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FORMULATION AND EVALUATION OF LIQUISOLID COMPACTS OF ETODOLAC

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ABSTRACT

In the present study, liquisolid compact technique is analyzed as a tool for enhanced dissolution of poorly water-soluble drug Etodolac. Etodolac is a pyranocarboxlyic acid and NSAID with anti-pyretic and anti-analgesic activities. Etodolac liquisolid compact formulations (6) were prepared by using Polyethylene glycol 400, Propylene glycol as solvents, microcrystalline cellulose, and hydroxypropyl methyl cellulose as carrier materials and aerosol as a coating material in different ratios. The prepared liquisolid compacts were evaluated for their pre-compression properties and out of 6 formulations F5 formulation was taken as optimized formulation based on fast dissolving property. The optimized formulation was punched into tablets by adding the excipients and the tablets were assigned for post-compression properties, drug-excipient interactions by Fourier Transform Infrared spectra (FTIR), X-Ray Diffraction (XRD). Liquisolid compacts containing Propylene Glycol (PG) as solvent produced higher dissolution rates in comparison with Polyethylene Glycol (PEG) of the same concentration. As liquisolid compacts illustrated significantly higher drug release rates, we conclude that it could be a promising favorable strategy in improving the dissolution of poorly water-soluble drugs.

KEYWORDS: Etodolac, NSAID, liquisolid compacts, carrier material, drug-excipient interactions.

1. INTRODUCTION

The active pharmaceutical ingredient in a solid dosage form should undergo dissolution before it is available for absorption from the gastrointestinal tract. A drug's solubility behavior is one of the most important determinants of dissolution and oral bioavailability. Over the few years, the number of poorly soluble drug candidates has increased enormously. The ability of such water-insoluble medicines to dissolve is a big barrier in the design of pharmacological dosage formulations. Several new chemical entities are not available to the general public due to poor oral bioavailability due to the poor dissolution.[1] For drugs belonging to the Bio-pharmaceutical classification system (BCS), class II (poor water solubility and high permeability) dissolution rate is often the rate-determining step and determines the rate and degree of absorption. Due to its convenience, good patient compliance, and low production cost, the oral route of drug administration remains the most favored route of drug administration. Drug absorption is frequently controlled by dissolution in the gastrointestinal system.[2] But the poor dissolution rate of water-insoluble drugs is a huge problem for pharmaceutical formulators to prepare in the form of tablets.[3] [4]

There are several methods to enhance the dissolution of poorly soluble drugs like the use of water-soluble salts and polymorphic forms, reducing particle size by increasing surface area, formation of water-soluble molecular complexes, solid dispersion, co-precipitation, lyophilization, microencapsulation, the inclusion of drug solutions or liquid drugs into soft gelatin capsules, solubilization in a surfactant system and manipulation of solid-state of the drug[5][6][7], For the past few years, pharmaceutical scientists have been working on the development of liquisolid compacts to increase the rate of dissolution of poorly soluble drugs, thereby improving drug efficacy.[8][9]

"Liquisolid compact technique" has proven to be an effective strategy for increasing the solubility and dissolution of poorly water-soluble drugs, as well as their bioavailability.[10]

Liquisolid technology is a method of converting a liquid into a free-flowing, easily compressible, and ostensibly dry powder through simple physical blending with a carrier and coating, thus enhancing the dissolution properties of the drug as defined by Spireas.[11] It is used to convert liquid medications into solid systems. The compounds with high porous surface and absorption properties such as cellulose derivatives, starch, lactose, and hydroxypropyl methylcellulose can be used as carrier and Aerosil can be used as coat material.[12] The prepared liquisolid compacts were evaluated for their pre-compression properties and out of 6 formulations F5 formulation was taken as optimized formulation based on

fast dissolving property. The optimized formulation was punched into tablets by adding the excipients and the tablets were assigned. Post compaction parameters such as weight variation, hardness, drug content uniformity, percentage friability, and disintegration time were examined for the prepared liquisolid tablets. In dissolution media, the in-vitro release characteristics of the medication from tablets formulated using direct compression and liquisolid techniques were examined. X-Ray Diffraction (XRD) and Fourier-Transform infrared spectroscopy (FT-IR) were performed.[13]

Etodolac is an anti-inflammatory, analgesic, and antipyretic NSAID that reduces prostaglandin production in the host by selectively inhibiting cyclooxygenase (COX)-2. Etodolac long-term therapy is mainly used to treat osteoarthritis, and rheumatoid arthritis and ankylosing spondylitis.[14] Short-term therapy is used in acute pain.[15] Also effective in post-operative pain management in oral surgery models.[16] [17]

2. MATERIALS AND METHODS

2.1 Materials

Etodolac was gifted samples by Hetero pharmaceuticals, Hyderabad, India. Microcrystalline Cellulose, Hydroxy Propyl Methyl Cellulose, PEG-400, Propylene Glycol, Aerosil were provided by SD Fine Laboratories, Hyderabad, India.

2.2 Formulation of Etodolac liquisolid compacts

The liquisolid compacts of Etodolac are prepared by selecting a non-volatile solvent for dissolving the drug. PEG 400 and Propylene glycol as liquid medicaments, HPMC and MCC as a carrier, and Aerosil as the coating material are selected for the preparation of Etodolac liquisolid compacts. Various ratios of carriers and liquid medicaments are selected. The desired amount of drug and liquid medicament were weighed and taken in a mortar and pestle and stirred continuously, until a homogenous drug solution was obtained. The selected amount of carrier and coating material was added as shown in table 1 and dried. Finally, a liquisolid compact formulation was prepared by adding the excipients.[18]

Table 1: Composition of different liquisolid compact formulations.

Formulation Code	Drug(mg) ETODOLAC	PEG (ml)	Propylene Glycol (ml)	HPMC (mg)	MCC (mg)	Aerosil (mg)
F1	300	300	0	0	400	80
F2	300	0	300	0	400	80
F3	300	300	0	400	0	80
F4	300	0	300	400	0	80
F5	300	0	600	400	0	80
F6	300	0	600	0	400	80

2.3 Evaluation of Etodolac liquisolid compacts

2.3.1. Micrometric properties[19]

2.3.1.1. Angle of repose

Angle of repose (θ) of liquisolid compacts measures the resistance to particles flow, and is calculated according to fixed funnel standing cone method. Where, (θ) is angle of repose, H/D is surface area of the free standing height of the microspheres heap that is formed on a graph paper after making liquisolid compacts.

$\theta = \tan^{-1}(h/r)$

2.3.1.2. Bulk density

Bulk density of formulated liquisolid compacts was determined by taking a known mass of Etodolac liquisolid compacts in a 5ml graduated measuring cylinder. The cylinder was dropped three times at a two-second interval from a height of one inch. The bulk density was calculated by following equation.

$$\text{Bulk Density} = \frac{\text{Weight of liquisolid compacts}}{\text{Bulk volume of liquisolid compacts}}$$

2.3.1.3. Tapped density

The volume of powder determined by tapping using a measuring cylinder carrying a weighed amount of sample is characterized as tapped density. Tapped density of liquisolid compacts was calculated by following equation.

$$\text{Tapped Density} = \frac{\text{Weight of liquisolid compacts}}{\text{Tapped volume of liquisolid compacts}}$$

2.3.1.4. Compressibility Index

Also called as Carr's index and is measured according to the following equation.

$$\text{Carr's Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

2.3.1.5. Hausner's ratio

Hausner's ratio is determined by comparing the tapped density to the bulk density using the equation:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \times 100$$

Table 2: Characterization of Powder Mixtures.

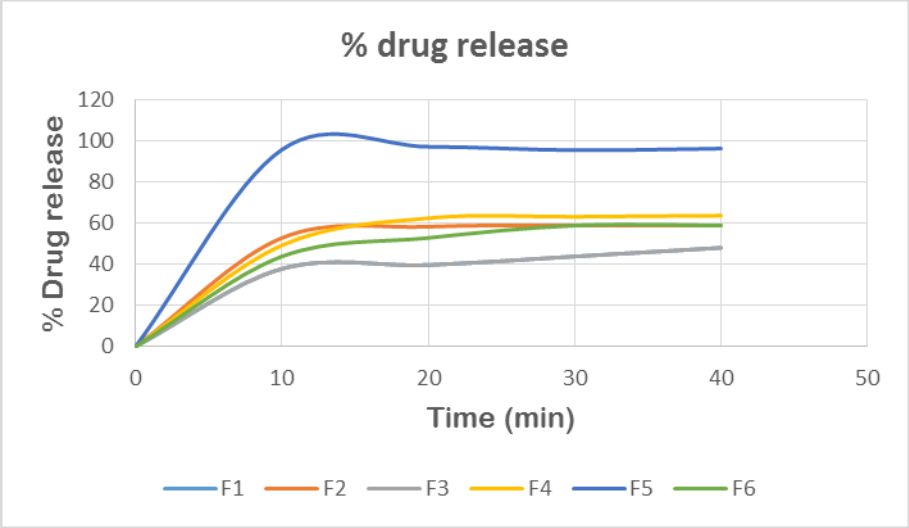
Formulation	Angle of repose(^{0})	Bulk density (g//cc)	Tapped density(g/cc)	Compressibility index (%)	Hausner's ratio
F1	27	0.49	0.48	19	0.98
F2	26.6	0.37	0.40	18	0.79
F3	28	0.46	0.49	17.7	0.9
F4	28.1	0.32	0.37	19.5	1.02
F5	20	0.25	0.29	16.1	1.47
F6	27.8	0.41	0.43	20.2	1.16

2.3.2. Invitro drug release study[20]

Invitro drug release studies of liquisolid compacts were carried out in 900ml of Phosphate buffer (pH 6.8) dissolving media at 100rpm and 37^{0}C using a USP class I dissolution device. 5ml of the sample was taken at each interval and replaced with equal volumes of fresh dissolving medium on each time. At 226nm, the sample was examined using a UV Spectrophotometer.

Table 3: Invitro % drug release.

Time (min)		% drug	Release			
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
10	37.8	52.8	37.8	49.2	95.7	43.8
20	39.6	58.2	39.6	62.4	97.1	52.8
30	43.8	58.8	43.8	63.1	95.4	58.81
40	48	58.8	48	63.6	96.2	58.8



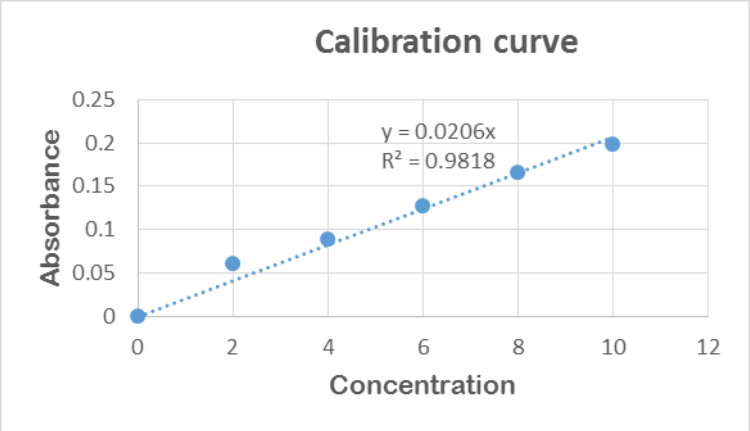
Graph-1: Dissolution profile comparison of all Etodolac liquisolid compacts.

2.3.3. Development of calibration curve

The calibration curve for Etodolac liquisolid compact was prepared in Phosphate buffer pH 6.8.

Table 4: Standard calibration curve of Etodolac liquisolid compacts.

Concentration(µg/ml)	Absorbance at 226nm
0	0
2	0.060
4	0.89
6	0.127
8	0.165
10	0.198



Graph-2: Calibration curve.

2.3.4. Selection of optimized formulation

Liquisolid compacts were prepared to improve the solubility of poorly soluble drug. So, 5 formulations were prepared. Among those 6 formulations, F5 formulation was released fast and has good solubility property. Thus that powder was taken as optimized formulation and mixed with the excipients such as CCS, Sodium saccharin, microcrystalline cellulose, Lactose, Magnesium stearate and Talc were added and punched as tablet. The optimized formulation tablets were subjected for post formulation studies.

2.3.4. Post formulation studies[21]

2.3.4.1. Thickness

The tablet thickness was calculated using Vernier calipers. It is expressed as mm.

2.3.4.2. Hardness

The hardness of the formulated tablets was estimated using Monsanto hardness tester. Three tablets were selected and force is applied diametrically. It is expressed in kg/cm^2.

2.3.4.3. Weight variation test

For the weight variation test, 20 tablets were individually weighed, the average weight was calculated, and the individual tablet weights were compared to the average. The percentage weight deviation was calculated and then compared with IP limits, it passes the weight variation test.

2.3.4.4. Friability

Roche friabilator was used for testing the friability of the prepared liquisolid compact tablets. In the friabilator, a pre-weighed sample (Wi) of tablets was placed and subjected to 100 rotations. In the friabilator, a pre-weighed sample (Wi) of tablets was placed and subjected to 100 rotations. Tablets were then reweighed (Wf) after being dedusted using a delicate muslin towel. The formula for friability (F) is as follows:

$F = (W_i - W_f) / W_i \times 100$

2.3.4.5. Drug content

Five tablets were weighed and powdered using a mortar and pestle. Accurately weighed 100mg of powder was taken into 50ml volumetric flask, dissolved in 50ml methanol and the solution was filtered through whatmann filter paper. 0.1ml of the filtrate was collected and diluted with 25ml of methanol and filter to remove the dust particulates. The drug content was determined at 236nm by UV – spectrophotometer.

2.3.5.6. Disintegration time

The disintegration time of the tablets was determined as per IP. The test was carried out using disintegration apparatus. 900ml distilled water was used as disintegrating media at 37±0.2^{o}C. Time required for complete disintegration of all the tablets were noted.

2.3.6.7. Wetting time and water absorption ratio

Individual tablet weights (Wa) were recorded and carefully placed on the surface of a double-folded piece of tissue paper in a 5cm diameter petriplate containing 6ml of water. Time taken for complete wetting was noted and recorded as the wetting time. Reweigh (Wb) the tablet. The following equation was used to calculate the water absorption ratio (R) with the tablet.

$R = 100 X (Wb - Wa) / Wb$

2.3.7.8. Invitro drug release study

Dissolution studies of Etodolac liquisolid compact tablet was performed using USP dissolution apparatus. This study was performed in 900ml of potassium dihyrogen phosphate buffer solution. The temperature was maintained at 37±0.5^{o}C and stirring speed was 100rpm. Samples were withdrawn periodically and refilled with fresh buffer solution. Samples were filtered and analysed by UV spectrophotometer at 226nm.

3. RESULTS AND DISCUSSION

3.1. Physico-chemical properties

Thickness, Hardness, Weight variation test, Friability, Disintegration time were measured according to USP or IP guidelines. The results were tabulated in table-2. All the data obtained were within the limit.

Table 5: Physico-chemical properties of liquisolid compacts.

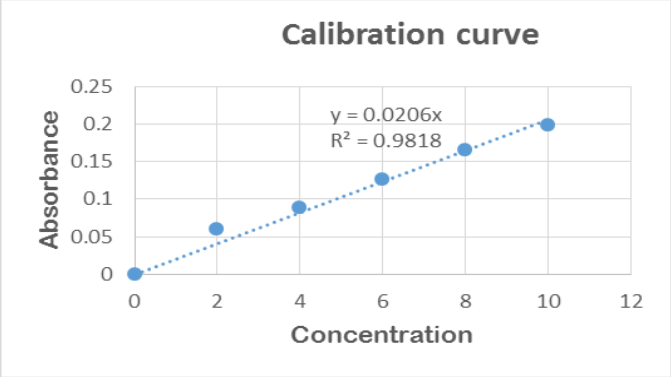
Formulation code	Thickness (mm)	Hardness (kg)	Weight variation	Friability (%)	Drug content	Disintegration time (sec)	Wetting time (sec)	Water absorption ratio
F5	3.04	2	Pass	0.754	99.6	15	10	55

3.2. UV Absorbance Studies

The absorbance of Etodolac at various concentrations was determined using UV Spectrophotometer. Based on the data obtained a standard calibration curve was drawn.

Table 6: Standard calibration curve.

Concentration(µg/ml)	Absorbance at 226nm
0	0
2	0.060
4	0.89
6	0.127
8	0.165
10	0.198

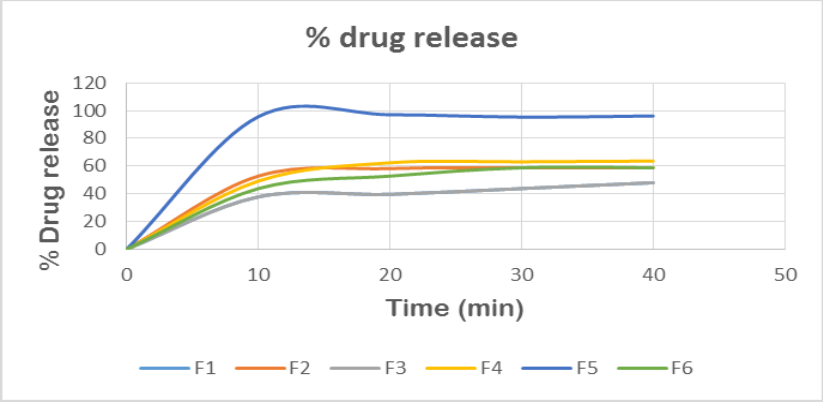


Graph-3: Calibration curve.

3.3 % Drug release

Table 7: % drug release.

Time (min)		% drug	release			
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
10	37.8	52.8	37.8	49.2	95.7	43.8
20	39.6	58.2	39.6	62.4	97.1	52.8
30	43.8	58.8	43.8	63.1	95.4	58.81
40	48	58.8	48	63.6	96.2	58.8



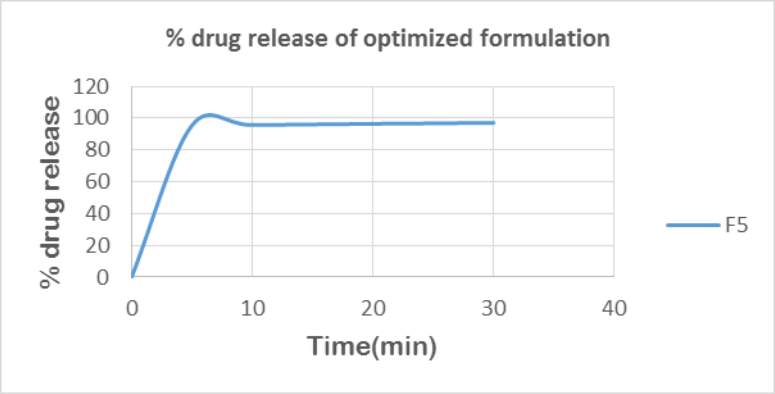
Graph-4: Dissolution profile comparison of all Etodolac liquisolid compacts.

3.4. Dissolution of Etodolac liquisolid compact tablet of optimized formulation

Dissolution of optimized formulation if Etodolac liquisolid compact tablets was performed at various time intervals.

Table 8: Dissolution of optimized formulation.

Time(min)	%drug release
0	0
5	95.4
10	95.7
20	96.5
30	97.1



Graph-5: Dissolution of optimised formulation.

3.5. FTIR (Fourier Transform Infrared Spectroscopy)

The FTIR spectrum of the pure Etodolac had shown characteristic peaks at 3206.83, 2912.17, 1746.73 and 1201.74 cm^{-1}, indicating N-H group, C-H group, C=C bonding and C-O group stretching respectively.

The FTIR spectrum of propylene glycol shows peaks at 3313.70, 1376.26 cm^{-1}, indicating OH group stretching, C-H group stretching respectively.

The FTIR spectrum of HPMC shows peaks at 3566.66, 2903.12, 1456.76 and 1058.92 cm^{-1}, due to the presence of OH group stretching, C-H group, and vibration of OH and C-O group stretching respectively.

The FTIR spectrum of MCC shows peaks at 3427.23, 2881.95, 1160.76 cm^{-1} indicates that OH group stretching, $-CH_2$group stretching, C-O-C stretching respectively.

The FTIR spectrum of Aerosil shows peaks at 3538.08 and 1327.57 cm^{-1} due to presence of OH stretching and Si-O linkage respectively.

The FTIR spectrum of CCS shows peaks at 3674.57, 2958.47, 1748.11 cm^{-1} due to presence of OH group stretching, CH group and CO group stretching respectively.

The FTIR spectrum of Sodium saccharin shows peaks at 1628.48cm^{-1} due to C=O absorption, 1586.21cm^{-1} due to C-C benzene ring stretching, $-SO_2$-N stretching at 1255.43 and 970.44 cm^{-1}, carbonyl bending was appeared at 675.04 cm^{-1}.

The FTIR spectrum of Etodolac liquisolid compact powder shows characteristic peaks at 3325.43 cm^{-1} due to secondary N-H stretching and 1698.45 cm^{-1} due to C=O stretching.

Thus, in the optimized liquisolid formulation, all of the Etodolac's characteristic peaks were detected in their actual ranges, proving that there was no interaction between the Etodolac and other excipients.

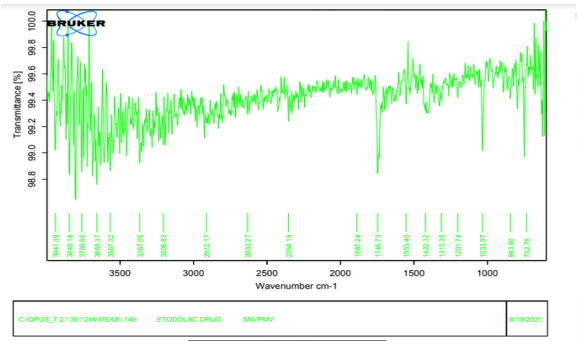


Figure-1: FTIR of Etodolac.

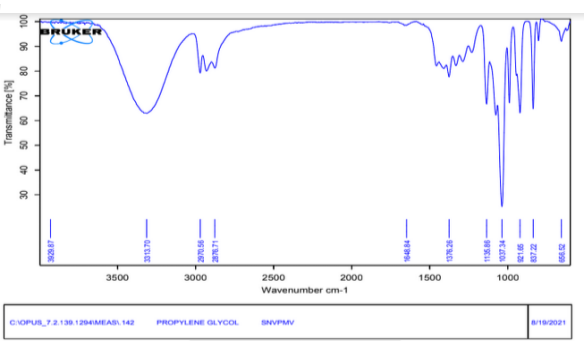


Figure-2: FTIR of Propylene glycol.

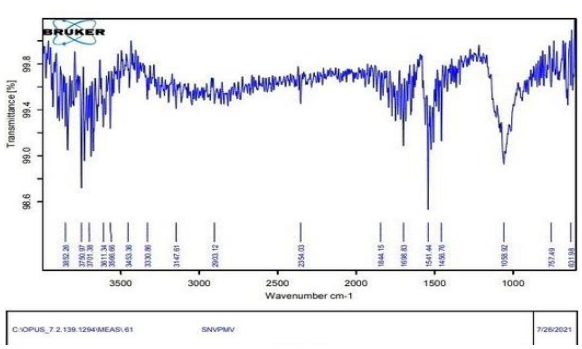


Figure-3: FTIR of HPMC.

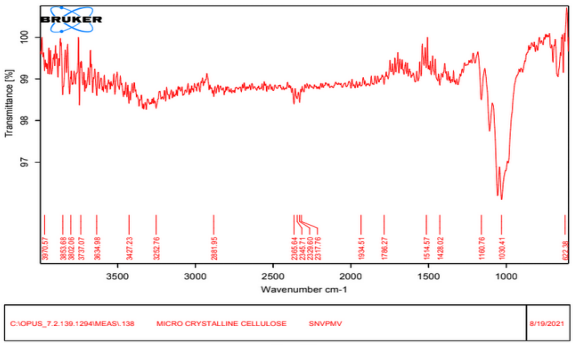


Figure-4: FTIR of MCC.

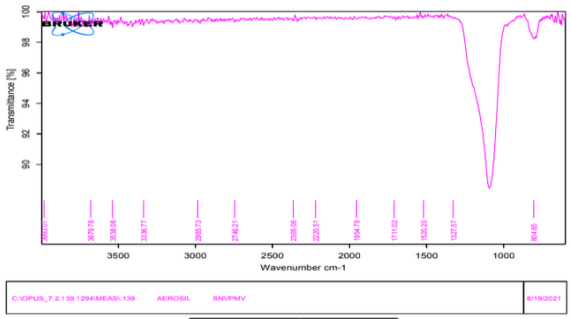


Figure-5: FTIR of Aerosil.

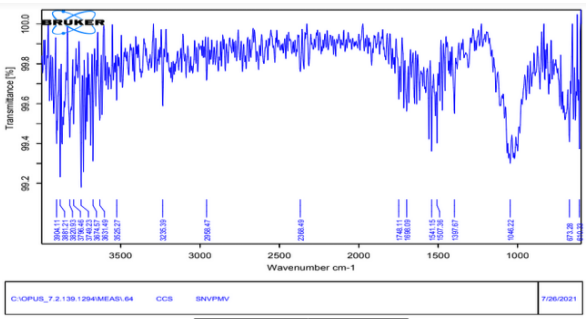


Figure-6: FTIR of CCS.

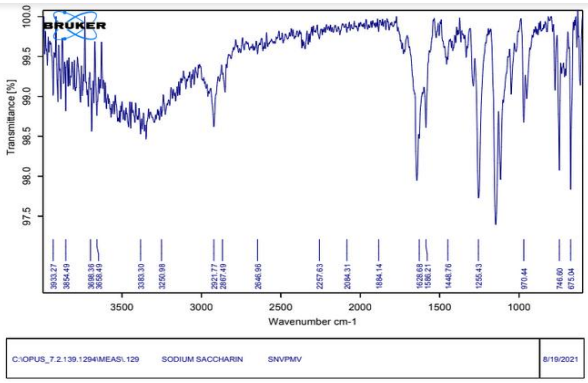


Figure-7: FTIR of Sodium Saccharin.

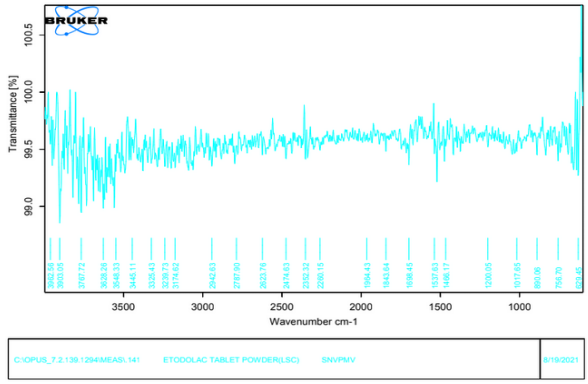


Figure-8: FTIR of Etodolac liquisolid compact.

4. X ray diffraction studies (XRD)

The XRD patterns of the Etodolac and liquisolid Etodolac compacts were shown in the figure-9, 10 respectively. The diffractograms of Etodolac proves that, the drug has crystalline structure. XRD diffraction patterns of liquisolid Etodolac compacts show the presence of characteristic peak of drug with minimized diffraction intensity, which shows manipulations in the crystallinity of drug with the optimized formulation. There was a decrease in the intensity of peak and decrease in the crystallinity of the drug, which was responsible for the increase solubility of the Etodolac drug by Liquisolid technique.

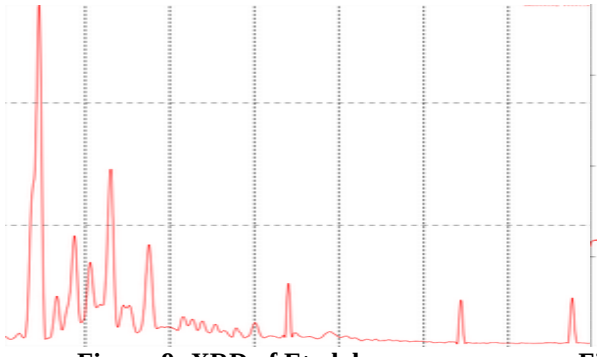


Figure-9: XRD of Etodolac.

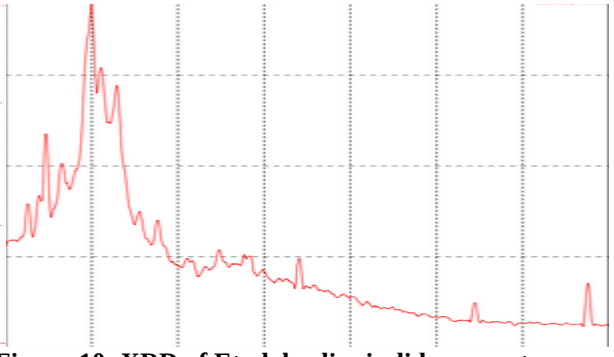


Figure-10: XRD of Etodolac liquisolid compact.

4. CONCLUSION

The study proved that the liquisolid technique was found to be a prospective approach for improving the dissolution of a poorly soluble drug like Etodolac, having high dose requirements and low water solubility. The dissolution of Etodolac was significantly increased in liquisolid formulation compared to marketed product. Among all the liquisolid formulations, F5 formulation was taken as optimized formulation, which showed fast drug release in in-vitro drug release studies. The flow properties of Etodolac liquisolid compacts showed an acceptable flow ability. The hardness, friability, weight variation, disintegration, wetting time and water absorption ratio were in the acceptable limits. XRD and FTIR spectra imply that there was no change in the crystalline state of the drug and no interactions between the drug and excipients. The higher dissolution rates exhibited by liquisolid compacts may also indicate enhanced oral bioavailability due to the increased wetting properties and increased surface area of the particles.

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