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Improvement of Dissolution Properties of Etoricoxib through Solid Dispersion Technique

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ABSTRACT

Etoricoxib, a non-steroidal anti-inflammatory drug, is used to Osteoarthritis, Rheumatoid arthritis and Acute Gouty arthritis. Etoricoxib is practically insoluble in water; hence present study was carried out to enhance dissolution properties of Etoricoxib through the preparation of Solid Dispersions using Mannitol, PEG 6000 and PVP K30 as carriers at various proportions by using Solvent Evaporation Method. The drug release profile was studied in 0.1N HCl containing 0.75 % SLS. U.V. Spectrophotometric method was selected for assay as well as in-vitro dissolution studies at 234nm. The FTIR used to characterize the solid state of solid dispersions. All the solid dispersions exhibited superior dissolution than pure drug. The drug dissolution studies followed first order kinetics.

KEYWORDS: Solid dispersion, Etoricoxib, Solvent evaporation method

I. INTRODUCTION

Etoricoxib [1] . (EXB) 5-Chloro-2-[6 methyl pyridine-3-yl]-3-[4-mehtyl sulphonyl phenyl] Pyridine a non steroidal anti inflammatory drug (NSAID) has been indicated for various painful indications and proved as effective as other NSAIDS with lower indication of gastrointestinal adverse effects and thus, resulted in a greater compliance with treatment. Etoricoxib is practically insoluble in water. The rate of dissolution can be increased by increasing the surface area of available drug by various methods like Micronization, Complexation and Solid dispersion [2](SD). Hence, an attempt was made to improve the dissolution characteristics using the solid dispersion technologies. Among various approaches to improve the dissolution rate of poorly soluble drugs, the preparation of solid dispersions has often proved to be successful[3-7]. Meloxicam[8]. Valdecoxib[9]. Aceclofenac[10]. Carbamazepine[11]. Glimipiride[12]. Etoricoxib[13]. Various hydrophilic carries, such as mannitol[14], poly ethylene glycols [15], Polyvinyl pyrrolidone[16]. Sugars[17]. Have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs. In the present work, solid dispersions of Etoricoxib with Mannitol, PEG 6000 and PVP K 30 were prepared in different drug: carrier ratios (1:1, 1:3, 1:6, 1:9) with solvent evaporation (SE) technique to improve solubility and dissolution characteristics. U.V. Spectrophotometric method was selected for assay as well as *in-vitro* dissolution studies at 234 nm in 0.1N HCl containing 0.75% SLS. The dissolution profile of best formulation i.e. Drug: PVP K30 (1:6) solvent evaporation method showed maximum dissolution rate. The increased in dissolution rate of the drug may be due to increased wettability, hydrophilic nature of the carrier and also possibility due to reduction in drug crystallinity.

II. MATERIALS AND METHODS

Etoricoxib was procured from Aurobindo Pharmaceuticals private limited; Hyderabad, Mannitol ,Dichloromethane and Methanol purchased from Qualigens fine chemicals Mumbai, Polyethylene glycol 6000 Purchased from S. D fine chemicals Ltd, Mumbai and Polyvinyl pyrrolidone K-30 Purchased from Himedia laboratories Pvt,Ltd , Mumbai, and all other materials used were of pharmaceutical grade.

III. PREPARATION OF SOLID DISPERSION

Solvent Evaporation Method:

The accurately weighed amounts of drug and polymer were dissolved in sufficient quantity (60ml) of solvent blend to obtain clear solution. Dichloromethane and methanol in the ratio of 2:1 was used as solvent blend for different carriers. The solvent blend was

removed by evaporation in a water bath at 45^0C under reduced pressure. The resulting residue was then transferred to glass desiccators and dried under vacuum to constant weight. The dried product was powdered and sifted through Sieve #100 and stored in a desiccator prior to use.

Estimation of Etoricoxib

A quantity of solid dispersion equivalent to 100 mg of Etoricoxib was accurately weighed and dissolved in 0.1 N HCl in 100 ml. An ultraviolet (UV) Spectrophotometric method based on the measurement of absorbance at 234 nm in 0.1 N HCl was developed and used for the estimation of Etoricoxib. The method obeyed Beer's law in the concentration range of 0-10 mcg/ml where concentration of standard solution was assayed repeatedly (n = 6).

Dissolution Rate Study

The dissolution rate of Etoricoxib as such and from its Solid Dispersions was studied using Disso 2000, Lab India 8-station Dissolution rate test apparatus with a paddle stirrer. The dissolution rate was studied in 900ml of 0.1 N HCL containing 0.75 % SLS. Sodium lauryl sulphate was added to the dissolution fluid to maintain sink condition. Etoricoxib (90 mg) or its solid dispersion equivalent to 90 mg of Etoricoxib, with speed of 50 rpm and temperature of 37 ± 1^0c were used in each test samples of dissolution medium (5 ml) were withdrawn through a filter (0.45 µ) at different time intervals, suitably diluted and assayed for Etoricoxib by measuring absorbance at 234 nm. The dissolution experiments were conducted in triplicate.

IV. RESULT AND DISCUSSION

All the solid dispersions prepared were found to be fine and free flowing powders. Low SD and C.V (<2%) in the percent drug content values indicated that the drug content was uniform in a batch of solid dispersion in all the cases. The drug release profile was studied in 0.1 N Hcl containing 0.75%S.L.S. Sodium lauryl sulphate was added to the dissolution medium to maintain sink condition during dissolution rate study. The dissolution profiles of various sold dispersions were shown in **Fig.1,2,3.**

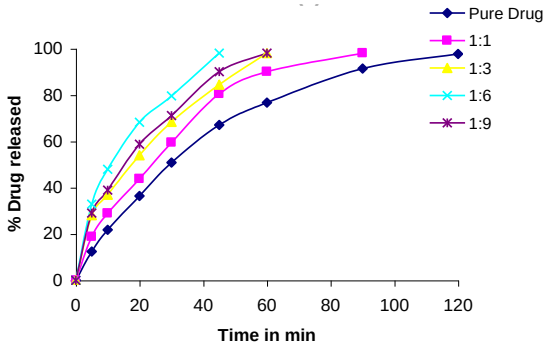

Fig 1: Dissolution profiles of Etoricoxib from Mannitol Solid Mixtures prepared by Solvent evaporation method.

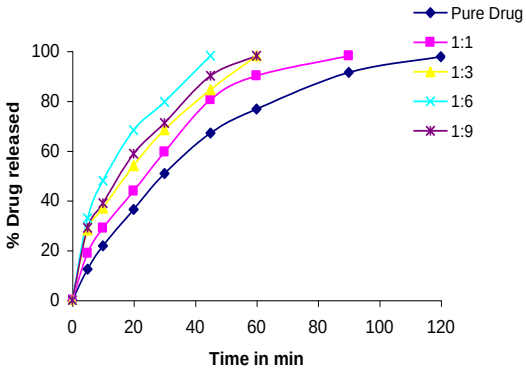

Fig 2: Dissolution profiles of Etoricoxib from PEG 6000 Solid Mixtures prepared by Solvent evaporation method.

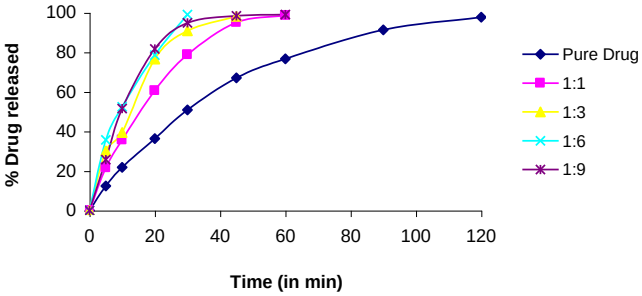

Fig 3: Dissolution profiles of Etoricoxib from PVP-K30 Solid Mixtures prepared by Solvent evaporation method.

All the solid dispersions showed marked enhancement in the dissolution of drug as compared to plain drug powder, the reason for the poor dissolution of pure drug could be poor wettability and agglomeration of particles, The dissolution rates are in the order of PVP K30>PEG 6000> Mannitol > Pure drug, and it is clearly evident from the T_{50}, DE_{20} and DP_{10} values of pure drug, and its solid dispersions. Shown in **Table I**. The dissolution of Etoricoxib as such and prepared solid dispersions followed First order kinetics. The dissolution rate constants (k_1) were calculated from the slopes of the first order linear plots of the dissolution data. Dissolution efficiency (DE_{20}) values based on the dissolution data were calculated according to Khan[18]. T_{50} (Time taken for 50% dissolution) values were recorded from the dissolution profiles.The dissolution rate of etoricoxib Increases with Increase in Mannitol, up to 1:6 ratio of drug; mannitol this increase in dissolution rate may be due to improved wettability by the carrier. At the higher level at 1:9 ratio the negative effect on dissolution appears. That may be due to increased accumulation of carrier molecule in the bulk to cause a saturation. By which further solubility of Etoricoxib is retarded. Carrier proportion led to an increase in dissolution rate up to 1:6 ratios. Further increase in polymer concentration shown decrease in the dissolution. And it can

be seen that the dissolution of Etoricoxib increases with increase in PEG 6000 up to 1:6 ratio of drug: PEG 6000. Further in case 1:9 ratio, no marked increase in dissolution was of observed. This might be due to complete dispersion of drug with PEG 6000 at 1:6 ratio. And it is clear that the dissolution rate increased with the increment of PVP K30 proportion up to the drug to PVP K30 1:6 ratio. Further, in case of 1:9 ratio decreases in dissolution rate was observed. This might be due to formation of viscous boundary layer around the drug particles, leading to decrease in the dissolution rate.

Table I: Dissolution parameters of various Eterocoxib: Mannitol, PEG 6000 and PVP K30 Solid dispersions prepared.

Product	***Percent Dissolved In 10 (min)**	***T_{50} (min)**	***DE_{20} (%)**	***K_1 (min-1)**	***r**
Etoricoxib	-	> 60	20	-	-
Etoricoxib : Mannitol($SE_)$					
1:1	26.02	25.50	24.37	0.0329	0.9932
1:3	28.80	21.4	28.78	0.0294	0.9771
1:6	32.92	17.0	32.50	0.0483	0.9942
1:9	28.62	31.0	22.50	0.0350	0.9412
Etoricoxib : PEG-6000(SE)					
1:1	28.92	11.50	25.12	0.0612	0.9683
1:3	37.0	17.10	31.18	0.0697	0.9830
1:6	47.98	10.00	43.72	0.0854	0.9848
1:9	38.92	20.7	27.12	0.0852	0.9598
Etoricoxib : PVP-K30(SE)					
1:1	35.74	15.50	35.00	0.0730	0.9928
1:3	39.47	13.0	42.50	0.0930	0.9929
1:6	57.49	6.0	52.75	0.2100	0.9962
1:9	52.55	10.0	45.00	0.0987	0.9949

$DP_{10=}$ Percent drug dissolved in 10 minutes,
$T_{50=}$ Time taken for 50% dissolution
$DE_{20=}$ Dissolution efficiency at t=20 minutes,
$K_{1\ (min-1)}$ =First order rate constant. (n=3)
r = **correlation coefficient (first order)**
* = Average of 3 determinations.

The comparison between dissolution profile of Etoricoxib: Mannitol, PEG 6000 and PVP K30 1:6 ratios Prepared by solvent evaporation method were shown in **Fig 4**. From this solid dispersions prepared by solvent evaporation technique with Etoricoxib: PVP K30 1:6 ratio has showed maximum dissolution rate was the best with higher values of PD10, DE20 and T50 among the solid dispersions Prepared with other carriers and plain drug. This increase in the dissolution rate may be due to increase in drug wettability, solubilization of the drug by the carriers and possibility due to reduction in the drug crystallinity. FT-IR spectroscopy was used to study the possible interaction between EXB and PVP-K30 in SDs. The spectra showed the characteristic peaks corresponding to the drug and carrier used was unchanged showing no significant interaction between drug and carrier, which are shown in Figures 5,6,7.

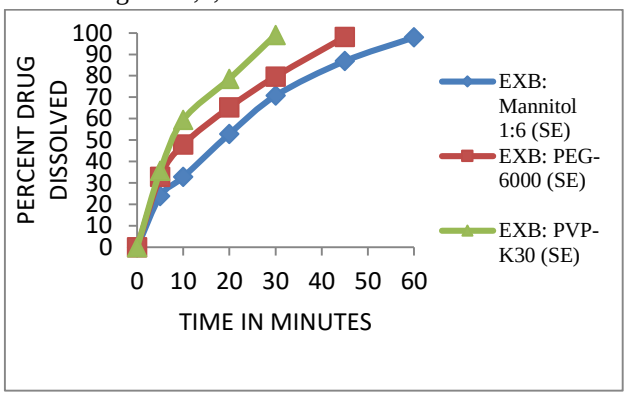

Fig 4: Comparison between dissolution profile of Etoricoxib: Mannitol, PEG 6000 and PVP K30 1:6 ratios Prepared by solvent evaporation method.

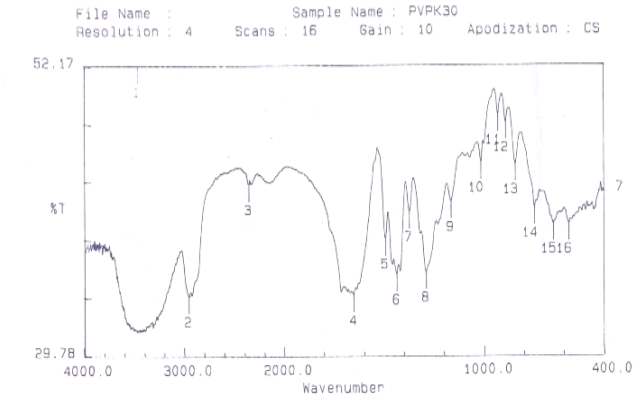

Fig 5: FTIR Spectra of PVP K 30

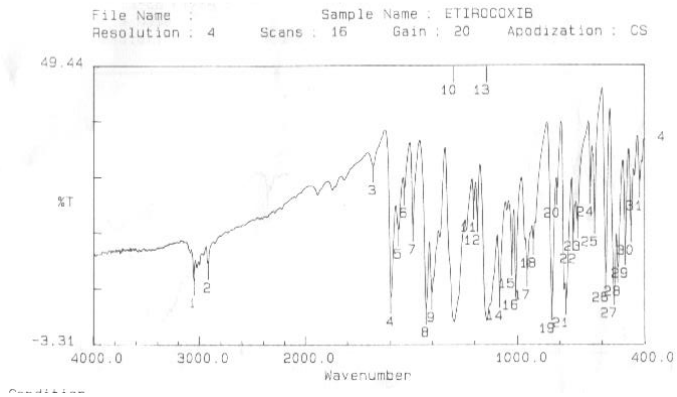

Fig 6: FTIR Spectra of Etoricoxib

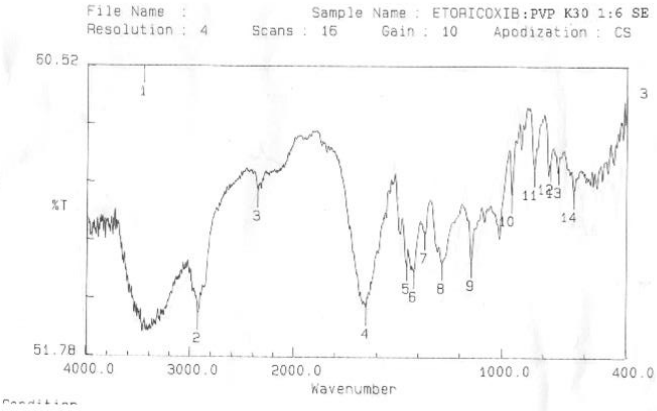

Fig 7: FTIR Spectra of Etoricoxib : PVP K 30 1: 6 SE

V. CONCLUSION

From the above studies, it was concluded that the Solid dispersion technique has been shown as successful approach to improve the dissolution rate of Etoricoxib. The method and the amount of carrier used to play an important role in the enhancement of dissolution rate. EXB: PVP K-30 1:6 ratio prepared by Solvent evaporation method exhibited higher dissolution rate than the corresponding solid dispersion prepared with using other carriers.

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