowdary*, Veeraiah Enturi, Debasish Swain and K. Ramachandra Reddy

University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, A.P, India

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 phosphate- a new modified starch, PVP and PEG 4000 were evaluated as a carriers in solid dispersions for enhancing the dissolution rate and efficiency of nimesulide, a BCS class II drug. Their individual and combined (interaction) effects in enhancing the dissolution rate and dissolution efficiency of nimesulide were evaluated in a 2³- factorial study. Among the individual effects PEG 4000 gave highest enhancement in the dissolution rate of nimesulide (14.23 fold), followed by starch phosphate (11.34 fold). Addition of PVP and PEG 4000 to the solid dispersions in starch phosphate has further enhanced the dissolution rate upto 75.70 fold and dissolution efficiency upto 26.67 fold.

Key words: Solid dispersions, Nimesulide, Starch Phosphate, PVP, PEG 4000, Factorial Study.

*Corresponding Author Email: prof.kprchowdary@rediffmail.com

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INTRODUCTION

Nimesulide, 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 techniques¹ 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 are simple, industrially useful approach for enhancing the solubility, dissolution rate and bioavailability of poorly soluble drugs.

Starch phosphate is one of the modified starches used in the frozen food industry^{2, 3}. It is produced by phosphorylation of free hydroxyl groups of anhydro-glucose units of starch molecule. We have earlier reported the preparation characterization and evaluation of starch phosphate as an efficient disintegrant in tablet formulations⁴.

The objective of the present study is to evaluate starch phosphate (a new modified starch), PVP K-30 and PEG 4000 as a carriers in solid dispersions for enhancing the dissolution rate of nimesulide. Their individual and combined (interaction) effects in enhancing the dissolution rate and dissolution efficiency of nimesulide were evaluated in a 2³- factorial study.

MATERIAL AND METHOD

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

Preparation of Starch Phosphate

Starch phosphate was prepared based on the method of Choi *et al*⁵ with some modifications. Potato starch (100 g) and disodium hydrogen orthophosphate anhydrous (30 g) were suspended in 100 ml of water and continuously stirred for 20 min. This starch slurry was then filtered and the wet starch mixture was conditioned for 12 h at room temperature (28⁰C). To enhance phosphorylation, this mixture was heated in a forced air oven at 130 °C for 3 h. The product obtained was ground and sized.

Estimation of Nimesulide

An UV spectrophotometric method based on the measurement of absorbance at 230 nm in phosphate buffer pH 7.4 was used for estimation of nimesulide. 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 0.80% and 1.6% respectively. No interference from excipients used was observed.

Formulation of Nimesulide Solid Dispersions as per 2³ Factorial Studies

In the 2³ factorial study, the three factors namely starch phosphate (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 nimesulide solid dispersions. Starch phosphate (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 nimesulide solid dispersions were prepared employing selected combinations of the three factors.

Preparation of Solid Dispersions of Nimesulide in Starch Phosphate

Solid dispersions of nimesulide in starch phosphate were prepared employing selected combinations of the three factors by solvent evaporation method. Nimesulide was dissolved in dichloromethane (10 ml) in a dry mortar to get a clear solution. Starch phosphate/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°C until dry. The dried mass was pulverized and sieved through mesh no. 100.

Dissolution Rate Study

Dissolution rate of nimesulide as such and from its solid dispersions prepared was studied in phosphate buffer pH 7.4 (900 ml) employing USP 8 station Dissolution Rate Test Apparatus (M/s Labindia Disso 8000) with a paddle stirrer at 50 rpm. Nimesulide or its solid dispersions equivalent of 50 mg of nimesulide was used in each test. A temperature 37±1°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 nimesulide at 230nm. All the dissolution experiments were replicated four times each (n=4).

RESULTS AND DISCUSSION

To evaluate the individual main and combined effects of starch phosphate (factor A), PVP K-30 (factor B) and PEG 4000 (factor C) on the dissolution rate of nimesulide, solid dispersions of

nimesulide 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 nimesulide from all the solid dispersions prepared was studied in phosphate buffer pH 7.4 (n=4). The dissolution profiles of various solid dispersions prepared are shown in Figure.1.

Table 1: Correlation Coefficient (r) Values in the Analysis of Dissolution Data of Various Formulations as per Zero Order and First Order Model

Solid Dispersion Formulation	Composition	Correlation coefficient (r) value	
		Zero order model	First order model
F ₁	Nimesulide	0.890	0.978
F _a	Nimesulide: Starch Phosphate (1:2)	0.920	0.947
F _b	Nimesulide-PVP (2%)	0.870	0.981
F _{ab}	Nimesulide: Starch Phosphate (1:2) -PVP (2%)	0.890	0.991
F _c	Nimesulide-PEG 4000 (2%)	0.873	0.945
F _{ac}	Nimesulide: Starch Phosphate (1:2) -PEG 4000 (2%)	0.914	0.992
F _{bc}	Nimesulide- PVP (2%) - PEG 4000 (2%)	0.912	0.987
F _{abc}	Nimesulide: Starch Phosphate (1:2) -PVP (2%)-PEG 4000(2%)	0.910	0.994

Dissolution data were analyzed as per zero order and first order kinetic models. The correlation coefficient 'r' values in zero order and first order are given in Table 1. 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 (DE₃₀) values were calculated as per Khan⁶.

$$DE_T = \frac{\int_0^T y_t \cdot dt}{y_{100} \cdot T}$$

Where y_t is percent of drug dissolved at any time t , y_{100} denotes 100% dissolution, and the integral represents the area under dissolution curve between time zero and T . The time T in this study was 30 minutes. The first order dissolution rate constants (K_1) and dissolution efficiency (DE₃₀) values are given in Table 2.

Table 2: Dissolution Parameters of Nimesulide Solid Dispersions Prepared as per 2³ Factorial Studies

Solid Dispersion Formulation	Composition	Dissolution Rate $K_1(\text{min}^{-1}) \times 10^2$		Dissolution Efficiency $DE_{30}(\%)$	
		($\bar{x} \pm \text{SD}$)	Increase in K_1 (no.of folds)	($\bar{x} \pm \text{SD}$)	Increase in DE_{30} (no.of folds)
F ₁	Nimesulide	0.11±0.12	-	2.58±0.05	-
F _a	Nimesulide: Starch Phosphate (1:2)	1.23±0.72	11.34	13.20±0.53	5.19
F _b	Nimesulide-PVP (2%)	0.55±0.07	5.145	19.65±0.28	7.62
F _{ab}	Nimesulide: Starch Phosphate (1:2) –PVP (2%)	1.95±1.01	17.88	51.28±0.27	19.9
F _c	Nimesulide-PEG 4000 (2%)	1.55±0.52	14.23	23.91±0.92	9.27
F _{ac}	Nimesulide: Starch Phosphate (1:2) -PEG 4000 (2%)	2.16±0.85	19.82	51.21±0.67	19.8
F _{bc}	Nimesulide- PVP (2%) – PEG 4000 (2%)	1.34±1.13	12.30	26.83±0.52	10.4
F _{abc}	Nimesulide: Starch Phosphate (1:2) -PVP (2%)-PEG 4000(2%)	8.24±0.46	75.70	68.79±0.91	26.7

Much variations was observed in the dissolution rate (K_1) and DE_{30} values of the solid dispersions prepared as per 2³ 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 F₁ contains nimesulide alone without the three factors (starch phosphate, 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 PEG 4000 gave highest enhancement in the dissolution rate of nimesulide (14.23 fold), followed by starch phosphate (11.34 fold). DE_{30} was also increased from 2.58% for nimesulide pure drug (F₁) to 23.91, 19.65 and 13.20 % respectively with solid dispersions F_c F_b and F_a. Addition of PVP and PEG 4000 to the solid dispersions in starch

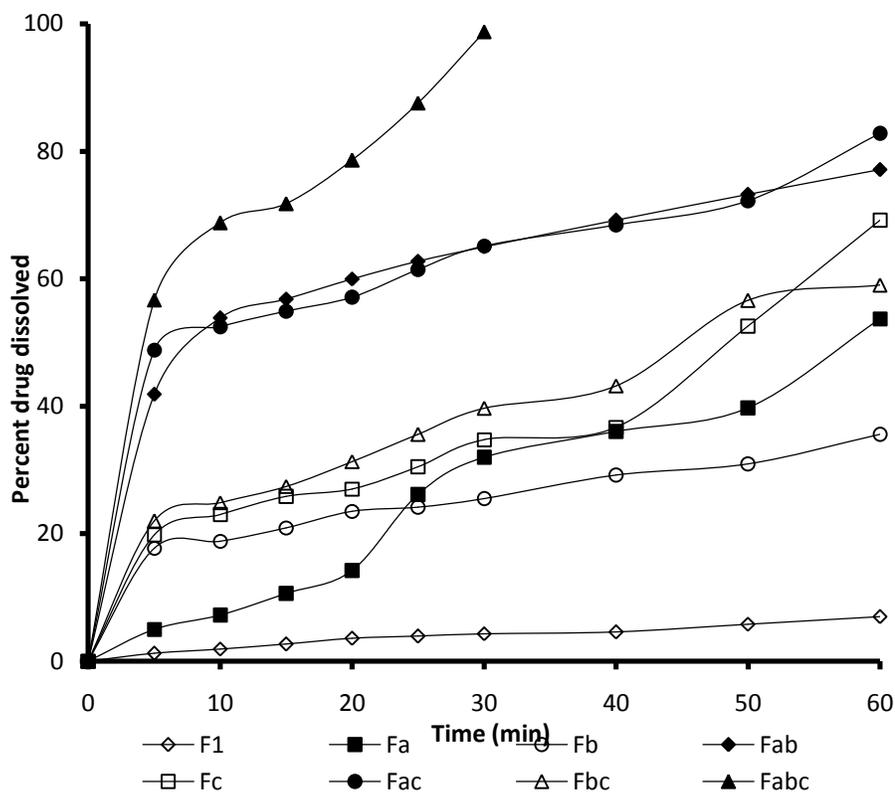


Figure 1: Dissolution Profiles of Nimesulide Solid Dispersions Prepared as per 2^3 Factorial Studies

phosphate has further increased the dissolution rate and efficiency of nimesulide. Solid dispersion formulations F_{ab} , F_{ac} , and F_{abc} respectively gave 17.88, 19.82 and 75.70 fold increases in the dissolution rate of nimesulide when compared to nimesulide pure drug (control). Dissolution efficiency (DE_{30}) was also increased by 19.8, 19.9 and 26.7 fold respectively with these solid dispersions when compared to nimesulide pure drug (control).

CONCLUSION

When the individual main and combined effects of the three factors namely starch phosphate (factor A), PVP K- 30 (factor B) and PEG 4000 (factor C) in enhancing the dissolution rate and dissolution efficiency of nimesulide were evaluated in a 2^3 - factorial study, PEG 4000 gave highest enhancement in the dissolution rate of nimesulide (14.23 fold), followed by starch phosphate (11.34 fold). DE_{30} was also increased from 2.58% for nimesulide pure drug (F_1) to 23.91, 19.65 and 13.20 % respectively with solid dispersions F_c , F_b and F_a . Addition of PVP and PEG 4000 to the solid dispersions in starch phosphate has further enhanced the dissolution rate upto 75.70 fold and dissolution efficiency upto 26.67 fold.

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