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Research Article

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Enhancement of solubility and dissolution rate of erlotinib hydrochloride by inclusion complexes with cyclodextrin derivative: Fabrication, characterization, and evaluation

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Abstract The purpose of the study was to explore the effect of cyclodextrin (CyD) on the solubility and dissolution rate erlotinib hydrochloride (Etn-H) by forming inclusion complexes (ICs). Natural CyD like hydrophilic β-CyD was used to prepare ICs with Etn-H. Phase solubility study showed erlotinib displayed maximum solubility in pH 1.2. Etn-H-β-CyD inclusion complexes were prepared by coprecipitation and kneading methods and compared with physical mixtures of Etn-H and cyclodextrin. Prepared ICs were verified by Fourier transform infrared spectroscopy and X-ray diffraction (PXRD) studies. *In-vitro* dissolution study was performed using phosphate buffer pH 7.4, distilled water, and HCl buffer pH 1.2 as dissolution medium for the selected ICs. Phase solubility study indicated impressive enhancement in the solubility of drug by developed of ICs, which was further increased by pH adjustment. The dissolution rate of Etn-H was markedly augmented by the complexation with β-CyD. PXRD curves showed sharp endothermic peaks indicating the reduction in the crystallinity of Etn-H. Optimized ICs was also found stable at ambient temperature up to 6 months for stability investigations. Among all Etn-H-cyclodextrin complexes, Etn-H-β-CyD (1:1, 1:3, 1:5) inclusion complex, prepared by coprecipitation method (1:5) showed increase 2.3-fold and 2.95-fold improvement in dissolution rate in comparison with pure Etn-H.

Keywords Solubility enhancement, inclusion complex, Erlotinib hydrochloride, Tyrosine kinase inhibitor, β-cyclodextrin (β-CyD), Anticancer

1. Introduction

Cancer has become one of the dangerous killers of human beings worldwide. Changes in reproductive factors, environmental exposure, and lifestyle, such as diet, use of chemicals, radiations and physical activity, are major contributors to cancer [1, 2, 3]. Hence, early identification and treatment play a vital role in survival. However, the solubility of most common cytotoxicity drugs, caused by their hydrophobic nature and their efficacies are reduced in the patient's body, thus a higher concentration is needed for treatment [4]. It is imperative to find a drug delivery carrier that reduces the conventional dosage of chemotherapeutic agents without altering their efficacy. Erlotinib hydrochloride (Etn-H) (Fig. 1) is an important tyrosine kinase inhibitor drug. To overcome these problems, it is important to introduce an effective method to enhance the solubility of Etn-H.

In the area of supramolecular chemistry and pharmaceutics, CyDs are the most common host molecules, and they are often used in drug delivery systems because of their good water solubility, high bioavailability, and simplistic functionalization [5]. Hydrophobic drugs can be incorporated in the cavity of CyDs to form inclusion complexes through non-covalent interaction without complex chemical reactions [6]. The formation of inclusion

complexes with CyDs has been used extensively to improve the solubility of poor-solubility drugs and their dissolution rate [7]. Moreover, the side effects of drugs have also been significantly overcome due to the shielding effect of CyDs [8]. Modified CyDs have been used successfully in many applications. Several derivatives of CyD have been reported as non-immunogenic, biocompatible, and suitable for human use by various regulatory agencies, including the United States Food and Drug Administration [9]. Several modified hydrophilic CyD derivatives, exemplified by HP-β-CyD [10], SBE-β-CyD (Fig. S1) [11] and DM-β-CyD [12] have been employed to increase aqueous solubility. Moreover, CyDs have chirality, which is attracting attention in the field of molecular recognition. The complex molecules can be included wholly or partially, and many studies have focused on the ability of CyDs to include guests of varying sizes in different stoichiometric ratios (1:1, 1:3, 1:5). Among the CyDs, studied the complexation of Etn-H with β-CyD. Thus, in order to issues related to the low water solubility and dissolution rate of Etn-H, the inclusion complexes of Etn-H with CyDs are investigated for their suitability as a drug carrier in this study. Recently, one previous attempt to enhance the aqueous solubility of RNA nucleosides has been demonstrated by preparing an inclusion complex using parent cyclodextrin [13]. Herein, to explore the host-guest interaction, Etn-H with CyDs inclusion complexes is systematically characterized by UV-Vis and fluorescence spectroscopy, FTIR and PXRD analysis. Solid Etn-H inclusion complexes were prepared and characterized for encapsulation efficiency and loading capacity using UV-Vis spectroscopy. Erlotinib hydrochloride [*N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazoline-4-amine] (Etn-H), is an epidermal growth-factor receptor inhibitor from the tyrosine kinase inhibitor class [14]. Etn-H promotes cell cycle arrest, apoptosis leading to inhibition of angiogenesis and cell invasion. Etn-H is used particularly in the treatment of pancreatic and non-small cell lung cancer [15]. Etn-H also found effective in the treatment of glioma, ovarian, and head and neck cancer [16]. Etn-H selectively inhibits tyrosine kinase present on the epidermal growth factor receptor (EGFR). Etn-H has poor aqueous solubility, high permeability and/or instability in GIT (extensive first-pass metabolism with rapid clearance). Further, Etn-H exhibits dose dependent major side effects, including rash, diarrhea, loss of appetite, erythematic, frontal alopecia and induces hematological side effects such as anemia, thrombopenia and neutropenia [17]. Thus, there is an urgent necessity to design a formulation having better solubility and absorption, increased bioavailability to reduce the dose and dose-depended adverse effects. Various methodologies exercised by solid dispersion [18], addition of cosolvents [19], complexation and size reduction [20] have been adopted to resolve the solubility challenges of BCS class II molecules. One of the extensively studied approaches to enhance their solubility and bioavailability is complexation with cyclodextrins (CyDs). CyDs are essentially cyclic oligosaccharides composed of minimum six d-(+)glucopyranose units attached through ά-(1,4) linkage. The ά, β-, γ- and 6-CyD are the natural cyclodextrins, with six, seven, eight and nine glucose units, respectively [21]. CyDs have a water loving surface responsible for its water solubility and a lipid soluble interior capable of forming inclusion complexes with a wide range of molecules with specific shape and size. These molecules may enter partly or entirely displacing the high-energy aqueous molecules from the inner cavity [22]. This feature affects the loaded drug physicochemical properties improving its water solubility, dissolution and bioavailability [23]. Among the several CyDs, studied the complexation of Etn-H with β-CyD, which has not been undertaken so far. Etn-H structure shown in Fig.1.

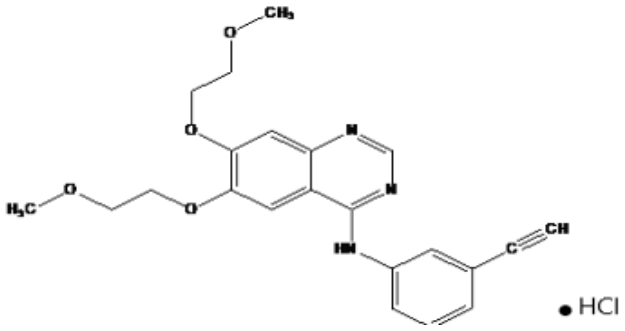

Figure 1: Chemical structure of Etn-H

Material and Method

Material

Etn-H was gifted by Cipla Pharmaceutical Company Mumbai, India, and beta cyclodextrin (β-CyD) from Sigma-Aldrich India. All other reagents were used of analytical grade.

Method

Phase solubility studies

The solubility studies of Etn-H and ICs prepared by TM, KM and CM were determined in distilled water, 0.1N HCl (pH 1.2) and phosphate buffer of pH 7.4 at 25°C. For every preparation, excess amount of ICs were added to the 25 ml of distilled water, 0.1 N HCl and phosphate buffer (pH 7.4) in a glass vial (screw capped) respectively. The vials were placed in incubator shaker at 25°C temperature for 24 hrs. The solutions were then filtered through a Millipore membrane filter 0.45 (micrometer), and the filtrates were further diluted and analysed by UV spectrophotometer at λ_{max} of 246 nm [24].

Preparation of inclusion complexes

(i) Trituration method (TM): Physical mixture was prepared by homogenous blending of previously sieved drug and β-cyclodextrin (β-CyD) in the ratio of 1:1, 1:3 and 1:5 with trituration in a pestle and mortar, and stored in a desiccating environment [25].

(ii) Coprecipitation method (CM): Coprecipitation is a formulation process of inclusion complexes in which reactions involve the simultaneous occurrence of nucleation, growth, coarsening, and/or agglomeration [26].

Drug and β-CyD were taken in ratio of 1:1, 1:3 and 1:5. Drug was dissolved in minimum quantity of methanol and was added drop wise to the solution β-CyD in minimum quantity of water previously maintained at 75 °C while stirring. Stirring was maintained for 1h at 75 °C. Then gradually it was cooled to room temperature while stirring. The precipitates were then filtered, dried and stored in a desiccating environment [27].

(iii) Kneading method (KM): When making most bread recipes, kneading the dough is a crucial step that cannot be skipped. Kneading means to work the dough, usually by hand, for the purpose of developing the glutens in the flour, which is what, gives baked goods their structure and texture [11].

Kneading complexes were prepared by weighing physical mixture in different ratio of 1:1, 1:3 and 1:5 in a mortar in least amount of methanol water mixture (1% v/v) and kneading thorough manually to obtain a homogeneous paste which was then dried in an oven at 50°C for 48 hrs. The dried complexes were pulverized into a fine powder and stored in a desiccator until further evaluation [28, 29].

Table 1: Formulations of ICs of Etn-H

Method	Erlotinib		
	Mixing ratio		
	1:1	1:3	1:5
Physical mixture (Trituration method)	ECyD TM1	ECyD TM2	ECyD TM3
Kneading method	ECyD KM1	ECyD KM2	ECyD KM3
Co-precipitation method	ECyD CM1	ECyD CM2	ECyD CM3

Characterization of ICs

Drug content

ICs of Etn-H equivalent to 10 mg were accurately weighed and dissolved in 10 ml of methanol, in a 100 ml volumetric flask, then the volume was made up with 0.1N HCl, solutions were mechanically shaken for 30 min and filter by 0.45 (micrometer) Millipore membrane filter. Then concentration of 10µg/ml was prepared and drug content was measured by UV spectrophotometer at λ_{max} of 246 nm [11].

Fourier transform infrared spectroscopy (FTIR)

Etn-H, β-CyD, TM and ICs were made into fine powder by mortar and pestle, placed into the sample holder of FTIR and recorded FTIR spectra in the spectral range of 4000-400 $cm^{-1}$of FTIR (Alpha II Bruker Germany) [30].

Powder X-ray diffraction pattern (PXRD)

Etn-H, β-CyD and ICs were analysed by PXRD diffractogram (Rigaku, Ultima IV, Japan) using Cu-Kα radiation of (40 kV, 320 mA) at 2º/min of analysing speed and 2º/2 cm per 2°θ of chart speed [31].

***In-vitro* drug dissolution studies**

The *in-vitro* dissolution study of Pure drug, ICs prepared by CM method drug equivalent to 10 mg of Etn-H was filled into the hard gelatine capsule and performed in 900 ml of 0.1N HCl (pH 1.2) at 37ºC ± 0.5ºC by USP type II dissolution test apparatus, (paddle type) at 50 rpm for 120 min. A 5 ml of aliquots were withdrawn from the vessels, maintaining sink environment with replacement of 5 ml fresh medium at time interval of 0, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110 and 120 minutes, filtered by Millipore membrane filter 0.45 (micrometer), then filtrates were diluted, and analysed by spectrophotometer (UV1800 Shimadzu, Japan) at λ_{max} of 246 nm; the experiment was repeated three times [31].

Results and Discussion

Phase solubility studies

The profile of phase solubility of Etn-H was found to be 2.96±0.22, 4.13±0.71, 2.23±0.25 µg/ml in distilled water, 0.1N HCl, and phosphate buffer pH 7.4, respectively. After the development of ICs the phase solubility was found as 21.96±0.21, 29.81±0.19 and 19.63±0.12 in distilled water, 0.1N HCl, and phosphate buffer pH 7.4, respectively. The results strongly suggest for the need to enhance the solubility and dissolution rate of Etn-H. The ECM3 ICs prepared by CM method demonstrating maximum solubility in 0.1N HCl (29.81±0.19 µg/ml) and was selected for further dissolution studies.

Table 2: Phase solubility studies data of TM and ICs of Etn-H in distilled water, 0.1N HCl (pH 1.2) and phosphate buffer (pH 7.4)

S. No.	Formulations	Solubility in distilled water (µg/ml)	Solubility in 0.1N HCl pH 1.2 (µg/ml)	Solubility in Phosphate buffer pH 7.4 (µg/ml)
1	Pure Drug (Etn-H)	2.96±0.22	4.13±0.71	2.23±0.25
2	ETM1	3.28±0.16	8.13±0.11	5.22±0.23
3	ETM2	5.56±0.62	8.29±0.62	6.31±0.27
4	ETM3	7.76±0.41	9.18±0.45	7.77±0.62
5	EKM1	9.42±0.82	13.69±0.51	9.38±0.74
6	EKM2	11.51±0.44	16.11±0.34	11.72±0.41
7	EKM3	16.63±0.87	23.85±0.42	13.66±0.34
8	ECM1	18.81±0.51	28.72±0.11	17.59±0.66
9	ECM2	20.66±0.71	29.53±0.37	18.71±0.38
10	ECM3	21.96±0.21	**29.81±0.19**	19.63±0.12

Data are expressed as mean ± S.D. (n=3)

*Implies $p < 0.001$ as compared to pure Etn-H

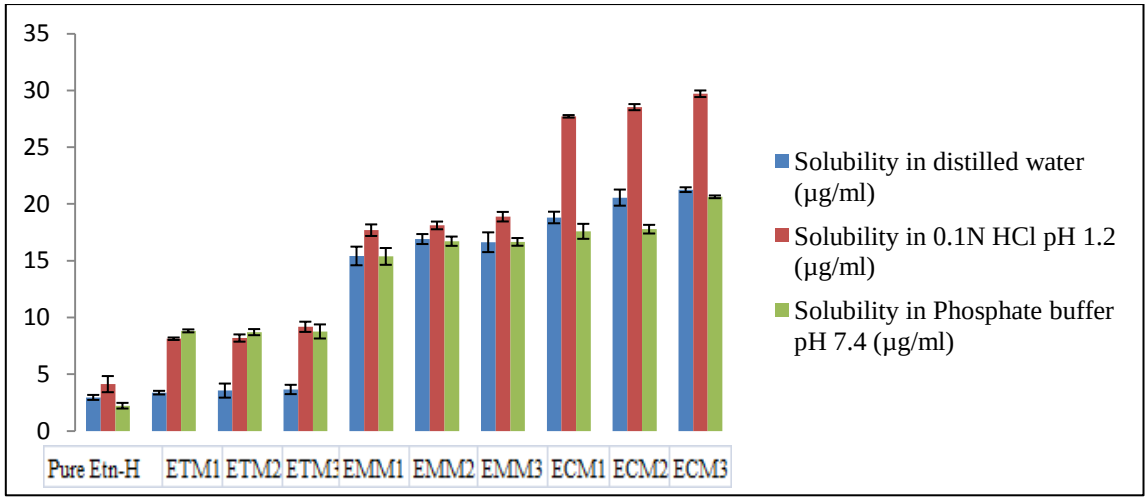

Figure 2: Bar graph of solubility of Etn-H, PM and ICs in distilled water, 0.1N HCl (pH 1.2) and phosphate buffer (pH 7.4)

Characterization of inclusion complexes

Drug content

Table 3: Drug contents of ICs of Etn-H

S. No.	Formulations	% Drug content
1	ETM1	92.26±0.21
2	ETM2	93.38±0.17
3	ETM3	94.41±0.62
4	EKM1	95.06±0.41
5	EKM2	96.65±0.27
6	EKM3	97.04±0.11
7	ECM1	98.03±0.49
8	ECM2	98.41±0.51
9	ECM3	98.98±0.21

Data are expressed as mean ± S.D. (n=3)

*Implies $p < 0.001$ as compared to pure Etn-H

The drug content for TM (92.26±0.21 to 94.41±0.62) and ICs prepared by KM (95.06±0.41 to 97.04±0.11) and by CM method (98.03±0.49 to 98.98±0.21) was obtained respectively, given in Table 4.

Fourier transform infrared spectroscopic (FTIR) studies

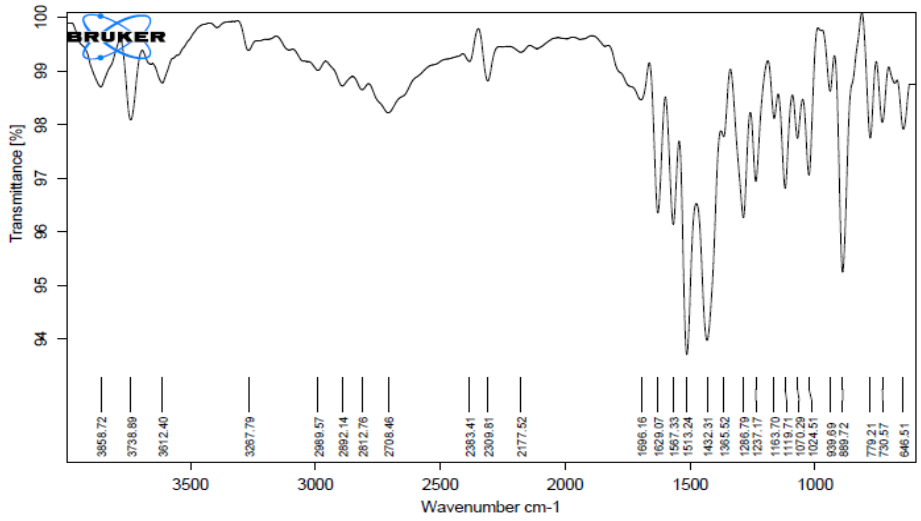

Figure 3: FTIR spectra of pure Etn-H

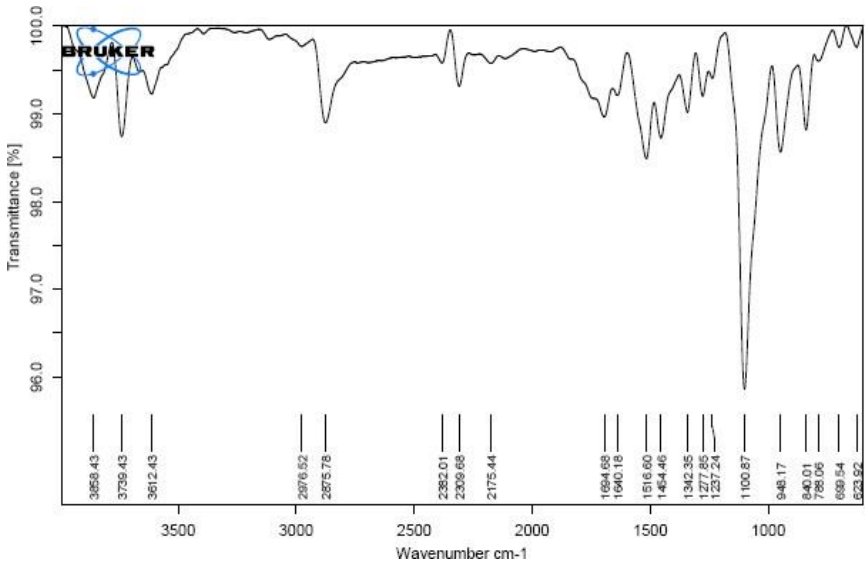

Figure 4: FTIR spectra of Etn-H-β-CyD, ICs (1:5)

FTIR spectra of Etn-H, β-CyD and ICs are presented in Fig. 3 and Fig. 4. The spectra of Etn-H exhibit characteristic peaks at 3269.58 cm^{-1} (=NH- stretching), 2711.46 cm^{-1} (≡C-H stretching), 2995.60 cm^{-1} (H-CH_3 stretching), 1628.84 cm^{-1} (NH bending), 1237.38 cm^{-1} (Ar-O bending), 1024.98 cm^{-1} (aliphatic-O-stretching), 646.34 cm^{-1} (≡C-H bending), 2311.92 cm^{-1} (C≡C stretching) and 1436.82 cm^{-1} (Ar-C-N stretching). In the spectra β-CyD showed a characteristic peak at 3300–3400 cm^{-1}(O-H streaching) and 1100.87 cm^{-1} (C-O stretching) were observed. No any interaction between the drug and polymer was seen, and the peaks of the functional groups of Etn-H were reserved well in the solid dispersion and intensity of peaks of polymer was increased while intensity of Etn-H peaks decreased in the. These findings revealed that excellent compatibility found between the drug and polymer.

Powder X- ray diffraction (PXRD) studies

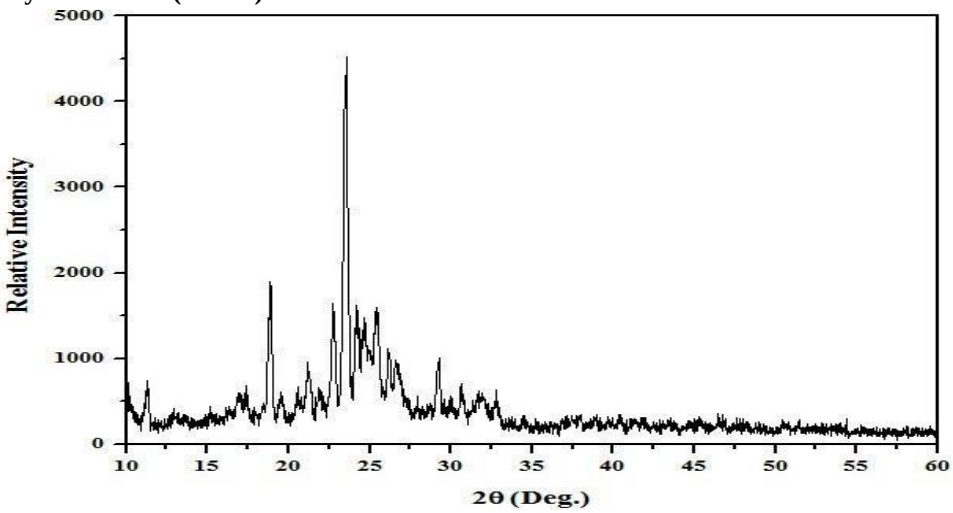

Figure 6: PXRD peaks of pure Etn-H

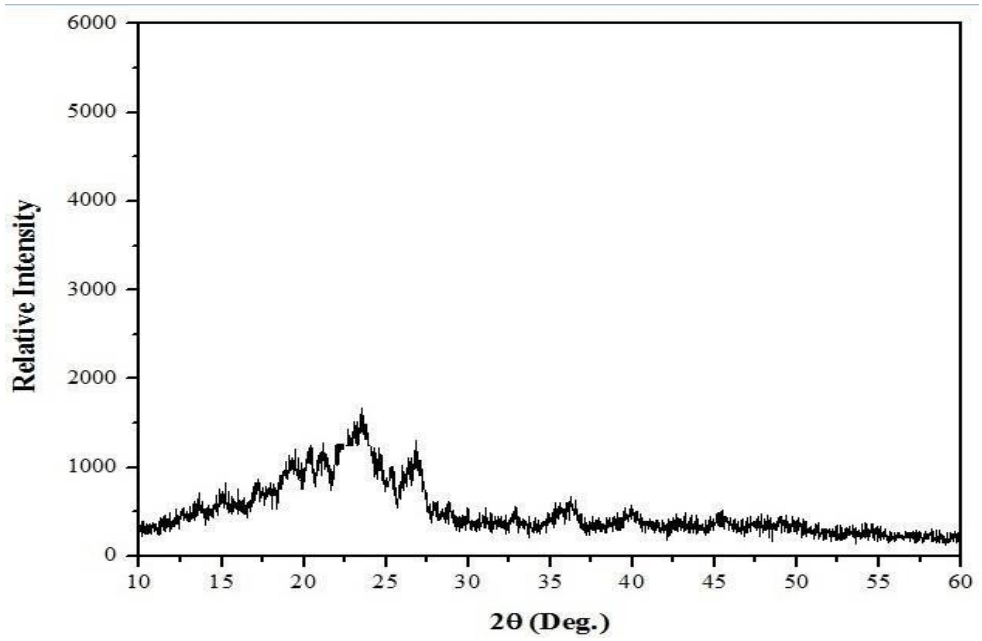

Figure 7: PXRD peaks of Etn-H-β-CyD ICs (1:5)

PXRD spectra of Etn-H, β-CyD and ICs prepared by CM method are presented in Fig. 6. The PXRD spectrum of the pure drug showed distinct sharp peaks at diffraction angle (2°θ); it confirms that the drug was present in the crystalline form. The PXRD of ICs prepared by CM method indicating the reduction in intensity and number of typical diffraction peaks of Etn-H. Suggests the reduction in the crystalline nature of drug. Thus the drug must have been converted from the crystalline state to the amorphous state in the ICs.

***In-vitro* drug dissolution studies:**

Table 4: Dissolution data of Etn-H, PM(trituration method), ICs prepared by KM and CM methods (1:5) in 0.1N HCl (pH 1.2)

Time (min)	Drug	ECyD PM1	ECyD PM2	ECyD PM3	ECyD CM1	ECyD CM2	ECyD CM3	ECyD KM1	ECyD KM2	ECyD KM3
0	0	0	0	0	0	0	0	0	0	0
10	5.37 ±0.41	8.74± 0.50	9.25± 0.83	9.91± 0.35	11.58 ±0.62	13.27 ±1.10	16.45 ±1.77	10.01± 0.29	11.83± 0.67	12.11± 1.14
20	9.75 ±0.53	13.63± 0.25	15.37 ±1.07	16.83 ±0.42	23.44 ±0.89	25.71 ±0.76	28.31 ±0.83	20.74± 1.13	22.28± 0.54	24.37± 0.50
30	17.20 ±0.82	20.56± 0.48	21.56 ±1.11	23.65 ±1.02	35.91 ±0.69	37.47 ±0.56	40.84 ±0.71	30.57± 0.93	33.55± 1.18	36.13± 0.43
40	25.61 ±0.62	27.81± 0.17	28.67 ±0.82	29.47 ±1.60	46.73 ±1.21	48.52 ±0.53	51.33 ±0.80	40.91± 0.43	42.46± 1.16	44.91± 0.95
50	29.84 ±0.78	34.93± 0.47	35.42 ±0.98	37.72 ±1.21	53.42 ±0.57	56.43 ±0.83	59.75 ±0.63	49.25± 1.15	50.11± 0.47	51.53± 0.26
60	33.53 ±0.48	37.65± 1.38	38.93 ±1.19	39.54 ±0.39	60.75 ±0.51	63.85 ±0.58	66.92 ±0.67	56.13± 1.57	57.44± 0.81	58.91± 0.57
70	38.59 ±0.73	42.36± 0.87	43.52 ±1.10	44.32 ±0.56	67.11 ±0.37	70.24 ±1.09	73.37 ±0.78	63.55± 0.72	64.36± 0.59	65.65± 0.73
80	40.18 ±0.55	44.77± 0.51	45.75 ±0.72	46.45 ±0.71	73.53 ±0.71	76.74 ±0.43	78.47 ±0.95	69.61± 0.63	70.84± 0.69	71.42± 0.72
90	42.88 ±0.80	47.26± 0.65	48.62 ±1.30	49.73 ±0.49	78.56 ±0.90	80.32 ±0.40	83.25 ±0.43	74.42± 0.36	75.63± 1.03	77.44± 0.58
100	44.14 ±0.44	50.53± 0.52	51.91 ±0.97	52.46 ±0.26	81.74 ±0.63	83.85 ±0.68	86.93 ±0.59	77.83± 0.72	80.61± 0.55	83.96± 0.40

110	45.45 ±0.87	50.34± 1.04	51.61 ±0.51	52.11 ±1.10	81.43 ±0.87	83.44 ±0.61	86.74 ±0.31	77.23± 0.48	80.34± 0.80	83.51± 0.60
120	45.45 ±0.62	50.14± 1.38	51.23 ±0.73	52.01 ±0.83	81.24 ±0.87	83.25 ±0.63	86.63 ±0.71	77.15± 0.56	80.01± 0.64	83.12± 0.78

Data are expressed as mean ± S.D. (n=3)

*Implies $p < 0.001$ as compared to pure Etn-H

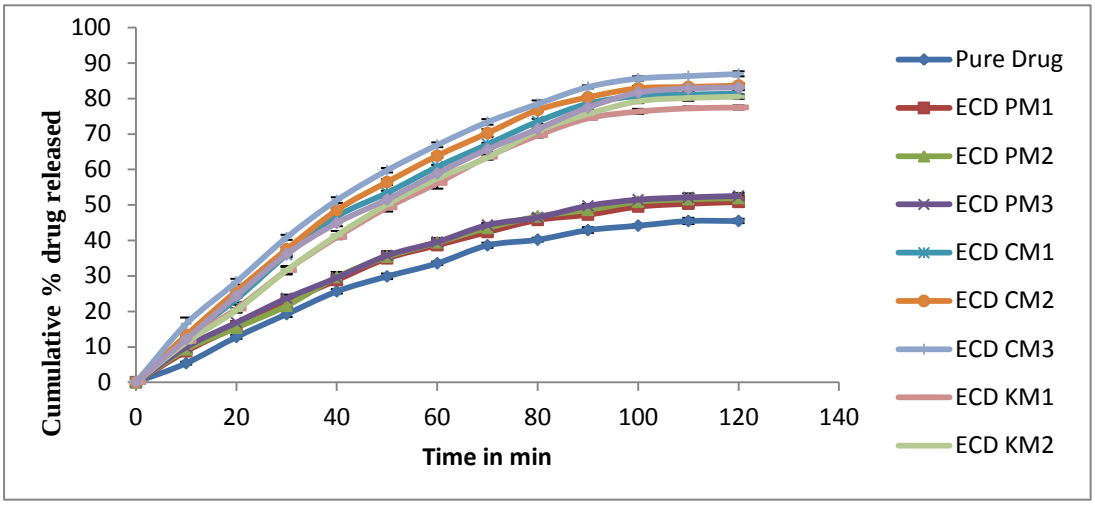

Figure 7: Dissolution profiles of Etn-H, PM(trituration method), ICs prepared by KM and CM methods (1:5) in 0.1N HCl (pH 1.2)

In-vitro dissolution profiles in 0.1N HCl (pH 1.2) of Etn-H, TM and its ICs prepared by CM, and KM method with the β-CyD in different ratio were shown in Fig. 7. Pure drug (Etn-H) release was found to be only 45.45±0.62 in 120 minutes, result strongly suggests for the need to enhance the dissolution. The results of *in-vitro* cumulative percent drug release indicated that the CM method improved the dissolution rate of Etn-H to a great extent. Drug release from ICs prepared by CM method was faster than from the pure drug, TM and ICs prepared by KM method. The drug release from the ICs prepared by CM method (ECM3) was found maximum at 100 minute (86.93±0.59), but after 100 minutes it's nearly constant. The maximum Cumulative percent drug release shown by ECM3 formulation was 86.63±0.71 in 120 minutes, this may be due to the molecular and colloidal dispersion of drug in hydrophilic carrier matrix of β-CyD. The reduction of crystallinity of drug resulting in improved release (supported by FTIR and PXRD); reduction of particle size to expand the effective surface area for dissolution solubilizing effect of β-CyD.

Conclusion

Herewith successfully designed and evaluated Etn-H-β-CyD inclusion complex. Etn-H-β-CyD was selected from preliminary phase solubility studies. Job plot analysis indicated 1:1, 1:3, 1:5 of the drug:β-CyD as an optimum stoichiometry ratio. From optimized formulation, 1:5 ratios of Etn-H and β-CyD was obtained as the optimum ratio with coprecipitation method (CM) as the optimized method. The complex phenomenon was characterized by PXRD and FT-IR analysis. The *in-vitro* dissolution investigations showed the increased dissolution rate and dissolution properties of the complex. Thus, Etn-H-β-CyD indicated higher solubility in comparison to pure drug. Thus, it concluded that the formation of an inclusion complex of the Etn-H with Etn-H-β-CyD is a successful technology to enhance its solubility and dissolution.

Consequently, this study revealed the potential of ICs to increase Etn-H solubility and dissolution performance. As a pharmaceutical intermediate, ICs can be further processed into tablets, capsules, pills and other formulations. However, *in-vivo* studies on Etn-H are needed for further comprehensive evaluation of its IC products.

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Conflicts of Interest
I herewith declare that have no conflicts of interest.

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