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SOLUBILITY ENHANCEMENT OF BCS CLASS II DRUGS

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ABSTRACT: One of the major barriers in the development of oral dosage form is poor solubility. Poor water solubility obstructs drug bioavailability and decreases its pharmaceutical development. Many drugs are in the pipeline to enhance solubility to formulate dosage form to be taken by the most preferred route of administration that is the oral route. Etodolac is nonsteroidal anti-inflammatory drug having a wide spectrum of activities but belongs to BCS class II. The attempt has been made in this work to improve solubility by forming ternary inclusion complexes of Etodolac with PVP K30 and β-Cyclodextrins. The ternary inclusion complexes were prepared by the physical mixing method and kneading method. The prepared complexes were analyzed by different analytical techniques comprising differential scanning calorimetry, infrared spectroscopy and solubility study. Special emphasis was given on the solubility evaluation of drugs and complexes. Based on observations and results, one can easily conclude about the usefulness of the complexation technique for the enhancement of solubility.

INTRODUCTION: Solubility, dissolution and gastrointestinal permeability are basic parameters that control the rate and extent of drug absorption and its bioavailability [1, 2]. The aqueous solubility of the drug plays an important role in drug absorption after oral administration [3, 4]. Inadequate aqueous solubility of active pharmaceutical ingredients is very challenging in the development process of new drug products [5].

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Near about 40% of drugs fail to reach the market because of their poor water solubility resulting in poor bioavailability [6]. Because of this reason, solubility is important to increase the therapeutic effectiveness, to attain maximum utility in newly developed drugs and also to obtain the desired concentration of the drug in systemic circulation [7].

The poorly water-soluble drug belongs to BCS class II. Dr. Gordon Amidon categorized this class as low solubility, high permeability candidate [8, 9]. When dissolution increases slightly, it produces a significant effect on bioavailability [10]. Various methods that enhance the solubility of poorly water-soluble drug include hydrotropic, complexation, solid dispersion, salt formation, emulsification, co-crystallization and nano-crystal

technologies [11]. Etodolac is 1, 8-Diethyl-1, 3, 4, 9-tetrahydropyrone (3, 4-b) indole -1-acetic acid and belongs to BCS class II; low solubility, high permeability. It is a nonsteroidal anti-inflammatory white or almost white crystalline powder practically insoluble in water and freely soluble in methanol, acetone, and chloroform, dose 200-500 mg daily [12]. It is a member of pyranocarboxylic acid class developed in the 1970s. Inclusion complexation is a more promising technique to enhance the solubility and bioavailability of poorly water-soluble drugs. Inclusion complex is the compounds having the characteristics structure of cavity in which one compound (host molecule) encircles another. The encircled compound is called as a guest compound, which is situated in the cavity of the host molecule without changing the structure of the host [13, 14].

Cyclodextrins (CD) are important for inclusion complex because they easily interact with a variety of molecular and ionic species. Cyclodextrins are a member of three eminent industrially produced, major cyclic oligosaccharides, and several rare ones. The three main cyclodextrins are crystalline in nature, homogeneous, and non-hygroscopic substance having a torus-like macro ring structure, composed of glucopyranose units [15, 16]. These are α, β, and γ cyclodextrins which are also called Schardinger's dextrins, having 6, 7 and 8 glucopyranose units [17, 18]. In pharmaceutical formulation, water-soluble polymers have been used for many years since they are chemically inert and form complexes with small molecules in aqueous solution [19].

Takeru Higuchi and coworkers examine interactions of various drugs with a number of water-soluble polymers like polyvinylpyrrolidone, polyethylene glycols and polypropylene glycols. The addition of a small amount of water-soluble polymer remarkably increases aqueous solubility [20]. The purpose of the present study was focused on the formation of ternary inclusion complexes of Etodolac with Beta cyclodextrins and PVP K 30. The physicochemical characteristic of the complexes was analyzed, including IR, DSC, and solubility study.

MATERIALS AND METHODS: The Etodolac API was kindly gifted by IPCA laboratories (Mumbai) in July 2019. PVP K 30 was received as a gift sample from Glenmark Pharmaceuticals Limited during December 2019; Beta-cyclodextrins was purchased from Modern Science Apparatus Pvt. Ltd. (Nashik) in December 2019.

Formation of Ternary Complex: The Ternary complex mainly consists of drug, water-soluble polymer, and CD; it increases drug solubilization compared to water-soluble polymer and CD individually. A Formulation containing drug: CD complexes with water-soluble polymer have proven to be capable of improving bioavailability [21]. In the presence of water, polymer facilitates the wet ability of particles, which accelerated dissolution rate [22]. It exhibits a synergistic effect between these components [23]. The Advantage of incorporating PVP K30 during the complexation of drugs with CD significantly increases the solubility and promotes the physicochemical properties of poorly water-soluble drugs [24, 25].

Determination of Solubility of Etodolac: The solubility of Etodolac in phosphate buffer and methanol was determined, and it was analyzed by UV-Visible spectrophotometer at 278 nm.

Percentage Yield: The Percentage yield of complexes of various combinations was calculated using the weight of the final product after drying with respect to the initial total weight of the drug and carrier used for the preparation of complexes.

Percent production yields were calculated as per the formula given below,

$$PY = WO / WT \times 100$$

PY: Product yield; WO: Practical mass (complexes); WT: Theoretical mass (carrier + drug).

Drug Content: About 10 mg drug equivalent of complexes (theoretical) were weighed accurately and transferred to 100 ml volumetric flask to which 20 ml methanol was added and sonicated for 15 min. The Final volume was made up with methanol to give 100 ppm stock solution. From this stock solution (100 µg/ml), 1 ml was withdrawn and further diluted up to 10 ml with methanol. This solution was used for the assay for drug content by UV spectrophotometer at 250 nm.

The Concentration of drug in stock solution was calculated by using the calibration curve and from which percent drug content was calculated,

$$\% \text{ Drug Content} = WA/WT \times 100$$

WA: actual drug content; WT: theoretical drug content.

Phase Solubility Study: Solubility study of Etodolac in distilled water was performed in the presence of Beta cyclodextrins and PVP K30. Known excess amount of drug (50 mg) alone and drug equivalent of inclusion complexes was accurately weighed and transferred to a flask containing 25 ml of distilled water. The flask was placed in a shaking incubator with temperature 25 °C, rotation 120 rpm, and 96 h. Aliquots from the flask were withdrawn and transferred to test tubes, and subjected to centrifugation at 2300 rpm for 10 min. From the supernatant, 1 ml of solution was removed and diluted up to 100 ml with distilled water to give 20 µg/ml, 10 µg/ml solution was prepared from this stock and analyzed by UV spectrophotometer.

Preparation of Inclusion Complexes: Ternary inclusion complexes include Etodolac: PVPK 30: Beta cyclodextrins (1:1:1 mol ratio) were prepared by the physical mixing method and kneading method.

Physical Mixing Method: The physical mixture of the ternary system was prepared by varying concentrations of PVP K30 and Beta cyclodextrins. Variation was made by keeping the drug constant and varying second accordingly **Table 1**. Sieving of this mixture was done by utilizing sieve no. 80.

Kneading Method: The Inclusion complex of Etodolac, PVP K30, and Beta cyclodextrins were prepared by the kneading method. In which distilled water was used to prepare drug: carrier complex in a mortar by grinding ingredients for half an hour.

After grinding, the wet mass was left to air dry at room temperature for 48 h with intermittent mixing and agitation. The complexes were made in different ratios concerning drugs and carriers **Table 1**.

TABLE1: FORMULATION OF INCLUSION COMPLEX OF ETODOLAC, PVP K30 AND BETA-CYCLODEXTRINS BY PHYSICAL MIXING METHOD AND KNEADING METHOD

Etodolac: PVP K30:β-Cyclodextrins*[1]			Etodolac: PVP K30:β-Cyclodextrins*[2]		
Physical Mixture →	Ratio	← Kneading Method	Physical Mixture →	Ratio	← Kneading Method
PM-1	1:1:1	KM-1	PM-6	1:1:1	KM-6
PM-2	1:2:1	KM-2	PM-7	1:1:2	KM-7
PM-3	1:3:1	KM-3	PM-8	1:1:3	KM-8
PM-4	1:4:1	KM-4	PM-9	1:1:4	KM-9
PM-5	1:5:1	KM-5	PM-10	1:1:5	KM-10

*1: Drug and β-CD are constant, *2: Drug and PVPK30 are constant

Characterization of Inclusion Complex:

Fourier Transform-Infrared Spectroscopy (FTIR): FTIR spectrophotometer (Shimadzu IR) is a valuable analytical tool used for the determination of FTIR spectra of pure components and different samples by the KBr disc method in the range of 4000-400 cm^{-1}.

Differential Scanning Calorimetry Studies (DSC): Differential scanning calorimetry is a widely used technique to detect the purity of a sample. DSC was used to record the thermograms. Samples (1-10 mg) were sealed in flat bottom aluminium pans. The scanning was performed in the range of 50-300 ºC at a heating rate of 10 ºC/min in nitrogen atmosphere Shimadzu-60 DSC.

RESULTS AND DISCUSSION:

Pre-formulation Study: Description: It is white, crystalline powder complying with the description that is found in the literature.

Melting Point: The melting point of the drug matches with the value found in the literature. The melting point of Etodolac is given in **Table 2**.

TABLE 2: MELTING POINT DETERMINATION

Drug	Literature	Practical
Etodolac	145-150 ºC	147ºC

Determination of λ_{max}: The Solution of Etodolac is prepared in phosphate buffer (pH7.4) and methanol and scanned between 200-400 nm **Fig. 1, 2** using UV spectrophotometer showed peaks at

two wavelengths 278 nm and 224 nm (phosphate buffer) and 280 nm and 226 nm (methanol).

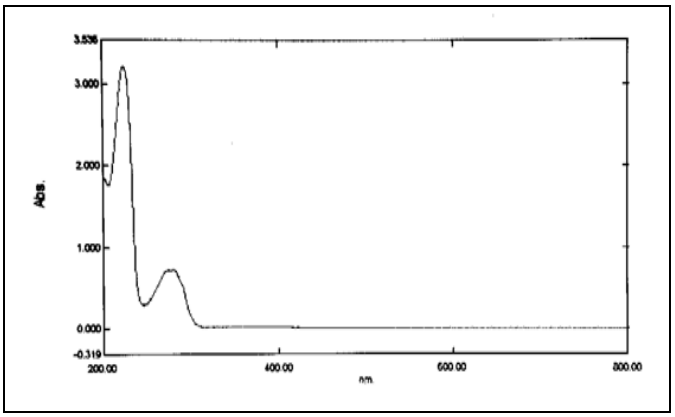

FIG. 1: UV SPECTRA OF ETODOLAC IN PHOSPHATE BUFFER (PH 7.4)

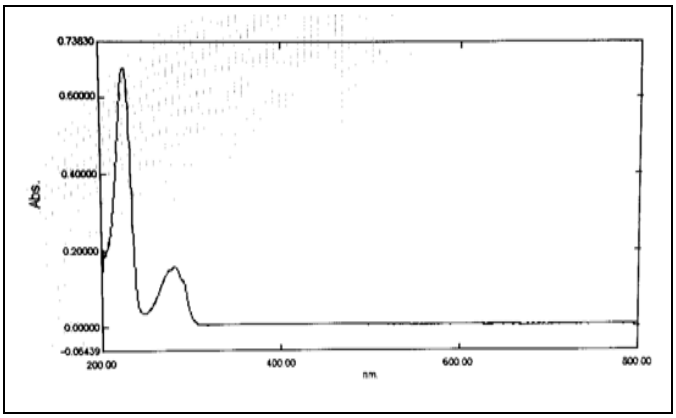

FIG. 2: UV SPECTRA OF ETODOLAC IN METHANOL

Calibration Curve of Etodolac: The Calibration curve of Etodolac was performed in phosphate buffer and methanol because it was soluble in both solvents. The calibration curve **Fig. 3** of Etodolac in phosphate buffer was found to be linear in the concentration range of 5-25 µg/ml **Table 3** having a coefficient of regression value R^2 = 0.999 and slope = 0.028.

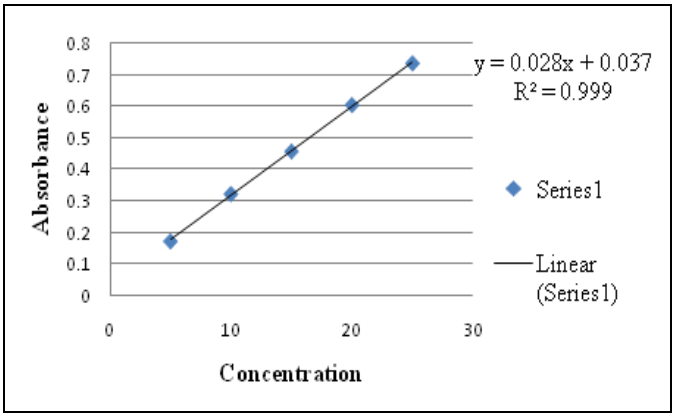

FIG. 3: CALIBRATION CURVE OF ETODOLAC IN PHOSPHATE BUFFER

TABLE 3: ABSORBANCE OF ETODOLAC IN PHOSHAPTE BUFFER (PH 7.4)

Sr. No.	Concentration	Absorbance
1	5	0.174
2	10	0.324
3	15	0.459
4	20	0.606
5	25	0.738

The calibration curve of Etodolac in methanol **Fig. 4** was found to be linear, in the concentration range of 5-30 µg/ml **Table 4** having a coefficient of regression value R^2 = 0.999 and slope = 0.032.

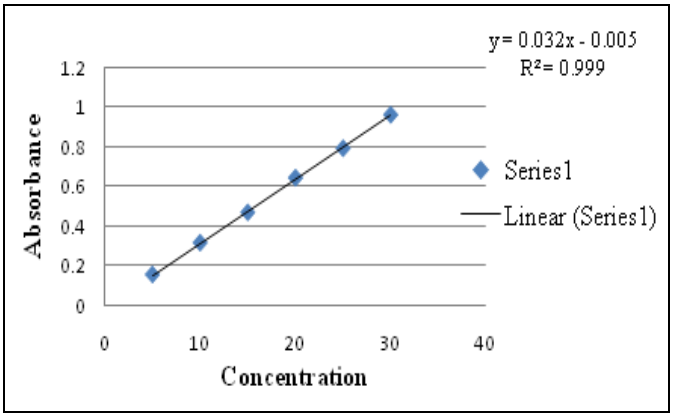

FIG. 4: CALIBRATION CURVE OF ETODOLAC IN METHANOL

TABLE 4: ABSORBANCE OF ETODOLAC IN METHANOL

S. no.	Absorbance	Concentration
1	5	0.157
2	10	0.318
3	15	0.471
4	20	0.646
5	25	0.795
6	30	0.964

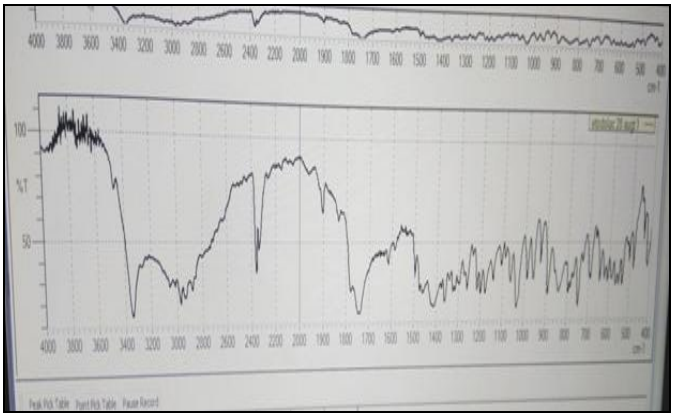

FIG. 5: FTIR SPECTRA OF ETODOLAC

FTIR Interpretation: The FTIR spectra of Etodolac showed the peaks at wavenumbers (cm^{-1}) which correspond to the functional groups present

in the structure of the drug. FTIR spectra of Etodolac are shown in **Fig. 5**.

TABLE 5: IDENTIFIED FUNCTIONAL GROUP PRESENT IN THE SPECTRA OF ETODOLAC

S. no.	Identified Functional group present in Etodolac	Observed value peak (cm^{-1})
1	N-H Stretch	3468.02
2	-OH	3342.64
3	C-H Stretch	2970.38
4	C-O Stretch	1741.72

Structural Formula of Etodolac: The FTIR spectrum of Etodolac exhibited characteristic signals shown in **Table 5**. The absorption bands shown by Etodolac are characteristic of the groups present in its molecular structure **Fig. 6**.

The presence of absorption bands corresponding to the functional groups present in the structure of Etodolac and the absence of any well-defined unaccountable peaks is a confirmation of the purity of the drug sample.

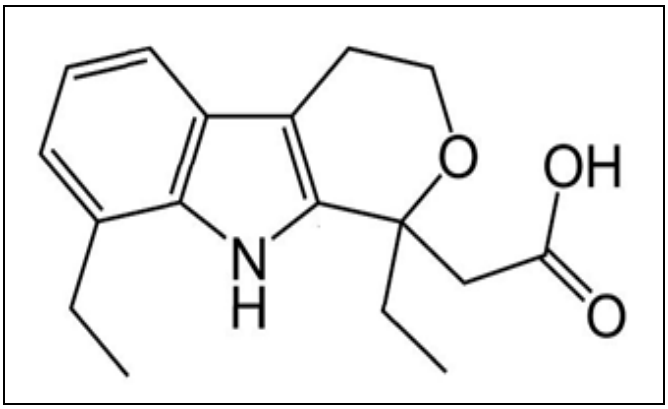

FIG. 6: STRUCTURE OF ETODOLAC

Differential Scanning Calorimetry (DSC): DSC was used to carry out thermal analysis of the drug. The DSC curve Etodolac shows a sharp endothermic peak at 151 ºC, corresponding to its melting and indicating its crystalline nature. The DSC Thermogram of plain Etodolac is given in **Fig. 7**.

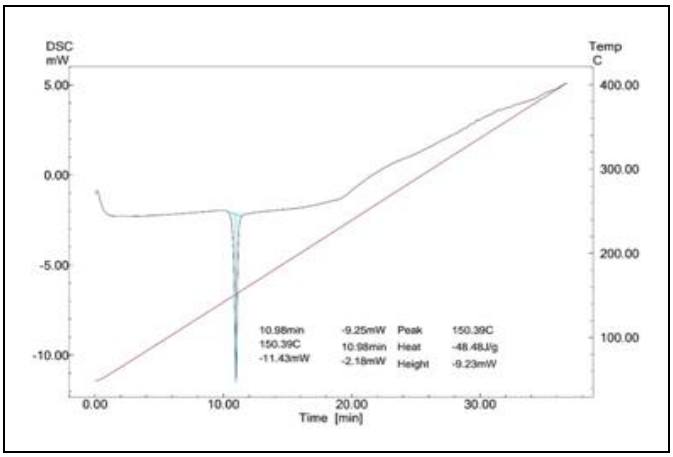

FIG. 7: DSC OF ETODOLAC

Characterization of Complexes: Prepared Complexes were evaluated for the following test

Percentage Yield: The Percentage yield of complex formed by the physical mixing method and Kneading method was found to be always in the range of 97 to 99%.

Loss in yield was due to the product remaining adhered to the walls of the evaporating dish or the mortar which could not be retrieved. The percentage yield of the different complexes is given in **Tables 6** and **7**.

A) Physical Mixture:

TABLE 6: PERCENTAGE YIELD OF TERNARY COMPLEX

S. no.	Drug carrier ratio	*1	Percentage yield (%)	*2	Percentage yield (%)
1	Eto: PVP K30: β-CD	1:1:1	97.65	1:1:1	97.62
2	Eto: PVP K30: β-CD	1:2:1	97.73	1:1:2	96.45
3	Eto: PVP K30: β-CD	1:3:1	98.12	1:1:3	97.65
4	Eto: PVP K30: β-CD	1:4:1	98.27	1:1:4	97.89
5	Eto: PVP K30: β-CD	1:5:1	98.35	1:1:5	97.23

B) Kneading Method:

TABLE 7: PERCENTAGE YIELD OF TERNARY COMPLEX

Sr. no.	Drug carrier ratio	*1	Percentage yield (%)	*2	Percentage yield (%)
1	Eto: PVP K30: β-CD	1:1:1	98.79	1:1:1	98.72
2	Eto: PVP K30: β-CD	1:2:1	98.92	1:1:2	97.56
3	Eto: PVP K30: β-CD	1:3:1	99.04	1:1:3	98.82
4	Eto: PVP K30: β-CD	1:4:1	98.27	1:1:4	97.89
5	Eto: PVP K30: β-CD	1:5:1	98.35	1:1:5	97.23

Drug Content: The drug content in all the tested combinations was found to be in the range of 98 to 100%, which is within the acceptable limit. The drug content of different combinations is given in **Tables 8** and **9**.

A) Physical Mixture:

TABLE 8: DRUG CONTENT OF TERNARY COMPLEX

S. no.	Drug carrier ratio	*1	Drug content (%)	*2	Drug content (%)
1	Eto: PVP K30: β-CD	1:1:1	98.19	1:1:1	98.12
2	Eto: PVP K30: β-CD	1:2:1	98.12	1:1:2	98.03
3	Eto: PVP K30: β-CD	1:3:1	98.25	1:1:3	97.69
4	Eto: PVP K30: β-CD	1:4:1	98.42	1:1:4	98.19
5	Eto: PVP K30: β-CD	1:5:1	99.42	1:1:5	98.32

B) Kneading Method:

TABLE 9: DRUG CONTENT OF TERNARY COMPLEX

Sr. no.	Drug carrier ratio	*1	Drug content (%)	*2	Drug content (%)
1	Eto: PVP K30: β-CD	1:1:1	99.92	1:1:1	99.82
2	Eto: PVP K30: β-CD	1:2:1	99.32	1:1:2	99.70
3	Eto: PVP K30: β-CD	1:3:1	99.72	1:1:3	98.84
4	Eto: PVP K30: β-CD	1:4:1	99.52	1:1:4	99.72
5	Eto: PVP K30: β-CD	1:5:1	99.37	1:1:5	99.97

Phase Solubility Study: To evaluate the effect on the solubility of Etodolac after the preparation of their ternary complexes using different carriers and various methods, saturation solubility studies were performed in distilled water. The results of saturation solubility of Etodolac and all its carrier combinations are shown in **Tables 10** and **11,** and a graphical representation is given in **Fig. 8**.

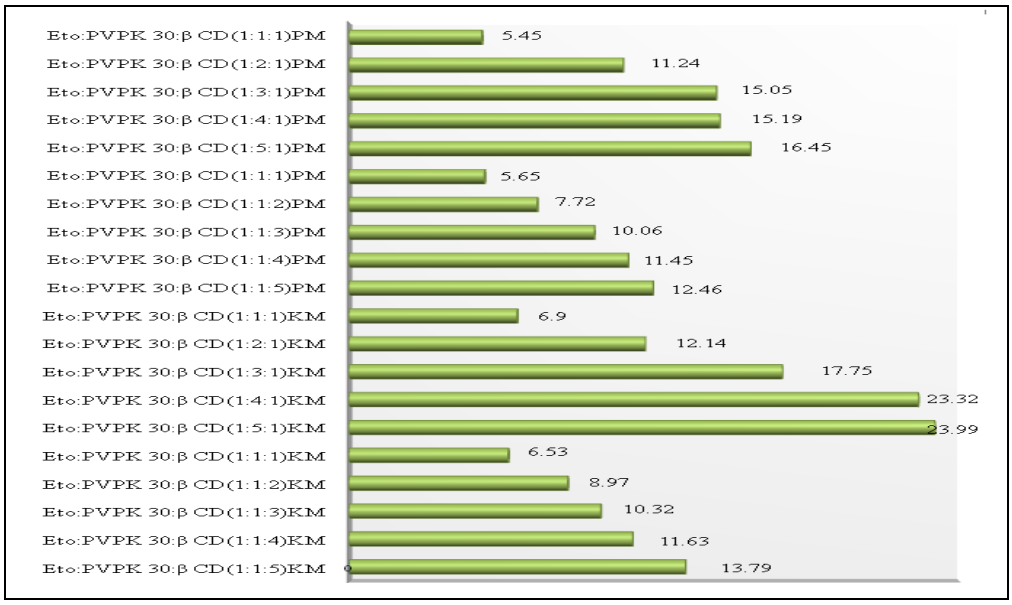

FIG. 8: GRAPHICAL REPRESENTATION OF PHASE SOLUBILITY STUDY

A) Physical Mixture:

TABLE 10: PHASE SOLUBILITY STUDY OF TERNARY COMPLEX

Sr. no.	Drug carrier ratio	*1	Phase solubility study	*2	Phase solubility study
1	Eto: PVPK30:β-CD	1:1:1	5.45 ± 0.0182	1:1:1	5.65 ± 0.006
2	Eto:PVPK30:β-CD	1:2:1	11.24 ± 0.0845	1:1:2	7.72 ± 0.0076
3	Eto:PVPK30:β-CD	1:3:1	15.05 ± 0.0907	1:1:3	10.06 ± 0.059
4	Eto:PVPK30:β-CD	1:4:1	15.19 ± 0.042	1:1:4	11.45 ± 0.0311
5	Eto:PVPK30:β-CD	1:5:1	16.45 ± 0.0305	1:1:5	12.46 ± 0.0515

B) Kneading Method:

TABLE 11: PHASE SOLUBILITY STUDY OF TERNARY COMPLEX

Sr. no.	Drug carrier ratio	*1	Phase solubility study	*2	Phase solubility study
1	Eto: PVPK30:β-CD	1:1:1	6.9 ± 0.0194	1:1:1	6.53 ± 0.009
2	Eto:PVPK30:β-CD	1:2:1	12.14 ± 0.0884	1:1:2	8.97 ± 0.0082
3	Eto:PVPK30:β-CD	1:3:1	17.75 ± 0.0319	1:1:3	10.32 ± 0.064
4	Eto:PVPK30:β-CD	1:4:1	23.32 ± 0.0910	1:1:4	11.63 ± 0.0314
5	Eto:PVPK30:β-CD	1:5:1	23.99 ± 0.096	1:1:5	13.79 ± 0.0529

*1: Drug and β-CD are constant, *2: Drug and PVP K 30 are constant

CONCLUSION: This study was a step towards the goal of rendering the molecules Etodolac to more water-soluble by using different pharmaceutical interventions. The prepared combinations were characterized by a phase solubility study. Based on the results of phase solubility studies, we can conclude that the complexation by kneading method was found advantageous over physical mixture. Though β- CD has proved its impact as a complexing agent, incorporation of PVP K 30 has been found advantageous in regards to increasing the solubility of a drug by complexation. Apart from the solubility method, linearity was observed in concentration and solubility. Solubility studies confirmed the improvement in drug solubilization and absorption from the complex as compared to pure drugs. Finally, we conclude that the aims and objectives of this work were fulfilled with the enhancement of the solubility of Etodolac. Nevertheless, the avenues for improvement of solubility and different formulations of Etodolac remain wide open in the wake that a number of carriers and methods are yet to be tried.

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CONFLICTS OF INTEREST: Nil

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