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# Formulation and Evaluation of Liquisolid Compact of Etoricoxib for Solubility Enhancement

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**ABSTRACT:** *Liquisolid compact technique is a novel concept for delivery of drug through oral route. This approach of delivering drug is mostly suitable for lipophilic drug and poorly or water insoluble drugs. The main objective of present study was to increase the solubility of water in soluble BSc class II drug etoricoxib. Etoricoxib is aliphilic drug that is practically insoluble in water and exhibit an excessively slow dissolution rate in class II compound in biopharmaceutics classification system. The liquid solid compacts were prepared using PEG 400 as non volatile solvent, microcrystalline cellulose as carrier, aerosil 200 as coating material and Sodium starch glycolate was used as super disintegrating agent. Several formulations of liquid solid compacts having different drug concentration in PEG 400 (non volatile solvent) with varying ratio of carrier to coating material were prepared. The liquid solid compacts were evaluated for Bulk characterization, Flow properties, solubility studies, drug content, FTIR studies, DSC studies and in vitro drug release studies. The saturated solubility studies and in vitro drug release studies shows that the increase in solubility of drug and enhanced drug release rate in liquisolid compacts compared to pure drug. The Formulation F5 and F4 is considered as best formulation as it has shown highest drug release in short time (1 hr). Our studies showed that the solubility of the drug can be significantly enhanced with increase in the carrier content there is increase in the solubility resulting and enhanced drug release rate.*

**Keywords:-***Liquisolid compacts, Etoricoxib, carrier material, coating material Solubility enhancement, in vitro drug release.*

## INTRODUCTION

The enhancement of dissolution profile, absorption efficiency and bio availability of water insoluble drugs is one of the major concern of present Pharmaceutical research. Different techniques are employed to enhance the dissolution of poorly soluble drugs like use of water soluble salt and polymorphic forms, solid dispersion, reducing particle size to increase the surface area, pH adjustment, co-precipitation, polymer modification Lyophilization, microencapsulation, liquid solid Technology. Liquisolid compacts technique is one of the novel and most promising technique for promoting drug dissolution rate and efficacy of poorly soluble or water insoluble drugs. The term “liquisolid medication” implies oily liquid



drug and solution or suspensions of water insoluble solid drugs carried in suitable non volatile solvent system. By using this formulation technique liquid medication may be transformed into a free flowing, readily compressible dry powder by simple physical blending with selected excipients referred to as the carrier and coating materials<sup>1,2</sup>.

Etoricoxib (5-chloro-2-[6-methyl pyridine-3-yl]-3-[4-methylsulfonylphenyl] pyridine) is a novel, selective second-generation, cyclooxygenase-2 inhibitor administered orally as an analgesic and anti-inflammatory drug. Etoricoxib does not inhibit prostaglandin synthesis in the gastric mucosa, even at doses above the clinical dose range of 60-120 mg<sup>3</sup>.

The main objective of the study is to investigate the possibility of improving the solubility and in vitro drug release rate of Etoricoxib. Liquisolid compacts were formulated by using PEG 400 as non volatile solvent, microcrystalline cellulose as carrier, aerosil 200 as coating material and Sodium starch glycolate was used as super disintegrating agent. The in vitro drug release profile of liquisolid compacts was compared with that of pure drug. Differential scanning calorimetry (DSC) and Fourier transform infra-red (FTIR) was performed to ensure that there was no possible interaction between drug and excipients<sup>4</sup>.

## I. MATERIALS AND METHOD

### 1. MATERIALS

Etoricoxib was received as a gift sample from Glenmark pharmaceuticals limited (Pithampur). Polyethylene glycol (PEG 400) was procured from central drug house (P) LTD (New Delhi). Microcrystalline cellulose (MCC) from Sd Fine-chem. limited (Mumbai). Sodium Starch glycolate (SSG) from Qualichems (Vadodara). Aerosil from Fine-chem. limited (Mumbai). All other solvent and reagent are used as of analytical grade.



## II. EXPERIEMENTALS

### 2.1 Identification of drug

#### 2.1.1 By UV Spectroscopy

In order to ascertain the optimum wavelengths of Etoricoxib, the solution of Etoricoxib in phosphate buffer was scanned on UV-Visible Spectroscopy in the range of 200-400 nm against phosphate buffer 7.4 pH as blank<sup>3</sup>. The spectrum of etoricoxib is shown in fig1.

#### 2.1.2 By melting point determination

Melting point determination of drug was performed using melting point apparatus (BTI-34) Melting point apparatus, Mumbai, India). In this method small amount of drug was filled in capillary tube open from both ends and it was placed along with thermometer in melting point apparatus. The temperature in the heating stand is ramped at user programmable fixed rate until the sample in the tube transition into the liquid state<sup>4</sup>. Melting point of drug sample is shown in table 1.

#### 2.1.3 By Fourier transform infrared spectroscopy analysis

Identification of Etoricoxib was done by FTIR Spectroscopy. The sample was analysed by FTIR instrument ( IR Affinity-1,(Shimadzu, Japan) was scanned and recorded<sup>5</sup>. The obtained IR spectrum is shown in fig 6.

### 2.2 Preparation of standard Calibration curve of Etoricoxib

Standard stock solution of Etoricoxib was prepared by dissolving 100 mg of drug in 100 ml of phosphate buffer 7.4 (1000 µg/ml) from the above stock solution 10 ml was taken and diluted to 100 ml in phosphate buffer 7.4 (100 µg/ml). From the above solution 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0 ml was taken and diluted upto 10 ml with phosphate buffer 7.4 to get series of solutions in concentration. Absorbance was noted using UV-VIS



Spectrophotometer at 288 nm against blank (phosphate buffer 7.4)<sup>6</sup>. The calibration curve of etoricoxib is shown in fig.2.

### **2.3 Solubility study**

Solubility of Etoricoxib was determined in distilled water and various non aqueous solvents like PEG 400, methanol, ethanol, HCl, chloroform, phosphate buffer 7.4. Excess amount of Etoricoxib was saturated in 10 ml of selected solvents in conical flask for determination of solute dissolved in each solvent and was shaken at 25°C for 24 hrs. After 24 hrs equilibrium would be attained and the sample was filtered through whatman filter paper. the samples was analysed after suitable dilution for the concentration of drug dissolved using UV-VIS Spectrophotometer<sup>6</sup>. The solubility of etoricoxib in different solvents are shown in table 2.

### **2.4 Method of preparation of liquisolid compact**

#### **a) Preparation of drug solution**

For the preparation of liquisolid compact of Etoricoxib, a non volatile solvent is selected for dissolving the drug from the results of solubility studies. liquisolid powder containing PEG 400 as the liquid medication, Microcrystalline cellulose as a carrier and Aerosil pH 200 as coating material was selected for the preparation of liquisolid compact. various ratio of carrier to coating material were selected according to solubility of Etoricoxib. The required quantities of drug and PEG 400 were accurately weighed and placed in a beaker and then stirred continuously, until a homogenous drug solution was obtained. Selected amounts (W) of the resultant liquid medications were incorporated into calculated quantities of carrier contained in themortar<sup>7</sup>.

#### **b) Mixing**

The mixing procedure was conducted in three stages. During the first stage, the system was blended at an approximate mixing rate of one rotation/ sec for approximately one minute in order to evenly distribute the liquid medication into the powder.

In the second mixing stage, calculated quantities of coating material were added to the system in blended for 2 min. The liquid/powder admixture was evenly spread as a uniform layer of the surfaces of mortar and left standing for approximately 5 min to allow the dug solution to be absorbed in interior of the powder particles<sup>7</sup>.

**Table 3.composition of optimized liquisolid system**

Formulation Code	ECB(drug)	Non volatile solvent (PEG400)	Carrier material(MCC)	Coating material(Aerosil)	Super disintegrant(SSG)
F1	60 mg	100 mg	200 mg	10 mg	20 mg
F2	60 mg	100 mg	205 mg	10 mg	15 mg
F3	60 mg	110 mg	200 mg	10 mg	20 mg
F4	60 mg	110 mg	205 mg	10 mg	15 mg
F5	60 mg	120 mg	200 mg	10 mg	20 mg
F6	60 mg	120 mg	205 mg	10 mg	15 mg

### III. Evaluation of liquisolid compacts

#### 3.1. Bulk characterisation of liquisolid systems.

Bulk characterisations of liquisolid system were estimated by Bulk density, Tapped density, Carr's index, and Hausner's ratio. The flow property was determined by Angle of repose. These properties were determined by using the following equations:<sup>8,9</sup>

Bulk Density = Mass (g)/ bulk volume

Tapped density= Mass (g)/tapped volume



Carr's index=  $\frac{\text{Tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$

Hausner's ratio=  $\frac{\text{tapped density}}{\text{bulk density}}$

Angle of repose=  $\tan^{-1} \frac{h}{r}$ .

The bulk characterisation and flow properties of liquisolid compacts are shown in table 3.

### 3.2. Determination of saturation solubility of liquisolid system

Solubility study was performed according to method reported by Higuchi and Connors. The liquisolid compact system F1,F2,F3,F4,F5,F6 were added in 10 ml distilled water taken in stoppered conical flask and were shaken for 24 hrs at  $37^{\circ}\text{C} \pm 1$  in orbital shaker. Two ml aliquots were withdrawn at 1 hr intervals and filtered through whatman filter paper. The filtered solution were analysed spectrophotometrically at 288 nm against blank<sup>10</sup>. The saturation solubility of liquisolid system is shown in fig 4.

### 3.3. Drug content of liquisolid systems

The liquisolid systems equivalent to unit dose of drug was weighed accurately and dissolved in 100 ml of phosphate buffer 7.4 and filtered through whatman filter paper. The solution were analysed by UV spectrophotometer at 288 nm and drug content calculated accordingly<sup>11</sup>. The drug content of various formulations are shown in table 4.

### 3.4. Fourier transform infrared (FTIR) spectroscopy

Fourier transform infrared was conducted using shimadzu 8300 spectrometer and the spectrum was recorded in the region of  $4000-400 \text{ cm}^{-1}$ . The procedure consisted of placing a sample powder dispersed in KBr (200-400 mg) and compressed into a disc by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained. The drug and excipients were scanned individually as well as combined from in order to find the drug – excipient interaction<sup>12</sup>. The IR Spectra of pure drug, carrier and formulations are shown in fig 6,7,8.



### 3.5. Differential scanning calorimetry (DSC)

Differential scanning calorimetry was performed using PerkinElmer 6000. Accurately weighed samples (about 2 mg) were placed in a sealed aluminium pans, under static air at a scan rate of  $10^{\circ}\text{C min}^{-1}$  over a 25 to  $250^{\circ}\text{C}$  temperature range. Indium oxide was placed in aluminium pans and used as a reference. The heat flows as a function of temperature is measured for the drug, carrier and liquisolid formulations<sup>13</sup>. The DSC graph of pure drug, carrier and F2, F5 batches are shown in fig 9.

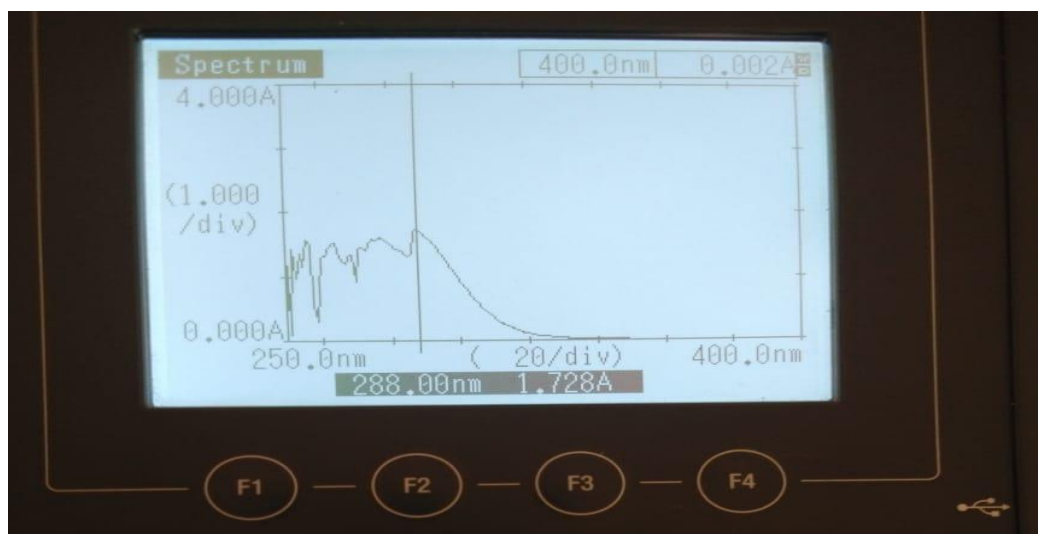
### 3.6. In vitro drug release studies

The in vitro drug release studies of liquisolid system was performed by using (USP type II apparatus Rotating paddle type) at rotation speed of 50 rpm in distilled water as a dissolution media at  $37^{\circ}\text{C}$  was used for in vitro drug release studies. One capsule was used in each test, accurately weighed amount of liquisolid compacts was filled in capsule and immersed in dissolution medium consisting of 900 ml of phosphate buffer 7.4 at  $37^{\circ}\text{C}$ . An aliquots 5ml from dissolution medium was withdrawn at specified times intervals (5,10,15,30,45,60 minutes) and replacing the same amount with the fresh medium in order to keep the total volume constant. The sample was filtered through whattman filter paper and assayed by measuring the absorbance at 288 nm using the UV-visible spectrophotometer<sup>14</sup>. The in vitro release of various formulations are shown in fig 10,11,12.

## IV. Result and Discussion

### 4.1. UV Spectroscopy

Peaks were obtained at 288 and 278 which shows that drug is pure.



**Fig.1. Lamda max of etoricoxib**

### 4.2. Melting point:

The melting point of drug sample was determined by using melting point apparatus. The melting point was found between the range of 136 -138<sup>0</sup>C. As given in the refrence. The melting point of drug sample is shown in table 1,

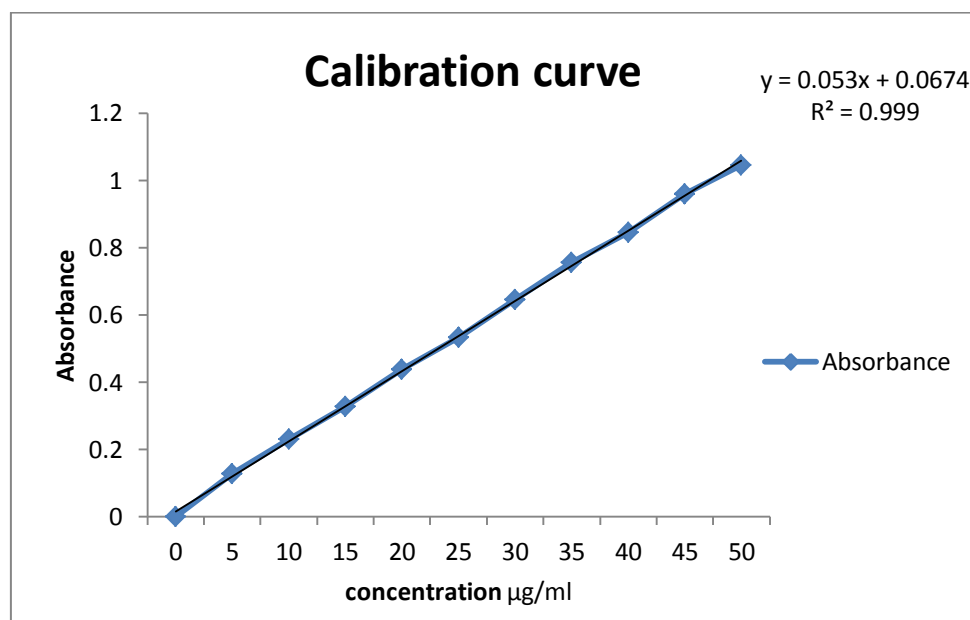
**Table 1: Melting Point of Etoricoxib**

Drug	Observed	Reference
Etoricoxib	136-138 <sup>0</sup> C	134 <sup>0</sup> -138 <sup>0</sup> C



### 4.3. Standard curve of etoricoxib

The UV spectrum of the drug in the range of 200-400 nm on UV visible spectrophotometer revealed that wavelength of maximum absorption of etoricoxib was 288 nm. From the graph of absorbance vs. Concentration for pure etoricoxib it was observed that the drug obeys Beer's Lambert law in concentration range of 5 to 50  $\mu\text{g/ml}$  ( $R^2=0.999$ ) at 288 nm.( Fig4.)



**Fig. 4. Calibration curve of Etoricoxib in phosphate buffer 7.4.**

### 4.4. Solubility studies

Quantitative solubility analysis of etoricoxib determined in different solvents and the results were illustrated in table. The etoricoxib drug was found to be more soluble in ethanol, phosphate buffer and PEG 400. The solubility of etoricoxib in various solvents are shown in table 2.

**Table.2 : solubility of etoricoxib in various solvents**

S.no	Solvents	Solubility mg/ml
1.	Water	0.033
2.	Ethanol	0.127
3.	Phosphate buffer 7.4	0.119
4.	Hcl	0.095
5.	PEG 400	0.126
6.	Chloroform	0.093

#### 4.5. Bulk characterization and flow properties of liquisolid compact systems

The bulk density of various formulations were found to be between 0.360-0.410, tapped density between 0.413-0.460, Hausner's ratio between 1.12- 1.15, carr's index between 11.01- 14.01. Which shows the good compressibility index of formulations. The angle of repose was found to be between 25.4<sup>0</sup>-28.9<sup>0</sup>C, which shows the excellent flow properties of formulation. Results of measurements such as Tapped density, Angle of repose, carr's index, Hausner's ratio are presented in the table 3.

**Table.3. Bulk Characterisation of formulations:**

Formulations	Bulk density(g/cm <sup>3</sup> )	Tapped density(g/cm <sup>3</sup> )	Hausner's ratio	Carr's ratio%	Angle of repose
F1	0.360	0.418	1.16	14.01	25.4 <sup>0</sup>
F2	0.363	0.413	1.14	13.02	30.06 <sup>0</sup>
F3	0.400	0.459	1.14	14.01	26.30 <sup>0</sup>
F4	0.390	0.443	1.13	12.01	26.95 <sup>0</sup>

F5	0.390	0.450	1.15	12.10	28.90 <sup>0</sup>
F6	0.410	0.460	1.12	11.10	27.60 <sup>0</sup>

#### 4.6. Determination of saturation solubility

Saturation solubility studies were carried out for pure drug, as well as for prepared liquisolid compacts. From the result of saturation solubility studies it was observed that there was increase in solubility of drug in liquisolid compact system as compared to pure drug. With increase in the concentration of carriers solubility of drug increased and the liquisolid compacts containing microcrystalline cellulose and sodium starch glycolate in (F4) and (F5) has increased the solubility up to five times.

This improves its wettability resulting in a significant increase in solubility. The saturation solubility of liquisolid system is shown in fig 4.

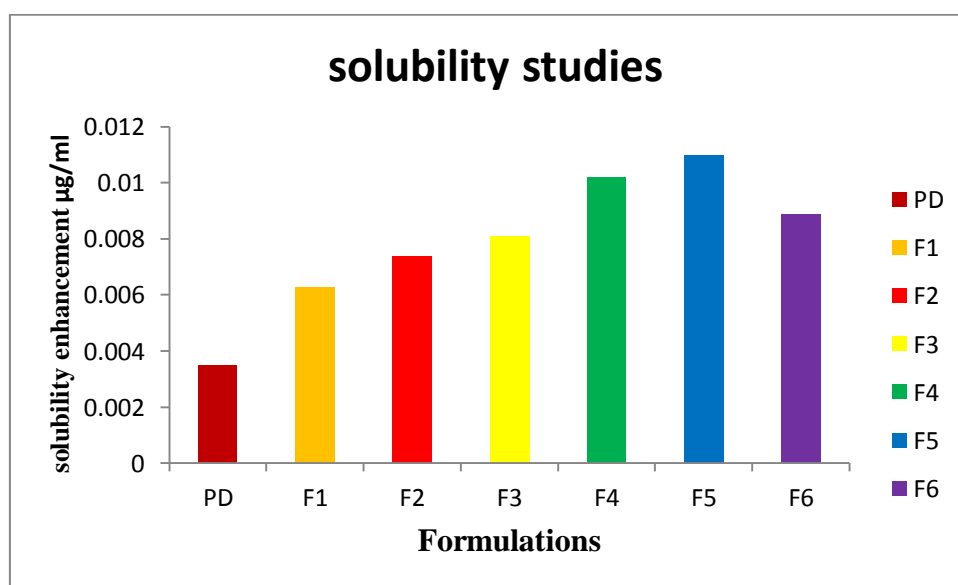


Fig. 5. - Compared of solubility of pure drug with formulation F1 toF6.

#### 4.7. Drug content of liquisolid systems

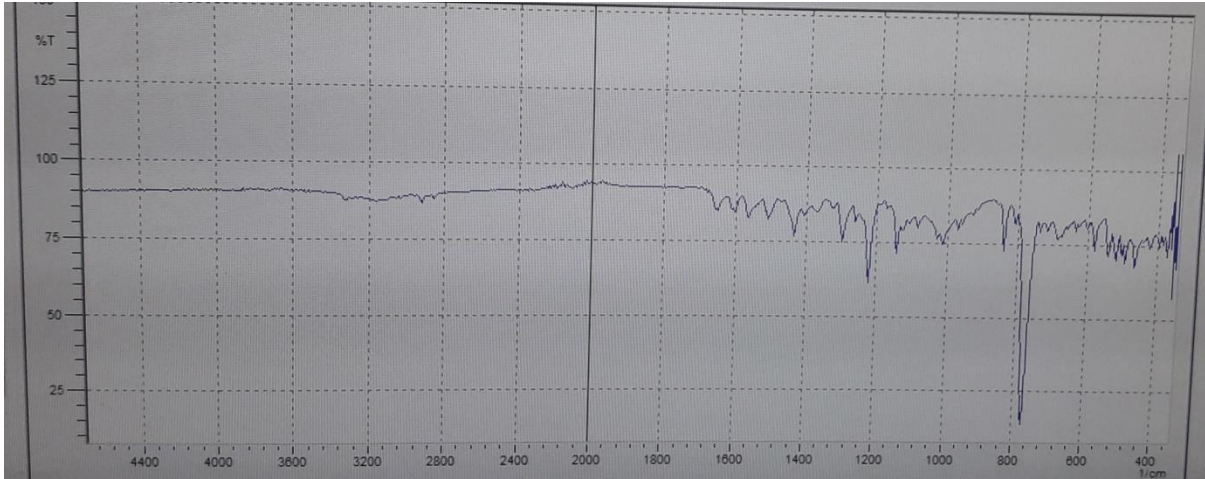
The drug content estimation was performed to ensure uniform distribution of drug. The drug content of liquisolid compact of etoricoxib was performed for all the prepared formulations. The result indicates that the drug content in all the formulations was found uniform between 88% to 96% which was analysed spectrophotometrically at  $\lambda_{max}$  288nm. The drug content of various formulations are shown in table 4.

**Table.4. Drug content of various formulation.**

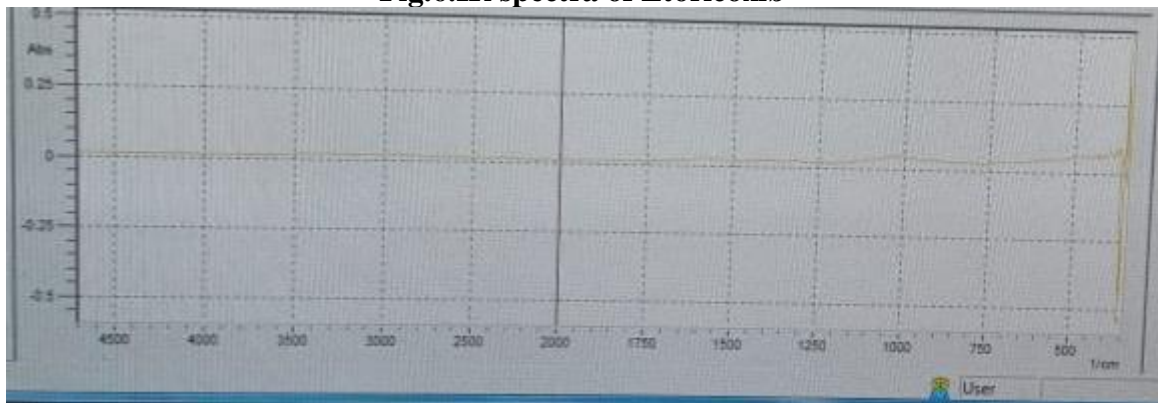
S.NO	Formulation Code	% Drug content
1.	F1	88%
2.	F2	90%
3.	F3	88%
4.	F4	94%
5.	F5	96%
6.	F6	92%

#### 4.8. Fourier transform infrared(FTIR) spectroscopy:

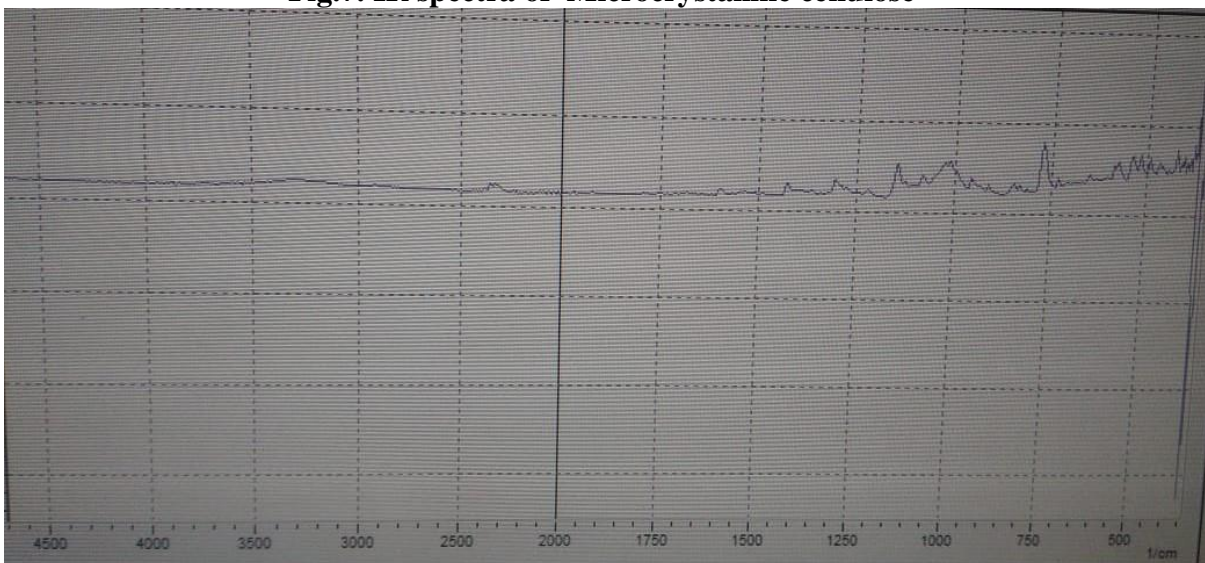
The IR spectra of Etoricoxib ,Carrier and formulation are given in the figures. The spectrum of pure Etoricoxib presented characteristic signals at 1600.1, 1402.2, 1400.3, 1400,1300, 1090.5, 100.2, 900, 889.2, 800.1, 750.1, 655.2, 600, 595.2, 545.2, 400 $cm^{-1}$ . and the spectrum of carrier was presented characteristic signals at 500, ,1050.1, 1058.81, 1650, 3000  $cm^{-1}$ .and the spectrum of liquisolid compact system was presented characteristic signals at at 1365.1, 1350.2, 1055.4,545.3, 500.1 $cm^{-1}$ .The results suggested that there was no interaction of between Etoricoxib and excipients. The IR Spectra of pure drug, carrier and formulations are shown in fig 6,7,8.



**Fig.6.IR spectra of Etoricoxib**



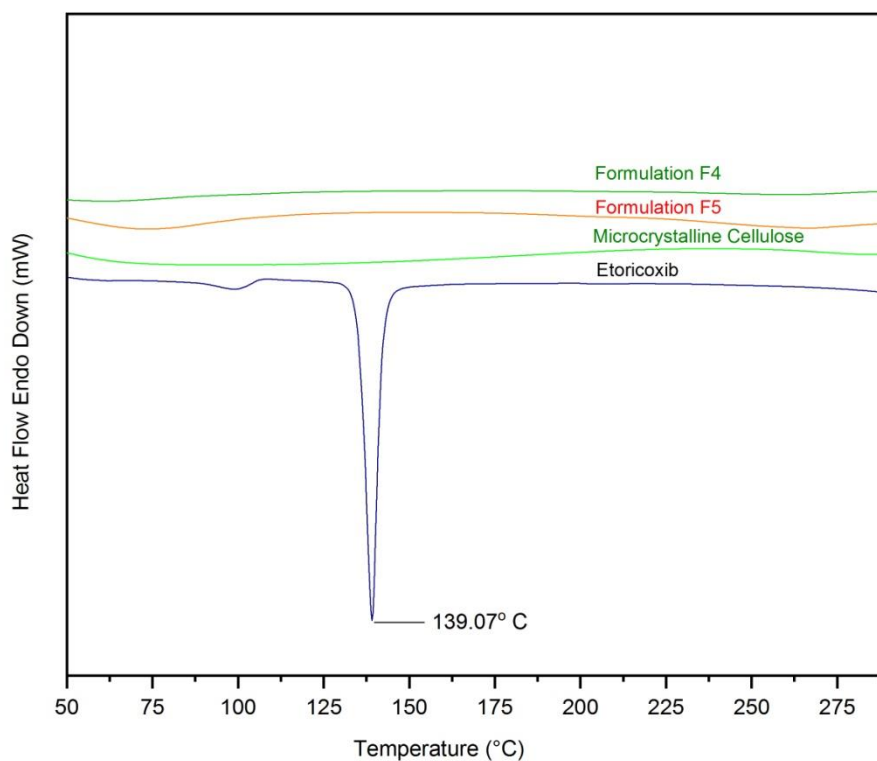
**Fig.7. IR spectra of Microcrystalline cellulose**



**Fig.8. IR spectra of liquisolid formulation(F5)**

#### 4.9. Differential Scanning Calorimeter (DSC):-

The DSC studies were performed to understand the nature of drug in formulation. The thermograms for pure Etoricoxib, carrier, and liquisolid formulations were presented in figure 8. The pure drug showed a melting endothermic peak at 139.07°C., Whereas thermograms of optimized formulations did not show any significant shifts in endothermic peaks. The disappearance of characteristic peaks of etoricoxib, correspond with formulation of drug solution in physical mixture due to the fact that drug is in a dissolved molecular state. Such disappearance of drug peak upon the formulation of liquisolid system indicates that there is no interaction between the drug and excipients, The DSC graph of pure drug, carrier and F2, F5 batches are shown in fig 9.



**Fig.9.DSC of pure drug, carrier and liquisolid formulations**

#### 4.10. In vitro drug release studies:-

The in vitro drug release profile of pure drug Etoricoxib, Liquisolid compacts in dissolution medium are shown in figure (9, 10, 11) Liquisolid compacts of Etoricoxib showed a significant increase in the drug release as compared with pure Etoricoxib. In the liquisolid formulations F1 and F2 showing 90.9% and 95.2% drug release, F3 and F4 showing 85.2% and 96.6% drug release, and F5 and F6 showing 97.2% and 85.3% drug release respectively. All the formulation showed improved drug release rate as compared to pure Etoricoxib. The in vitro release of various formulations are shown in fig 10,11,12.

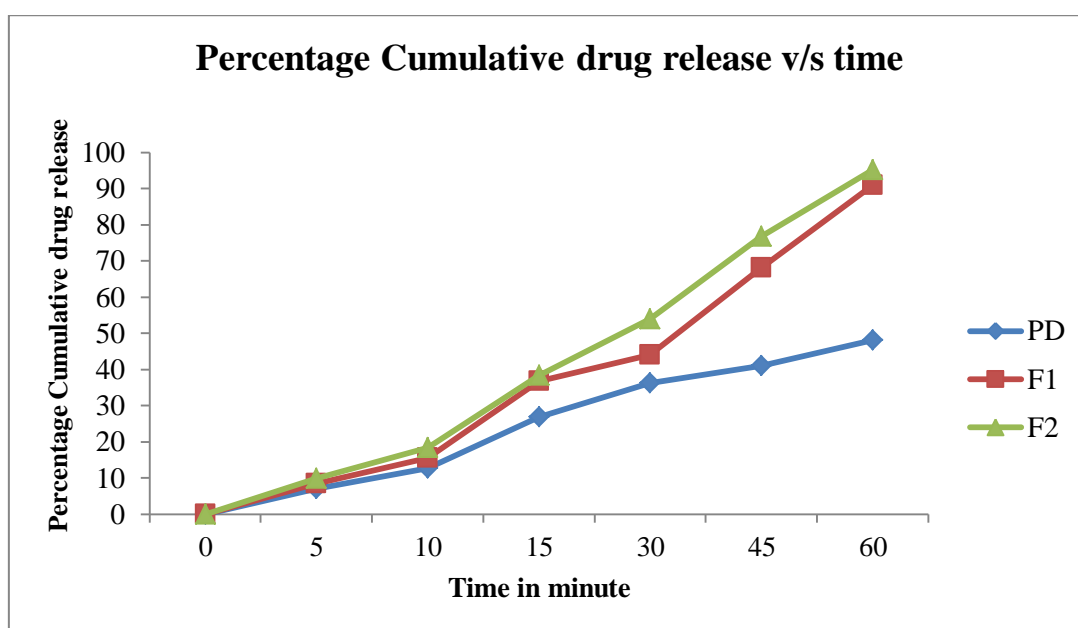


Fig. 10. Comparison of drug release profile of pure Etoricoxib & F1, F2 Batches

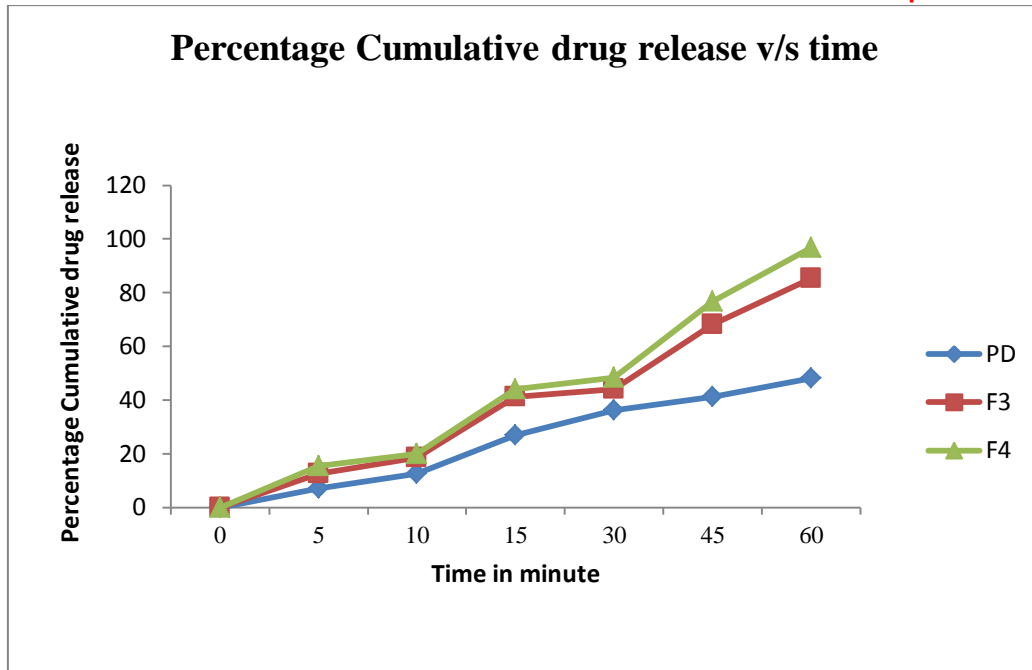


Fig.11. Comparison of drug release profile of pure Etoricoxib & F3,F4 Batches

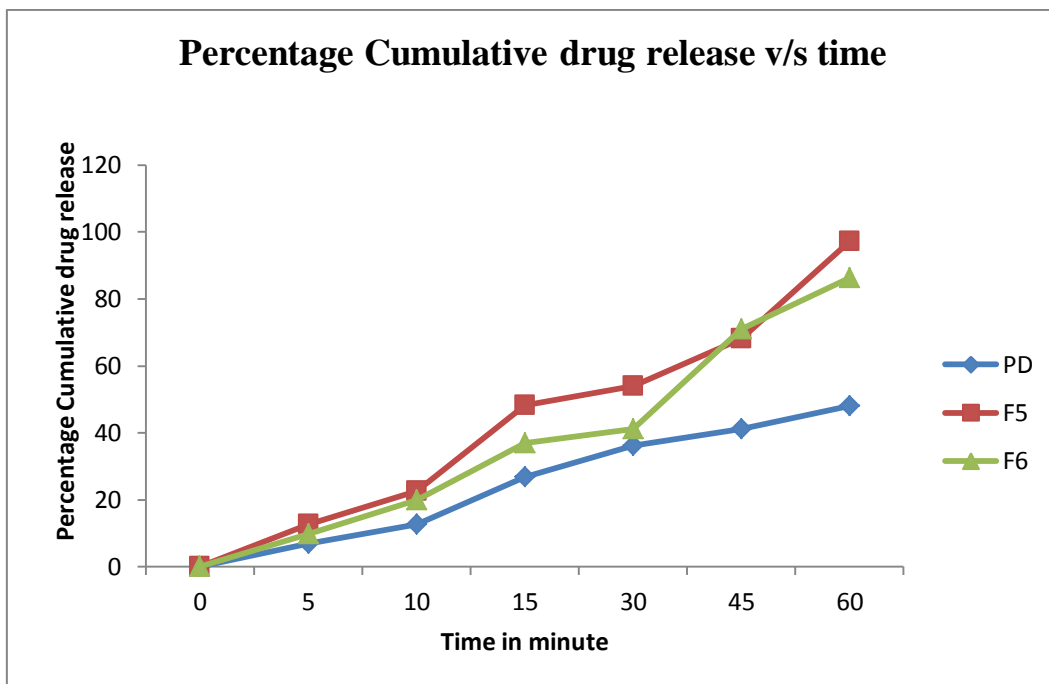


Fig.12. Comparison of drug release profile of pure Etoricoxib & F5,F6 Batches





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## Conclusion

The observations showed that there was a poor drug release in case of conventional formulation. Improvement of aqueous solubility in such case is valuable goal to improve therapeutic efficiency. Thus liquisolid compacts of etoricoxib were formulated by using liquisolid technique showed better enhancement in drug release rate and solubility of drug.

From the invitro drug release studies the optimized formulation f-5 showed fast drug release when compared to pure drug. The formulation(F5) showing 97.2 % drug release. In conclusion, the liquisolid compacts technique can be promising alternative for the formulation of water – insoluble drugs.

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