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Enhancement of Dissolution Rate of Valdecoxib by Solid Dispersion in Starch Phosphate and Gelucire - A Factorial Study

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ABSTRACT

Valdecoxib, 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 valdecoxib in combined carriers, a water dispersible new modified starch namely starch phosphate and a water soluble surfactant namely Gelucire 50/13 for enhancing the dissolution rate and dissolution efficiency of valdecoxib in a 2^2 factorial study. The individual and combined effects of the starch phosphate (Factor A) and Gelucire 50/13 (Factor B) in enhancing the dissolution rate and dissolution efficiency of valdecoxib were evaluated in a 2^2 factorial study. Solid dispersions of valdecoxib in starch phosphate (a new modified starch) and Gelucire 50/13 (surfactant) 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 valdecoxib could be significantly enhanced by solid dispersion in starch phosphate (a water dispersible modified starch) and Gelucire 50/13 (a surfactant). ANOVA indicated that the individual effects of starch phosphate (factor A) and Gelucire 50/13 (factor B) in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) were highly significant ($P < 0.01$) and the combined (interaction) effects of the two factors were also significant ($P<0.05$). A 19.70, 22.31 and 45.63 fold increase in the dissolution rate (K_1) and a 20.46, 21.03 and 32.90 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 (valdecoxib pure drug). The combination of starch phosphate (a water dispersible modified starch) and Gelucire 50/13 (a surfactant) gave a markedly higher enhancement in the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of valdecoxib than is possible with them individually. Hence solid dispersion of valdecoxib in combined carriers consisting of starch phosphate and Gelucire 50/13 is recommended to enhance the dissolution rate and dissolution efficiency of valdecoxib, a BCS class II drug.

Keywords: Valdecoxib, Starch phosphate, Gelucire 50/13, Factorial study, Solid dispersions

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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. Valdecoxib, 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 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. Surfactants are used as carriers in solid dispersions of poorly soluble drugs to enhance their solubility and dissolution rates. Gelucire 50/13 is a non-ionic surfactant consisting of a mixture of glycerol and PEG 1500 esters of long-chain fatty acids. The suffixes 50 and 13 refer to its melting point and its hydrophilic/lipophilic balance (HLB), respectively. Gelucire 50/13 has been used successfully to improve the dissolution properties of poorly water-soluble drugs by preparing solid-dispersion systems [2-4].

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 a filler, disintegrent and binder. Starches are modified to alter one or more of its key physical or chemical properties. Starch phosphate is a chemically modified starch used in frozen food industry [5, 6]. Starch phosphate is a white, crystalline and non-hygroscopic powder. It has good swelling property (400%) in water. Starch phosphate is reported as an efficient disintegrent [7, 8, 11], a directly compressible vehicle and as a carrier in solvent deposited systems [9, 10, 12].

Though starch phosphate and surfactant, Gelucire 50/13 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 valdecoxib in combined carriers, a water dispersible new modified starch namely starch phosphate and a water soluble surfactant namely Gelucire 50/13 for enhancing the dissolution rate and dissolution efficiency

of valdecoxib in a 2^2 factorial study. The individual and combined effects of the starch phosphate and Gelucire 50/13 in enhancing the dissolution rate and dissolution efficiency of valdecoxib were evaluated in a 2^2 factorial study.

EXPERIMENTAL

Materials:

Valdecoxib was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. Gelucire 50/13, dichloromethane (Qualigens) and methanol (Qualigens) were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Preparation of Starch Phosphate:

Starch phosphate was prepared based on the method of Choi et al [13] with some modifications. Potato starch (100 g) anddi-sodium 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 (28^0C). 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 Valdecoxib:

An UV Spectrophotometric method based on the measurement of absorbance at 245 nm in 0.1N hydrochloric acid was used for the estimation of valdecoxib. 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 as per 2^2 factorial design:

Solid dispersions of valdecoxib in starch phosphate and Gelucire 50/13 as per 2^2 factorial design were prepared by kneading method. The required quantities of drug and Gelucire 50/13 were dissolved in the solvent consisting of methanol- dichloromethane (1:1) to get a clear solution in a dry mortar. Starch phosphate 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.

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Estimation of Drug Content of Solid Dispersions:

From each batch four samples of solid dispersion equivalent to 20mg of the medicament were taken into a series of 100 ml conical flasks 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 0.1N hydrochloric acid and assayed for the valdecoxib content at 245 nm.

Dissolution Rate Study:

Dissolution rate of valdecoxib 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. Valdecoxib or its solid dispersion equivalent to 50 mg of valdecoxib 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 valdecoxib at 245 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).

Analysis of Data:

Results of dissolution rate study were analyzed as per Analysis of Variance (ANOVA) of 2^2 factorial design.

RESULTS AND DISCUSSION

Solid dispersions of valdecoxib in starch phosphate (a new modified starch) and Gelucire 50/13(surfactant) were prepared as per 2^2 factorial design by kneading method with a view to enhance the dissolution rate and dissolution efficiency of valdecoxib. The individual main and combined (interaction) effects of starch phosphate (factor A) and Gelucire 50/13 (factor B) on the dissolution rate and dissolution efficiency (DE_{30}) of valdecoxib were evaluated in a 2^2 factorial study. For this purpose two levels of starch phosphate (0 and 1:2 ratio of drug : carrier) and two levels of Gelucire 50/13 (0 and 10%) were selected and the corresponding four treatments involved in the 2^2 factorial study were valdecoxib pure drug (F1); valdecoxib- starch phosphate (1:2) solid dispersion (SD_a); valdecoxib – Gelucire 50/13 (10%) solid dispersion (SD_b) and valdecoxib – starch phosphate (1:2) – Gelucire 50/13 (10%) 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 valdecoxib as such and from various solid dispersions was studied in water to evaluate the individual and combined effects of the two

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factors involved. The dissolution profiles of various solid dispersions prepared are shown in Fig.1.The dissolution parameters of valdecoxib and its solid dispersions prepared are given in Table 1.

All solid dispersions prepared gave rapid and higher dissolution of valdecoxib when compared to valdecoxib 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 valdecoxib 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 0.8096-0.9143. The corresponding dissolution rate (K_1) values of various products were estimated. Dissolution Efficiency (DE_{30}) values were calculated as described by Khan[14]. The dissolution parameters are summarized in Table 1.

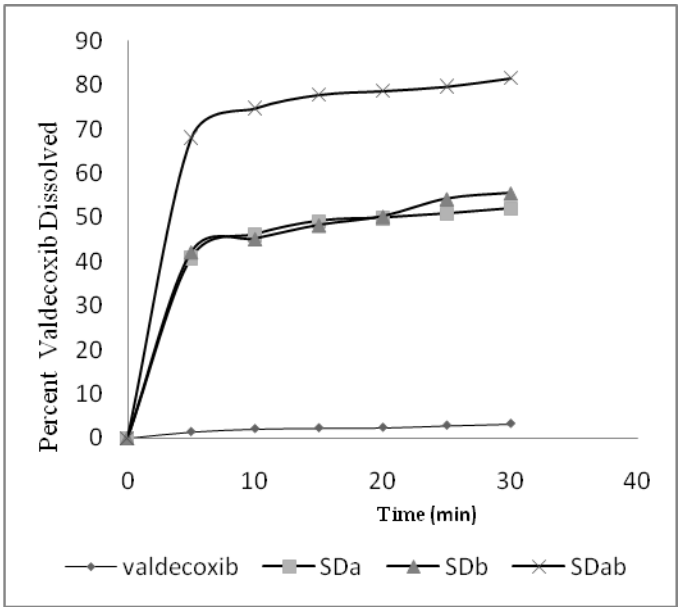

Fig. 1: Dissolution Profiles of Valdecoxib and its Solid Dispersions in Starch Phosphate and Gelucire 50/13 as per 2^2 – Factorial Study

Table 1: Dissolution Parameters of Solid Dispersions of Valdecoxib in Starch Phosphate and Gelucire 50/13 Prepared as per 2^2 Factorial Design.

Formulation	PD_{10} (%)		DE_{30} (%)		$K_1 \times 10^3$ (min^{-1})	
	$\bar{X}$ ± s.d	Increase in PD_{10} (no. of folds)	$\bar{X}$ ± s.d	Increase in DE_{30} (no. of folds)	$\bar{X}$ ± s.d	Increase in K_1 (no. of folds)
F1	2.1±0.03	-	2.1±0.02	-	0.96±9.23	-
SD_a	46.2±3.05	22.00	43.5±1.41	20.46	18.9±0.55	19.70
SD_b	45.2±0.23	21.52	44.7±0.33	21.03	21.4±1.00	22.31
SD_{ab}	74.6±1.76	35.52	69.9±0.18	32.90	43.8±0.90	45.63

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All the dissolution parameters namely PD_{10}, DE_{30} and K_1 indicated rapid dissolution of valdecoxib from the solid dispersions prepared employing starch phosphate and Gelucire 50/13 as carriers alone and in combination. 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 phosphate (factor A) and Gelucire 50/13 (factor B) in enhancing the dissolution rate and dissolution efficiency of valdecoxib. The results of ANOVA are given in Tables 2-3.

Table 2: ANOVA of Dissolution Rate (K_1) Values:

Source of Variation	D.F	S.S	MSS	F- ratio
Total	11	2776.50	252.40	-
Treatment	3	2772.20	924.06	1720.78
Error	8	4.30	0.537	-
Factor A (starch phosphate)	1	1220.48	1220.48	2272.77
Factor B (Gelucire 50/13)	1	1537.48	1537.48	2863.09
Factor AB	1	14.473	14.473	26.95

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

ANOVA indicated that the individual effects of starch phosphate (factor A) and Gelucire 50/13 (factor B) in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) were highly significant ($P < 0.01$) and the combined (interaction) effects of the two factors were also significant ($P<0.05$).

A 19.70, 22.31 and 45.63 fold increase in the dissolution rate (K_1) and a 20.46, 21.03 and 32.90 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 (valdecoxib pure drug). The enhancement in the dissolution rate observed with solid dispersion in starch phosphate is due to the deposition of drug in minuscular form on the surface of the water dispersible carrier starch phosphate. In the case of solid dispersion in Gelucire 50/13 the enhancement in dissolution rate is due to improved wettability and solubilizing effect of surfactant Gelucire 50/13. In the case of combined carriers both the above mechanisms are operating giving a marked enhancement in the dissolution rate. Thus the combination of starch phosphate (a water dispersible modified starch) and Gelucire 50/13 (a surfactant) gave a markedly higher enhancement in the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of valdecoxib than is possible with them alone.

Table 3: ANOVA of dissolution efficiency (DE_{30})values

Source of variation	D.F	S.S	MSS	F- ratio
Total	11	9086.90	826.08	-
Treatment	3	7086.31	2362.10	9.445
Error	8	2000.59	250.07	
Factor A	1	3321.00	3321.00	13.20
Factor B	1	3570.06	3570.06	14.20
Factor AB	1	2339.65	2339.65	9.35

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

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CONCLUSION

The dissolution rate (K_1) and dissolution efficiency (DE_{30}) of valdecoxib could be significantly enhanced by solid dispersion in starch phosphate (a water dispersible modified starch) and Gelucire 50/13 (a surfactant). ANOVA indicated that the individual effects of starch phosphate (factor A) and Gelucire 50/13 (factor B) in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) were highly significant ($P < 0.01$) and the combined (interaction) effects of the two factors were also significant ($P<0.05$). A 19.70, 22.31 and 45.63 fold increase in the dissolution rate (K_1) and a 20.46, 21.03 and 32.90 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 (valdecoxib pure drug). The combination of starch phosphate (a water dispersible modified starch) and Gelucire 50/13 (a surfactant) gave a markedly higher enhancement in the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of valdecoxib than is possible with them alone. Hence solid dispersion of valdecoxib in combined carriers consisting of starch phosphate and Gelucire 50/13 is recommended to enhance the dissolution rate and dissolution efficiency of valdecoxib, a BCS class II drug.

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