IJPSR (2012), Vol. 3, Issue 1 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 09 September, 2011; received in revised form 18 October, 2011; accepted 23 December, 2011

A FACTORIAL STUDY ON FORMULATION DEVELOPMENT OF IBUPROFEN TABLETS EMPLOYING STARCH 1500 AND PVP K 30

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Keywords:
Factorial Study,
Solid Dispersions,
Ibuprofen Tablets,
Dissolution Rate,
Starch 1500,
PVP K 30

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ABSTRACT

Ibuprofen, 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 ibuprofen in Starch 1500, a modified starch and polyvinyl pyrrolidone (PVP K 30) was investigated to enhance the dissolution rate and to develop ibuprofen tablets with fast dissolution characteristics. The individual and combined (interaction) effects of Starch 1500 and PVP K 30 on the dissolution rate of ibuprofen solid dispersions and tablets were evaluated in a series of 2^2 – factorial experiments. Solid dispersions and tablets of ibuprofen 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 ibuprofen in Starch 1500 enhanced the dissolution rate of ibuprofen by 1.40 fold. Addition of PVP K30 to the solid dispersion in Starch 1500 has further enhanced the dissolution rate by 2.31 fold. Drug – PVP K30 solid dispersion gave highest enhancement in the dissolution rate (3.43 fold) of ibuprofen. Tablets formulated employing solid dispersions of ibuprofen in Starch 1500 gave highest enhancement in the dissolution rate, 3.69 fold increase when compared to the plain tablets prepared with ibuprofen as such. Tablets prepared employing drug – PVP K 30 and drug – Starch 1500 - PVP K 30 solid dispersions gave relatively low dissolution. Though PVP K 30 gave highest dissolution rate in solid dispersions, it hindered and lowered the dissolution rate of tablets because of its binding property. Ibuprofen tablets formulated employing solid dispersions in Starch 1500 gave very fast dissolution, 85% in 10 min. Hence ibuprofen tablets with fast dissolution characteristics could be developed employing its solid dispersions in Starch 1500.

INTRODUCTION: Ibuprofen, 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 ibuprofen 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 ibuprofen in Starch 1500, a modified starch and polyvinyl pyrrolidone (PVP K 30) was tried to enhance the dissolution rate and to develop ibuprofen 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 ibuprofen solid dispersions and tablets were evaluated in a series of 2^2 factorial experiments. Ibuprofen solid dispersions and tablets were prepared employing the selected combinations of the two factors as per 2^2 factorial designs and were evaluated.

EXPERIMENTAL:

Materials: Ibuprofen, Starch 1500 and croscarmellose sodium were gift samples from M/s Eisai Pharmatechnology and Manufacturing Pvt. Ltd.; Visakhapatnam. Polyvinyl pyrrolidone (PVP K 30), lactose, ethyl cellulose (50 cps), talc and magnesium stearate was procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Estimation of Ibuprofen: An UV spectrophotometric method based on the measurement of absorbance at 221 nm in phosphate buffer pH 7.2 was used for estimation of ibuprofen. 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 0.8% and 1.6% respectively. No interference from the excipients used was observed.

Preparation of Solid Dispersions of Ibuprofen 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 ibuprofen 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) were 0 and 1:2 ratio of drug: carrier. PVP K 30(factor B) was studied at two levels 0 and 2 % concentration. The selected combinations as per 2^2 – factorial design are ibuprofen (1), ibuprofen – Starch 1500 (1:2) solid dispersion (a), ibuprofen-PVP K 30 (2%) solid dispersion (b) and ibuprofen-Starch 1500 (1:2) – PVP K 30 (2%) solid dispersion (ab).

The above mentioned solid dispersions were prepared by kneading method. Ibuprofen 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^{o}C until dry. The dried mass was powdered and sieved through mesh no: 100.

Preparation of Ibuprofen Tablets: Tablets each containing 100 mg of ibuprofen 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%), ethyl cellulose (0.2%), lactose (qs), talc (2%) and magnesium stearate (2%) were included in all the tablet formulations.

The required quantities of ibuprofen (or) ibuprofen – Starch 1500 (1:2) solid dispersion, diluent (lactose) and ethyl cellulose were mixed thoroughly in a dry mortar by following geometric dilution technique. The granulating fluid alcohol was added and mixed thoroughly to form dough mass. The mass was passed through mesh no.12 to obtain wet granules. Wet granules were dried at 50^{o}C for 2 h.

The dried granules were passed through mesh no.16 to break the aggregates. Croscarmellose sodium and the lubricants (talc and magnesium stearate) 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.

Dissolution Rate study: Dissolution rate of ibuprofen from the solid dispersions and tablets prepared were studied in phosphate buffer pH 7.2 (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 ibuprofen was used in each test. A temperature of 37±1^{o}C was maintained throughout. Samples of dissolution medium (5 ml) were withdrawn through a filter (0.45µ) at different time intervals and analyzed for ibuprofen at 221 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 ibuprofen, solid dispersions of ibuprofen 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 ibuprofen as such and from all the solid dispersions prepared was studied in phosphate buffer of pH 7.2. Dissolution efficiency (DE_{15}) values were calculated as per Khan [2].

The dissolution rates (K) and dissolution efficiency (DE_{15}) values are given in **Table 1**. Many variations were observed in the dissolution rate (K) and DE_{15} values of the solid dispersions prepared due to the effects of the factor involved. Dissolution rate (K) 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 ibuprofen solid dispersions were highly significant (P<0.01). Solid dispersion of ibuprofen in Starch 1500 enhanced the dissolution rate of ibuprofen by 1.40 fold. Addition of PVP K 30 to the solid dispersions in Starch 1500 has further enhanced the dissolution rate by 2.31 fold. Drug – PVP K 30 solid dispersions gave highest enhancement in the dissolution rate of ibuprofen (3.43 fold).

TABLE 1: DISSOLUTION PARAMETERS OF IBUPROFEN SOLID DISPERSIONS FORMULATED AS PER 2^2 – FACTORIAL DESIGN

Solid Dispersion Formulation (Code as per 2^2 – Factorial Design)	Dissolution Rate (mg/min)	Increase in Dissolution Rate (No. of Folds)	Dissolution Efficiency DE_{15} (%)	Increase in DE_{15} (No. of Folds)
1	2.30	-	22.3	-
a	3.23	1.40	25.8	1.15
b	7.90	3.43	64.3	2.88
ab	5.33	2.31	42.6	1.91

To evaluate the individual and combined effects of Starch 1500 and PVP K 30 on the dissolution rate of ibuprofen tablets, tablets each containing 100 mg of ibuprofen 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.

The dissolution rate of ibuprofen from all the tablets prepared was also studied in phosphate buffer pH 7.2. The dissolution rate (K) 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 ibuprofen tablets were also highly significant (P<0.01%). Formulation F_1 contains ibuprofen alone without Starch 1500 and PVP K 30 and hence it is considered as plain (or) control tablets.

TABLE 2: FORMULAE OF IBUPROFEN TABLETS PREPARED AS PER 2^2 FACTORIAL DESIGN

Ingredient (mg/tablet)	Formulation			
	F_1	Fa	F_b	F_{ab}
Ibuprofen	100	100	100	100
Starch 1500	-	200	-	200
PVP K 30	-	-	8	8
Lactose	275.2	75.2	267.2	67.2
Croscarmellose sodium	8	8	8	8
Ethyl cellulose	0.8	0.8	0.8	0.8
Talc	8	8	8	8
Magnesium stearate	8	8	8	8
Total Weight (mg)	400	400	400	400

Tablets formulated employing solid dispersions of ibuprofen in Starch 1500 (Fa) gave highest enhancement in the dissolution rate (K) and dissolution efficiency (DE_{15}) of ibuprofen. These tablets gave a 3.71 fold increase in the dissolution rate of ibuprofen when compared to plain tablets (F_1). Ibuprofen tablets prepared employing its solid dispersions in PVP K30 (F_b) and Starch 1500 – PVP K 30 solid dispersions (F_{ab}) gave dissolution lower than that of plain tablets (F_1). Though PVP K 30 gave highest enhancement in the dissolution rate of solid dispersions, it hindered and lowered the dissolution rate of ibuprofen tablets because of its binding or adhesive property (**table 3**).

Ibuprofen tablets formulated employing its solid dispersions in Starch 1500 gave a very fast dissolution, 85% in 10 min. Thus, ibuprofen tablets with fast dissolution characteristics could be designed employing its solid dispersions in Starch 1500, a modified starch.

TABLE 3: DISSOLUTION PARAMETERS OF IBUPROFEN TABLETS FORMULATED AS PER 2^2 – FACTORIAL DESIGN

Formulation (Code as per 2^2 – Factorial Design)	Dissolution Rate (mg/min)	Increase in Dissolution Rate (No. of Folds)	Dissolution Efficiency DE_{15} (%)	Increase in DE_{15} (No. of Folds)
1	2.31	-	40.9	-
a	8.54	3.71	61.4	1.50
b	1.11	0.48	9.4	0.22
ab	5.15	2.23	38.2	0.93

Hence, solid dispersions of ibuprofen in Starch 1500 could be formulated in to tablets with fast dissolution characteristics. Solid dispersions in PVP K 30 alone and Starch 1500 – PVP K 30 combination were found not suitable for formulation into tablets with fast dissolution characteristics.

CONCLUSIONS:

1. Solid dispersion of ibuprofen in Starch 1500 enhanced the dissolution rate of ibuprofen by 1.40 fold. Addition of PVP K30 to the solid dispersion in Starch 1500 has further enhanced the dissolution rate by 2.31 fold. Drug – PVP K30 solid dispersion gave highest enhancement in the dissolution rate (3.43 fold) of ibuprofen.

2. Tablets formulated employing solid dispersions of ibuprofen in Starch 1500 gave highest enhancement in the dissolution rate, 3.69 fold increase when compared to the plain tablets prepared with ibuprofen as such. Tablets prepared employing drug – PVP K 30 and drug – Starch 1500 - PVP K 30 solid dispersions gave relatively low dissolution.

3. Though PVP K 30 gave highest dissolution rate in solid dispersions, it hindered and lowered the dissolution rate of tablets because of its binding property.

4. Ibuprofen tablets formulated employing solid dispersions in Starch 1500 gave very fast dissolution, 85% in 10 min.

5. Hence, solid dispersions of ibuprofen in Starch 1500 could be formulated in to tablets with fast dissolution characteristics. Solid dispersions in PVP K 30 alone and Starch 1500 – PVP K 30 combination were found not suitable for formulation into tablets with fast dissolution characteristics.

REFERENCES:

1. Chowdary, K. P. R. and Madhavi, B. L. R. Novel Drug Delivery Technologies for Insoluble Drugs, 42(9), 2005, 557-564.
2. Khan K. A.The Concept of Dissolution Efficiency. J Pharm Pharmacol, 27, 1975, 48-49.

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