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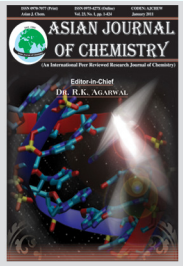

# Factorial Study on the Evaluation of Formulation Variables on the Dissolution Rate of Etoricoxib Tablets

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The individual main and combined effects of commonly used binders, disintegrants and β-cyclodextrin on the dissolution rate of etoricoxib tablets were evaluated in a $2^3$ factorial study. Etoricoxib tablets were formulated employing selected combinations of binder, disintegrant and β-cyclodextrin as per $2^3$ factorial design and the tablets were evaluated for various physical properties, dissolution rate ($k_1$) and dissolution efficiency ($DE_{10}$). Dissolution parameters ($K_1$ and $DE_{10}$) were subjected to ANOVA of factorial design. The individual main effects of binder, disintegrant and β-cyclodextrin on the dissolution rate ($K_1$) were significant ($p < 0.05$). Whereas all combined (or interaction) effects were not significant ($p > 0.05$). The individual main effects of binders and β-cyclodextrin on the dissolution efficiency ($DE_{10}$) were significant ($p < 0.05$). The main effects of disintegrant and all combined effects on $DE_{10}$ were not significant ($p > 0.05$). Tablets formulated employing poly(vinyl pyrrolidone) as binder and potato starch as disintegrant gave highest dissolution rate of etoricoxib, 95 % in 1 h.

**Key Words: Etoricoxib tablets, Formulation variables, Dissolution rate, Factorial study.**

## INTRODUCTION

Etoricoxib, a potent widely prescribed antiinflammatory 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 etoricoxib is dissolution rate limit and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. The very poor aqueous solubility of the drug also gives rise to difficulties in the formulation of solid dosage forms and leads to poor and variable dissolution rate and oral bioavailability. The formulation variables greatly influence the dissolution rate and bioavailability of the drug from tablet dosage forms. Binder is a critical ingredient in tablets that influences tablets characters. The effect of binding agent on the dissolution rate of poorly soluble drugs such as hydrochlorthiazide, furosemide, nicotinic acid, aspirin, paracetamol, tolubutamide, phenylbutazone and nimesulide was reported earlier[1,2]. Disintegrant is another critical ingredient in tablets that influnces dissolution rate and bioavailability of the drug from tablets. The effect of disintegrant on the dissolution rate of poorly soluble drugs such as itraconazole and sparfloxacin from tablets was reported earlier[3,4]. Among various approaches complexation with cyclodextrins has gained good acceptance in recent years for enhancing the solubility and dissolution rate of poorly soluble drugs[5]. The objective of the present study is to evaluate the effect of commonly used binders, disintegrants and β-cyclodextrin on the dissolution rate of etoricoxib tablets. The study was conducted as per $2^3$ factorial design to evaluate the individual main effects and combined effects of the three factors involved.

## EXPERIMENTAL

Etoricoxib and croscarmellose were gift samples from M/s Natco Pharma. Ltd., Hyderabad. β-Cyclodextrin was a gift sample from M/s Cerestar Inc., USA. Lactose I.P, Acacia (Loba chemie), Poly(vinyl pyrrolidone) (PVP, K40), Potato starch (Loba chemie),Talc I.P. and magnesium stearate I.P. were procurred from commercial sources. All other materials used were of pharmacopoeial grade.

**Estimation of etoricoxib:** An UV spectrophotometric method based on the measurement of absorbance at 284 nm in phosphate buffer of pH 7.4 was used for the estimation of the etoricoxib. The method obeyed Beer-Lambert's law in the concentration range of 1-10 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.

**Preparation of etoricoxib tablets:** Compressed tablets each containing 60 mg of etoricoxib were prepared by conventional wet granulation method as per the given formulae in Table-1. The required quantities of etoricoxib, lactose and half the amount of potato starch were mixed thoroughly in a dry mortar by following geometric dilution technique. In the case of formulations containing croscaremallose, it was add after drying granules before compression. The binder solution was added and mixed thoroughly to form dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60 ºC for 4 h. The dried granules were passed through mesh No. 16 to break the aggregates. The lubricants, talc (2 %), magnesium stearate (2 %), remaining disintegrant (potato starch) and croscarmellose were passed through mesh No. 100 on to dry granules and blended in a closed polyethylene bag. The tablet granules were compressed in to tablets on a rotary multi station tablet punching machine (M/s Cadmach Mechinary Co. Pvt. Ltd., Mumbai) to a hardness of 6-8 kg/cm$^2$ using 9 mm round and flat punches. All the tablets prepared were evaluated for content of active ingredient, hardness, friability, disintegration time and dissolution rate.

**Content of active ingredient:** Five tablets were accurately weighed and powdered. Tablet powder equivalent to 60 mg of etoricoxib was taken into boiling test tube and extracted with 4 × 10 mL quantities of methanol. The methanolic extracts were collected into 50 mL of volumetric flask and the volume was made up to 50 mL with methanol. The solution was subsequently diluted with phosphate buffer pH 7.4 and assayed for drug content by UV spectrophotometric method.

**Hardness:** Hardness of the tablets was tested using a Monsanto hardness tester.

**Friability:** Friability of tablets was determined in a Roche friabilator.

**Disintegration time:** Disintegration times were determined in Thermonic tablet disintegration test machine using distilled water as fluid.

**Dissolution rate study:** The dissolution rate of etoricoxib from the tablets was studied in 900 mL of phosphate buffer of pH 7.4 using DISSO 2000 (LABINDIA) eight station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature of 37 ± 1 ºC was maintained through out the study. One tablet containing 60 mg of etoricoxib was used in each test. Samples of dissolution media (5 mL) were withdrawn through a filter (0.45 µ) at different intervals of time, suitably diluted and assayed for etoricoxib at 284 nm. The samples of dissolution fluid withdrawn at each time was replaced with fresh fluid. Each dissolution rate study was replicated four times (n = 4).

## RESULTS AND DISCUSSION

Tablets each containing 60 mg of etoricoxib (Table-1) were prepared employing selected combinations of three factors A (binder: acacia or PVP), B (disintegrant: potato starch or croscarmellose) and C [β-cyclodextrin (β-CD): absence or at 1:2 ratio of drug: β-CD] as per $2^3$ factorial design to evaluate their individual main and combined or interaction effects on the dissolution rate of etoricoxib tablets. The physical properties of the prepared tablets are given in Table-2. The hardness of the tablets was in the range 5.5-7.0 kg/cm$^2$. Weight loss in the friability test was less than 0.8 % in all the cases. Etoricoxib content in the tablets was within 100 ± 5 % of the labeled claim. All the tablets disintegrated within 10 min. Thus, the tablets prepared were of good quality and fulfilled the official (I.P.) specifications of uncoated tablets. Dissolution of etoricoxib from the tablets prepared was studied in phosphate buffer of pH 7.4. Each dissolution test is replicated four times (n = 4). Dissolution data were analysed as per zero order and first order kinetics. In each model the correlation coefficient value (r) was calculated. In all the cases 'r' values in the first order model were higher than those in the zero order model indicating that the drug release from the tablets followed first order kinetics. Dissolution efficiency (DE) values in each case were calculated as suggested by Khan *et al.*[6]. The first order dissolution rate constants ($K_1$) and $DE_{10}$ values are given in Table-3. Much variations were observed in the dissolution rate ($K_1$) and $DE_{10}$ values of various tablets due to formulation variable (*i.e.*, factors A, B, C).

TABLE-2
HARDNESS, FRIABILITY, DISINTEGRATION TIME AND DRUG CONTENT OF ETORICOXIB TABLETS PREPARED

| Formulation | Drug content (mg/tab) | Hardness (Kg/cm$^2$) | Friability (%) | Disintegration time (min) |
|---|---|---|---|---|
| $F_1$ | 58.2 | 6.5 | 0.8 | 5.20 |
| Fa | 59.2 | 6.0 | 0.6 | 2.30 |
| Fb | 59.6 | 5.5 | 0.6 | 4.15 |
| Fab | 58.4 | 6.0 | 0.4 | 5.20 |
| Fc | 60.5 | 5.5 | 0.5 | 6.20 |
| Fac | 60.2 | 7.0 | 0.6 | 7.30 |
| Fbc | 58.2 | 6.0 | 0.7 | 6.40 |
| Fabc | 59.2 | 6.5 | 0.8 | 7.40 |

TABLE-1
FORMULAE OF ETORICOXIB TABLETS PREPARED AS PER $2^3$ FACTORIAL DESIGN

| Ingredient (mg/tablet) | Formulation | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | $F_1$ | Fa | Fb | Fab | Fc | Fac | Fbc | Fabc |
| Etoricoxib | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |
| Lactose | 119.8 | 119.8 | 141.8 | 141.8 | – | – | – | – |
| β-CD | – | – | – | – | 120 | 120 | 120 | 120 |
| Potato starch | 33 | 33 | – | – | 33 | 33 | – | – |
| Cros carmellose | – | – | 11 | 11 | – | – | 11 | 11 |
| Acacia | 4.4 | – | 4.4 | – | 4.4 | – | 4.4 | – |
| PVP | – | 4.4 | – | 4.4 | – | 4.4 | – | 4.4 |
| Magnesium stearate | 4.4 | 4.4 | 4.4 | 4.4 | 4.4 | 4.4 | 4.4 | 4.4 |
| Talc | 4.4 | 4.4 | 4.4 | 4.4 | 4.4 | 4.4 | 4.4 | 4.4 |
| Total weight (mg) | 226 | 226 | 226 | 226 | 226 | 226 | 204 | 204 |

TABLE-3
DISSOLUTION PARAMETERS OF ETORICOXIB TABLETS PREPARED

| Formulation | $T_{50}$ (min) | $PD_{30}$ (%) | $K_1$ $min^{-1}$ | $DE_{10}$ (%) |
|---|---|---|---|---|
| $F_1$ | 16.50 | 60.99 | 0.0133±0.0028 | 52.12±26.86 |
| Fa | 11.50 | 73.19 | 0.0364±0.0235 | 56.95±6.99 |
| Fb | 17.25 | 61.08 | 0.0151±0.0044 | 40.25±5.69 |
| Fab | 17.50 | 57.53 | 0.0112±0.0017 | 56.12±10.87 |
| Fc | 35.50 | 45.64 | 0.0112±0.0012 | 34.50±19.84 |
| Fac | 28.75 | 51.62 | 0.0144±0.0016 | 23.15±6.49 |
| Fbc | 36.25 | 46.56 | 0.0143±0.0027 | 35.87±5.17 |
| Fabc | 24.00 | 53.94 | 0.0273±0.0168 | 34.62±12.05 |

To evaluate the individual main and combined effects of the three factors namely binder (**A**), disintegrant (**B**) and β-CD (**C**), the studied was conducted as a $2^3$-factorial study. The three factors were studied each at two levels. A total of eight formulations of etoricoxib tablets corresponding to eight treatments (selected combinations of levels of the three factors) as per $2^3$-factorial study were made and were evaluated. The dissolution parameters $K_1$ and $DE_{10}$ were subjected to ANOVA to find out the significance of individual main and combined effects of the factors involved. The results of ANOVA are given in Tables 4 and 5.

TABLE-4
ANOVA OF $K_1$ VALUES OF ETORICOXIB TABLETS PREPARED

| Source of variation | DF (n-1) | SS | M.S.S | F ratio | Significance |
|---|---|---|---|---|---|
| Total treatments | 31<br>7 | 49.57<br>23.13 | 3.304 | 3.00 | ($p < 0.05$) |
| Fa | 1 | 9.37 | 9.37 | 8.50 | ($p < 0.05$) |
| Fb | 1 | 7.79 | 7.79 | 7.07 | ($p < 0.05$) |
| Fab | 1 | 4.21 | 4.21 | 3.82 | ($p > 0.05$) |
| Fc | 1 | 12.34 | 12.34 | 11.20 | ($p < 0.05$) |
| Fac | 1 | 0.58 | 0.58 | 0.531 | ($p > 0.05$) |
| Fbc | 1 | 0.27 | 0.27 | 0.245 | ($p > 0.05$) |
| Fabc | 1 | 0.46 | 0.46 | 0.421 | ($p > 0.05$) |
| Error | 24 | 26.43 | 1.101 | – | – |

The results of ANOVA of dissolution rate ($K_1$) indicated that the individual main effects of the three factors (*i.e.*, binder, disintegrant and β-cyclodextrin) were significant ($p < 0.05$), whereas all combined (or interaction) effects of the factors were not significant ($p > 0.05$). The binder and disintegrant used and inclusion of β-cyclodextrin has significantly influenced the dissolution rate of etoricoxib tablets.

The results of ANOVA of $DE_{10}$ values indicated that the individual main effects of binder and β-cyclodextrin were significant ($p < 0.05$), whereas the individual effect of disintegrant and combined or interaction effects of the three factors were not significant ($p > 0.05$). Thus the binder used and β-CD influences the dissolution efficiency (DE) of etoricoxib tablets. Among all etoricoxib tablets prepared formulation (Fa) formulated employing PVP as binder (factor A) and potato starch as disintegrant (factor B) gave highest dissolution rate of etoricoxib, 95 % in 1 h.

TABLE-5
ANOVA FOR $DE_{10}$ VALUES OF ETORICOXIB TABLETS PREPARED

| Source of variation | DF (n-1) | SS | M.S.S | F ratio | Significance |
|---|---|---|---|---|---|
| Total treatments | 31<br>7 | 9047.57<br>4119.68 | –<br>588.52 | –<br>2.866 | ($p < 0.05$) |
| Fa | 1 | 990.12 | 990.12 | 4.822 | ($p < 0.05$) |
| Fb | 1 | 325.12 | 325.12 | 1.583 | ($p > 0.05$) |
| Fab | 1 | 225.78 | 225.78 | 1.099 | ($p > 0.05$) |
| Fc | 1 | 2938.78 | 2938.78 | 14.31 | ($p < 0.05$) |
| Fac | 1 | 5.281 | 5.281 | 0.025 | ($p > 0.05$) |
| Fbc | 1 | 0.03125 | 0.03125 | 0.000152 | ($p > 0.05$) |
| Fabc | 1 | 0.5 | 0.5 | 0.00243 | ($p > 0.05$) |
| Error | 24 | 4927.87 | 205.32 | – | – |

## Conclusion

Much variations were observed in the dissolution rate ($K_1$) and dissolution efficiency ($DE_{10}$) of etoricoxib tablets formulated employing selected combinations of binder, disintegrant and β-CD as per $2^3$ factorial design. The individual main effects of binders, disintegrants and β-cyclodextrin on the dissolution rate ($K_1$) were significant ($p < 0.05$). Whereas all combined (or interaction) effects were not significant ($p > 0.05$). The individual main effects of binders and β-cyclodextrin on the dissolution efficiency ($DE_{10}$) were significant ($p < 0.05$). The main effect of disintegrant and all combined effects on $DE_{10}$ were not significant ($p > 0.05$ ).

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