SHORT COMMUNICATIONS

A 2³ Factorial Studies on Factors Influencing Meloxicam β-Cyclodextrin Complexation for Better Solubility

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Using a 2³ factorial design of experiment, the effect of three factors such as concentration of added PVP (0.1 and 0.25% w/v), drug: β-CD molar ratio (1:1 and 1:2) and autoclaving (121° for 30 min) on aqueous solubility of meloxicam β-CD complex prepared by solvent evaporation method was investigated. The ANOVA results on solubility values showed that increase in PVP concentration from 0.1% to 0.25% (w/v) significantly enhanced the solubility of the drug in alkali (pH 7.4) whereas increase in the drug β:CD molar ratio from 1:1 to 1:2 improved significantly the solubility of the drug in acid (pH 1.2). Effect of autoclaving failed to reach significant levels in both the systems. PVP concentration of 0.25% w/v with drug: β-CD molar ratio of 1:2 showed significant interaction which can be considered as optimum for achieving enhanced drug solubility in both acid and alkali. In vitro dissolution tests in acid (pH 1.2) revealed that only 38% of the drug was released from tablets of meloxicam, whereas 77% to 93% of the drug was released from tablets of meloxicam β-CD complexes over a period of one hour following first order rate kinetics.

Meloxicam is a relatively new non-steroidal anti-inflammatory drug with a recommended dose of 7.5 mg once daily for post operative pain, osteoarthritis and primary dysmenorrhea. Its structure and physical properties were studied by Luger et al[1]. The solubility of meloxicam is very low in acidic environment which may delay its absorption from the GI tract and there by its onset of action.

Cyclodextrins are a group of structurally related saccharides that are formed by enzymatic cyclization of starch by a group of amylases termed glycosyl transferases. β-cyclodextrin is extensively used to trap certain drug molecules inside its cavity and thereby modify their physico-chemical and biological activity. β-CD has been reported to form inclusion complexes with naproxen[2], flurbiprofen[3], metronidazole[4], indomethacin[5], hydrocortisone[6] and nimesulide[7]. For the preparation of drug-β-CD complexes, methods such as kneading,

neutralisation, freeze drying, spray drying and solvent evaporation are reported[8]. Several factors such as method of preparation[9], drug: β-CD molar ratio[10,11], temperature and pH of the complexing solution[12,13] and addition of polymers such as PVP[14] HPMC[15] are found to influence the drug β-CD complexation and their aqueous solubility.

From the literature citations it is not clear whether the reported effects of the factors are independent or some combination of these factors are better for achieving the desired solubility enhancement. An extremely useful design for quantifying the treatment effects statistically under such conditions is the factorial design[16]. In the present work, an attempt has been made to investigate the effect of three factors such as PVP concentration (0.1% to 0.25% w/v), drug:β-CD molar ratio (1:1 and 1:2) and autoclaving on aqueous solubility and dissolution rate from tablets.

Meloxicam was a gift sample from Recon Ltd, Bangalore. β-cyclodextrin was obtained from Carestar Inz,

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TABLE 1 : MELOXICAM-β-CD TREATMENT OF COMBINATIONS SHOWING THE SOLUBILITY VALUES WITH THE VARIANCE RATIOS

Treatment Combinations	Level of factors			Mean solubility			Analysis of variance			
	PVP [% w/v]	Drug:β-CD ratio	Autoclaving	Acid [μg/ml]	Alkali [mg/ml]	d f	Mean sum of Squares		F values	
							Acid	Alkali	Acid	Alkali
1.	0.10	1:1	nil	31	2:36	1	2.25	0.1336	0.152	3.89
A	0.25	1:1	nil	28	3:18	1	42.25	2.2127	2.85	64.54***
B	0.10	1:2	nil	51	2.84	1	812.25	0.0018	54.8**	0.0525
C	0.10	1:1	autoclaved	29	2:31	1	30.25	0.564	2.04	1.6545
AB	0.25	1:2	nil	40	2.92	1	182.25	0.5738	12.3*	16.736**
AC	0.25	1:1	autoclaved	39	3.73	1	56.25	0.3373	3.8	9.896*
BC	0.10	1:2	autoclaved	51	2.54	1	12.25	0.0716	0.826	2.088
ABC	0.25	1:2	autoclaved	42	3:19	1	30.25	0.00016	2.04	0.0049
						7				
Residual error						7	14.82	0.0343		
Total						15				

Critical 'F' value to be significant at 1% and 5% levels are 12.20 and 5.59 respectively.

USA. PVP, magnesium stearate and MCC were purchased from Loba chemicals. Sodium citrate B.P., Lactose I.P., maize starch and SLS were procured from S.D. Fine Chemicals, Mumbai.

The inclusion complexes were prepared using the solvent evaporation method. The required amount of meloxicam and β-CD in 1:1 or 1:2 molar ratios were dissolved in 25% ammonia solution with added PVP and allowed to stand over night. The ammonia from the solutions was removed by vacuum distillation and the ammonia free solutions autoclaved in a sealed container at 121° for 30 min. Finally the solutions were concentrated under reduced pressure to dryness. The dried product obtained was pulverized and stored in a desiccator.

A 2^3 factorial design of the experiment was utilised for preparing the treatment combinations. As there are three factors at two levels, there will be eight possible treatment combinations. The treatment combinations and their levels are given in Table-1.

The solubility of meloxicam and meloxicam β-CD

complexes were determined at room temperature (28°) in both pH 1.2 acid and pH 7.4 alkali by following standard procedure. Drug content was determined spectrophotometrically at 362 nm using Jasco-V-530 UV Visible spectrophotometer.

Among the eight treatment combinations, A, B and AB were selected for tablet preparation along with the pure drug. Meloxicam β-CD complexes or the pure drug were mixed thoroughly with lactose, maize starch, sodium citrate and sodium starch glycollate as tablet additives. The mixture was granulated using alcoholic solution of PVP (10% w/v) as a binder by passing through sieve No 20 and dried at 55°. The lumps were broken by resieving through the same sieve. The granules retained on sieve No 40 were used for compression. The required amount of MCC and SLS were added to the dry granules before addition of magnesium stearate and talc. The lubricated granules were compressed into tablets each weighing 200 mg (containing 7.5 mg of meloxicam) using a Minipress multi station tablet compression machine

fitted with 9 mm flat punches and dies to a pressure of 4 to 5 kg.

In vitro drug dissolution was carried out using Electrolab TDT-06T USP XXIII dissolution apparatus. Hydrochloric acid (pH 1.2) maintained at $37\pm0.1°$ was used as elution fluid with a stirrer speed of 100 rpm. The drug release was determined spectrophotometrically after suitable dilution using phosphate buffer of pH 7.5 as a reagent blank.

The results showed that pure drug gave a solubility of 1.3 µg/ml and 700 µg/ml in acid and alkali respectively. Drug β-CD complexes prepared using 1:1 and 1:2 molar ratios of Drug:β-CD without added PVP gave a solubility values of 13.2 µg/ml and 15.6 µg/ml in acid, 900 µg/ml and 1000 µg/ml in alkali. These results indicated that the acid solubility of meloxicam has been enhanced considerably by formulation of an inclusion complex with β-cyclodextrin. The solubility values obtained from all the eight treatment combinations in both the solvent systems are given in table-1. Analysis of variance was carried on the solubility values and the obtained treatment effects along with their statistical significance shown in Table-1.

The results of Analysis of variance indicated that the interaction between the combination of all the three factors (ABC) is not statistically significant in both the systems (F=2.04 and 0.0049). All the three factors were found to exert their influence on the drug solubility independently without producing any interaction. Among the three two way interactions, AB, BC and AC, only AB interaction showed significant improvement in the solubility in both the solvent systems. The variance ratio (F=12.3 and 16.736) revealed that the effect of Drug:β-CD molar ratio was influenced more by the concentration levels of PVP in enhancing the drug solubility in acid and alkali.

The interaction between the Drug:β-CD molar ratio and autoclaving (BC) failed to show any significant effect (F=0.826 and 2.088) in both solvent systems, whereas the interaction between autoclaving X PVP concentration (AC) has shown significant effect in alkali (F=9.896) but not in acid (F=3.8). It can be concluded that autoclaving might have potentiated the effect of PVP in enhancing the drug solubility in alkali. Similar results have been reported by Loftsson *et al.*[14] in the case of enhanced aqueous solubility of hydrocortisone-2-hydroxy

time (min)
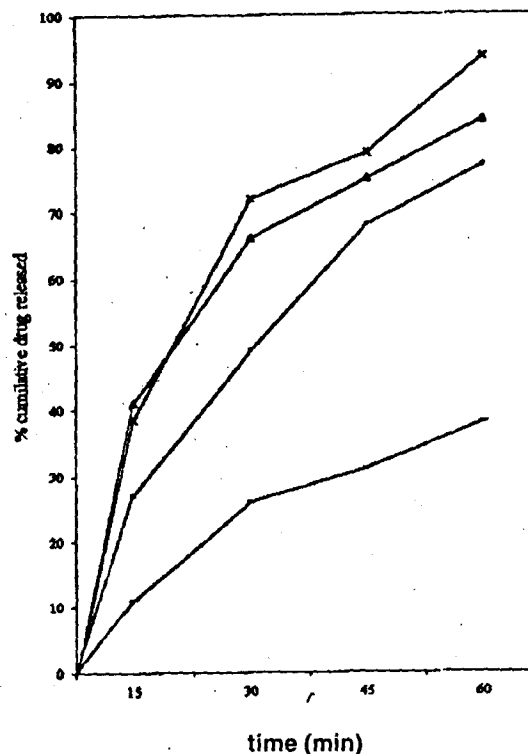
Fig. 1: *In vitro* release of meloxicam (—) and meloxicam-β-CD treatment combinations (—•— A-Δ-B x AB) from tablets at pH 1.2

propyl β-CD with added PVP or HPMC followed by autoclaving.

Normally, if a large interaction exists, the effects corresponding to the interaction do not have much meaning as such. But in the present work the variance ratio values from the main effects were found to be higher than the interaction effects. The Drug:β-CD molar ratio (B) was found to exert a significant effect on the solubility of meloxicam in acid (F=54.8). The results obtained in the present work were found to agree well with the observations made by Loftsson[15] that drugs which posses aqueous solubility in µg/ml range generally demonstrate much greater enhancement in their solubility than the drugs possessing solubility in mg/ml range by complexation with β-CD or its derivatives.

The PVP concentration at higher level on the contrary was found to enhance the alkali solubility of the drug (F=64.54) without any significant effect on the acid solubility (F=2.85).

Among the eight treatment combinations A,B and AB were selected for preparing tablets along with the

pure drug. The *in vitro* release pattern in acid from the tablets is shown graphically in Fig. 1. The results indicated that only 38% of the drug was released from tablets of meloxicam, where as 77%, 84.07% and 93.46% of the drug was released from tablets of complex A, B and AB respectively by obeying first order rate kinetics. The release rate constants were found to be -0.00783, -0.0267, -0.0287 and -0.045 mg/min from tablets of meloxicam and treatment combination A, B and AB respectively.

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