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EFFECTS OF POLYMERS ON COMPLEXATION EFFICIENCY OF ACECLOFENAC-BETA CYCLODEXTRIN INCLUSION COMPLEX

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ABSTRACT

Aceclofenac (ACF) is a poorly water soluble analgesic drug. An effort has been made to enhance the solubility through forming inclusion complex with an aim to improve the complexation efficiency of β-Cyclodextrin (βCD). The inclusion complex was formed by kneading method. Hydrophilic polymers such as Poly Vinyl Pyrolidone (PVP), Sodium Carboxy Methyl Cellulose (SCMC), Hydroxy Propyl Methyl Cellulose (HPMC) and hydrophobic polymer such as Ethyl Cellulose (EC) were used to enhance the solubility as well as the CE of ACF- βCD inclusion complex. Phase solubility studies were carried out to evaluate the solubilizing power of β-cyclodextrin (βCD) along with the optimized concentration of polymers. Complexation efficiency and stability constant was calculated from the phase solubility studies. Higher values of solubility constant for ternary complexes clearly proves the beneficial effects of added polymers. CE was enhanced maximum by EC but the dissolution rate followed the following sequence PVP>HPMC>SCMC>EC. Selected ternary mixtures of ACF-βCD inclusion complex were subjected to characterization by Differential Scanning calorimetry (DSC), Fourier Transform InfraRed Spectroscopy (FTIR) and Scanning Electron Microscope (SEM) techniques. The results suggested the formation of inclusion complex with limited or no chemical interaction.

KEYWORD: *Cyclodextrin, Aceclofenac, Complexation Efficiency, Stability Constant*

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INTRODUCTION

High throughput screening methods savors favorable application in identifying lead compounds. It is widely accepted that majority of the lead compounds synthesized are characterized by low aqueous solubility which possibly will lead to low dissolution and lower bioavailability[1]. Cyclodextrins (CDs) are natural cyclic oligosaccharides with 6, 7, or 8 glucose residues (α-, β-, and γ-CD, resp.) linked by a (1–4) glycosidic bond. The β-form is the most commonly employed for inclusion complexation purposes since it is the most accessible and the lowest-priced cyclodextrin[2]. It has been attributed that CDs can from inclusion and non-inclusion complexes in aqueous solution which may lead to erroneous, inaccurate solubility, and stability constant. Furthermore production cost, toxicity of CDs should also be considered while formulating an inclusion complexes of lipophilic drugs [3- 4]. The amount of CDs used for forming complexes may further be increased because of other excipient used in the formulation. Complexation Efficiency (CE) of inclusion complexes should be measured and enhanced to reduce the amount of CDs which will further envisage to lower the production cost and related toxicity of CDs [5]. Several strategies has been reported to enhance the CE of CDs such as use of water soluble polymers [6]-, Hydroxy acids [9], organic bases [9], drug ionization, salt formation [10]. Water-soluble polymers forms a ternary complex with drug/cyclodextrin increasing the observed stability constant of the drug/cyclodextrin complexes. The interaction between the auxiliary substances are mostly electrostatic bonds i.e. ion- to- ion, ion-to-dipole and dipole-to-dipole bonds but other types of forces, such as Vander wall's forces and hydrogen bridges, may frequently participate in the complex formation [11-13].Aceclofenac, a phenylacetic acid derivative (2-{2,6-dichloro-phenyl) amino phenyl acetoxy acetic acid], widely used (NSAID) nonsteroidal anti-inflammatory drug, indicated for the symptomatic treatment of pain and inflammation. Studies have envisaged that Aceclofenac (ACE) shows dissolution rate limited absorption due to low solubility that gives rise to difficulties in pharmaceutical formulations for oral delivery, subsequently may lead to variable bioavailability[14]. The impoverished aqueous solubility of ACE has been conquered by numerous techniques such as solid co grinded solution [15], solvent deposition [16], hydrotropy[17], solid dispersion[16, 18]. Even though many approacheds has been used, but inclusion complexes using CDs is regarded as the best suited technique to enhance the solubility of drugs owing to its capacity of preserving the pharmacophore. Moreover CDs complexes are only a physical interaction using hydrogen bonding, no chemical interaction is possible. Moreover the method also limits any interaction between the other excipients and Aceclofenac. The present study encompasses the use of water soluble polymers such as Hydro Propyl Methyl Cellulose (HPMC), Sodium Carboxyl Methyl Cellulose (SCMC), Poly Vinyl Pyrollidone K 30 (PVP30),.HPMC, SCMC and PVP was choosen for its water solubilizing property. Organic bases such as Arginine and Lysine may also be used which mainly contribute in establishing hydrogen bonds with drug molecules and hence may contribute for enhanced aqueous solubility with limited CDs molecules.

MATERIALS AND METHODS

Materials

Aceclofenac (AC) was obtained as a gift sample from Arbro Pharmaceutical Limited, India. β Cyclodextrin (β-CD), was procured from Himedia Laboratories Private Limited, India. HPMC, SCMC, and PVP K-30, was procured from SD-Fine Chemicals. All other chemicals and solvents were of analytical grade. Phase Solubility Studies: Phase solubility studies in phosphate buffer (pH 7.4) were carried out for both binary and ternary systems. Excess amount of drug was added to 10 mL of double distilled water containing increasing concentration of β-CD with or without fixed polymer concentration (0.2%w/v for HPMC, 0.1% w/v for EC, 0.2% w/v for PVP, 0.2% w/v for SCMC).The suspensions were sonicated on a sonicator at 60^{0}C for one hour. After cooling to ambient temperature, the samples were allowed to equilibrate on a water bath shaker for at least three days at 37±0.5^{0}C and the samples were analyzed spectrophotometrically (Shimadzu, pharmaspec 1700) at 276 nm. Apparent stability constant and complexation efficiency were estimated from the straight line obtained from the phase solubility diagram using the following equation[5, 19-21].

$$K1{:}\,1 = \text{Slope}/S0\ (1 - \text{Slope}) \quad (1)$$

Where So was the intrinsic solubility of gemfibrozil in absence of cyclodextrins. $K_{1:1}$ is the stability constant of ACF-β CD inclusion complex in molar ration of 1:1

$$\text{Complexation efficiency (CE)} = \text{Slope}/\ (1 - \text{Slope}) \quad (2)$$

Significant differences between the complexation efficiencies of binary and ternary mixtures were calculated by applying ANOVA test. The statistical significance was calculated at 5% α level. Preparation of Solid Complexes: ACF-β-CD inclusion complexes were prepared in 1:1 molar ratio with and without polymer. The mixture was processed through kneading method for 30 minutes and dried in an oven for 20 minutes. The dried mixture was further processed for grinding using pestle mortar. The dried kneaded mass was powdered and passed though sieve (size 100) for uniformity. The binary mixture and ternary mixture containing optimized concertation of polymer was further subjected for Intrinsic Dissolution Rate (IDR) using USP apparatus Type 1. Pure drug, binary mixture complex and ternary mixture complex was compressed in form of tablets measuring diameter of 5.2 cm^2. The IDR was conducted in 900 ml of phosphate buffer, pH7.50 stirred at 100 rpm at 37^{0}C. At fixed time intervals 10mL aliquots were withdrawn and analyzed spectrophotometrically at 276nm.The dissolution runs were done in triplicate and the IDR was determined[22- 23].

Differential scanning calorimetry (DSC)
DSC analysis was performed using DSC (perkin elmer DSC 6). 5 mg samples were heated in sealed empty aluminum pans at a rate of 10 °C min–1 in a 40–250 °C temperature range under a nitrogen steam. The instrument was calibrated using indium.

Fourier transform infrared spectroscopy (FTIR)
FTIR spectra were recorded on samples prepared in KBr using FT 761. Data were collected over a spectral region from 4000 to 650 cm–1 with resolution 4 cm–1 and 100 scans.

Scanning electron microscopy (SEM)
Scanning electron microscopy (SEM) was performed for selected mixtures to confirm the formation of inclusion complex using scanning electron microscope (Zeiss EVO 50, UK). CD inclusion complex were silver coated in vacuum and examined under a magnification of ×4000.

RESULTS AND DISCUSSION

Solubility studies: Equilibrium solubility studies elucidated the concentration amount of polymer exhibiting highest increment of solubility of ACF. The optimized amount is envisaged to increase CE thereby decreasing the amount of CD used in formation of inclusion complexes of ACF. It was deduced that 0.2%w/v for HPMC, 0.1% w/v for EC, 0.2% w/v for PVP, 0.2% w/v for SCMC would be used for preparing ternary complexes of ACF- β-CD (Figure 1). Linear relationship existed between the amounts of ACF solubilized with an increasing amount ofβ-CD. A_L type curve was established owing to the linear relationship (Figure 2). Similar solubility behavior was also exhibited in presence of optimized concentration of polymers. It was further established that that the amount of polymers added to ACF-β-CD complex system have profound effect of the stability constant and complexation efficiency (Table 1). Many reasons may be attributed to it such as hydrophobic bonds, vanderwaal's forces and promoting the release of high energy water molecules present in the cavity. It was further calculated that only 3.77 β-CD molecules (Table 1) with PVP, SCMC, HPMC for water soluble polymers and 1.16 β-CD molecules (Table 1) EC were required with EC to solubilize one molecule of ACF as compared to 38 β-CD molecules in case of binary mixture (Table 1)($P<0.0001$).

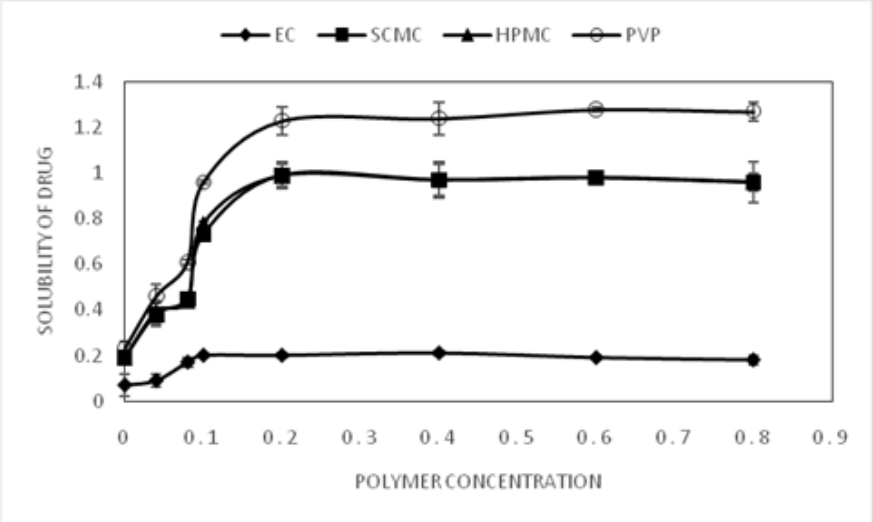


Figure 1
Equilibrium solubility studies

Table 1
Effect of polymers on complexation efficiency and stability constant of Aceclofenac.

Polymers	Correlation coefficient (r^2)	Intercept	Stability constant	Complexation efficiency (C.E)*	Drug:β-CD ratio
PVP	0.989	2.6205	273	0.36±0.012	3.78
HPMC	0.9981	2.2819	295	0.35±0.014	3.78
SCMC	0.9994	2.047	305	0.36±0.019	3.77
EC	0.9957	0.2124	576	5.99±0.009	1.16

n=3, readings in triplicate

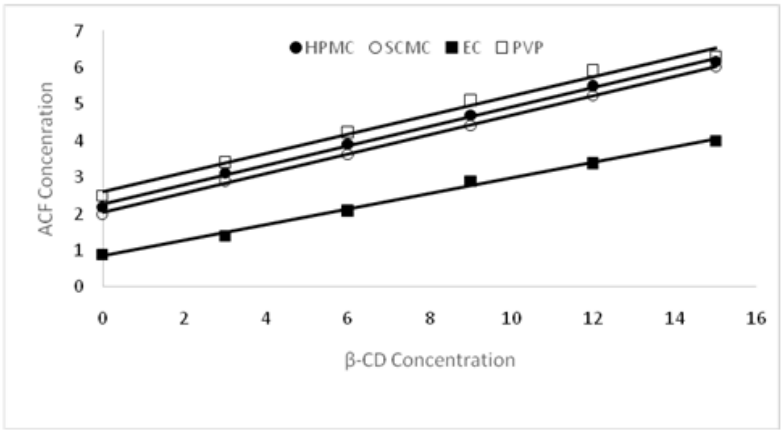


Figure 2
Phase solubility studies of ACF and different polymers

Intrinsic dissolution rate

The ternary mixture(s) displayed higher IDR (Figure 3) in comparison to the binary systems and pure drug which can be attributed due to improvement in drug wettability, formation of readily soluble complexes in dissolution medium and also due to the hydrophilic nature of polymer[1]. Amongst the ternary systems PVP showed maximum IDR and the rank order was PVP>HPMC>Sod CMC>EC (Table 2). The reason for decrease in the solubility may be attributed due to appreciable increase in the viscosity of the mixture in aqueous solution, which may form a channel around the drug complex thus decreasing the release of the drug and hence affecting the IDR. Moreover the hydrophobic material such as EC may also decrease the solvent penetration which eventually may lead to reduced diffusion of the drug from the complex. EC may also form a more tortuous with β-CD resulting in slower drug release [24].

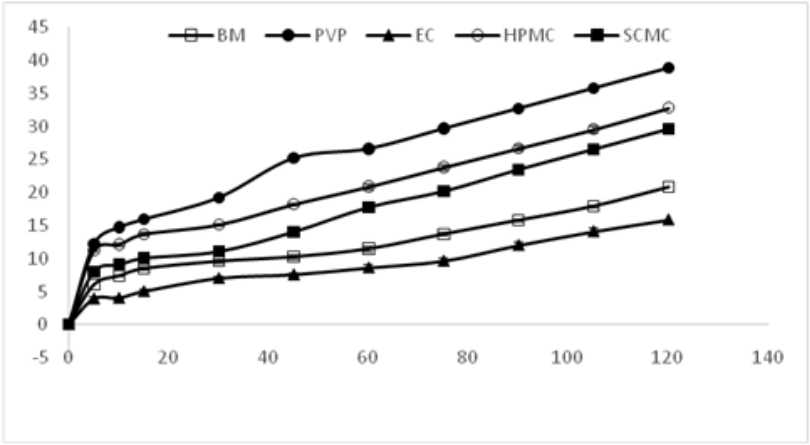


Figure 3
IDR of Binary Mixture and Ternary Mixture of ACF - β – CD Inclusion Complex in Phosphate Buffer pH 7.4

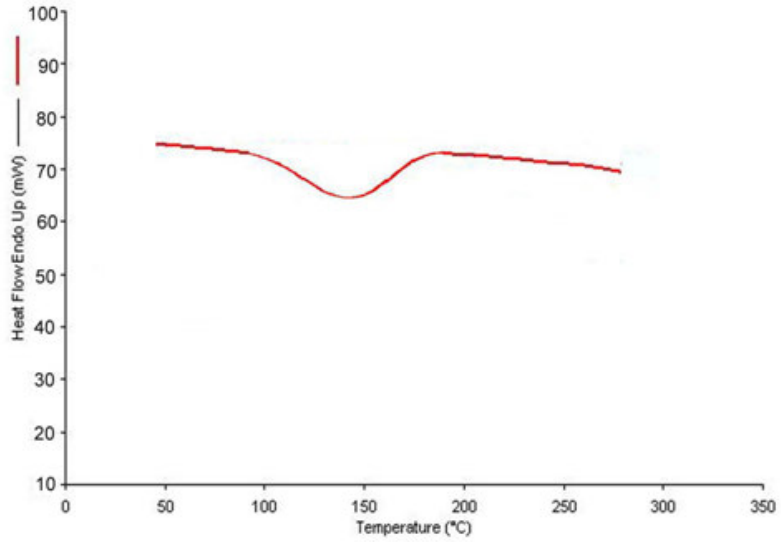
Table 2
IDR of binary and ternary inclusion complexes.

	Binary mixture	PVP	EC	HPMC	SCMC
IDR(mg/cm^2/min)*	0.0344±0.004	0.064±0.002	0.026±0.003	0.054±0.003	0.049±0.002

n=3, readings in triplicate

Differential scanning calorimetry (DSC)

DSC is a reliable and good technique to the formation of inclusion complexes of drugs. The DSC curve of ACF produces an endothermic curve at 160ºC confirming its melting point and the purity of ACF.DSC curve of binary mixture and ternary system containing PVP did not show significant differences. Appearance of broad peak may be attributed to the formation of inclusion complex between ACF and β-CD (Figure 4).



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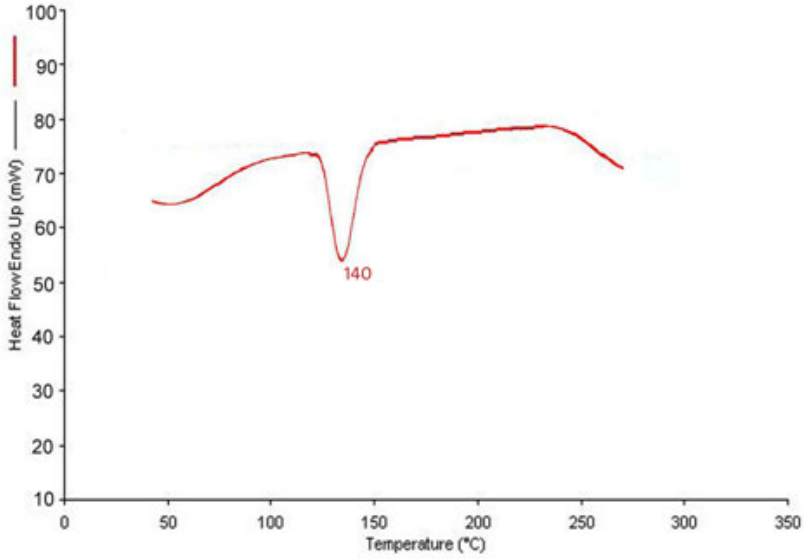

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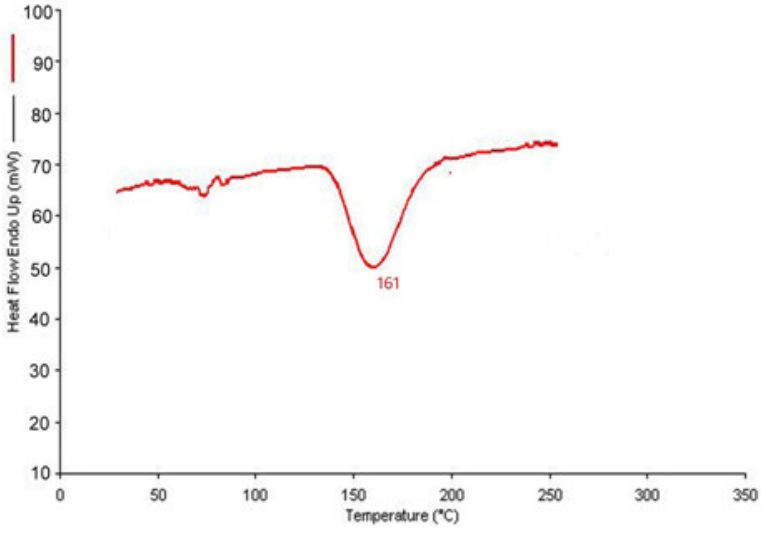
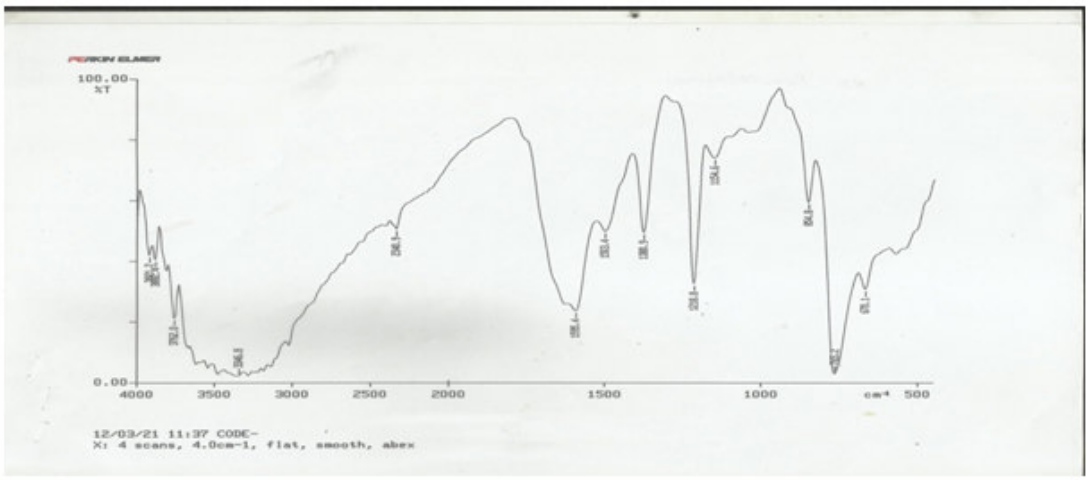


(C)

Figure 4
DSC graph A: Beta Cyclodextrin, B: Aceclofenac C: Kneaded Ternary Complex Containing PVP

Fourier transform infrared spectroscopy (FTIR)

The IR Spectra of ACF, BM and Ternary mixture containing PVP does not show formation of any new peak , indicating no or minimal chemical interaction however disappearance of some of the peak subsumes the formation of ACF- β-CD inclusion complex by physical interaction only. (Figure 5).



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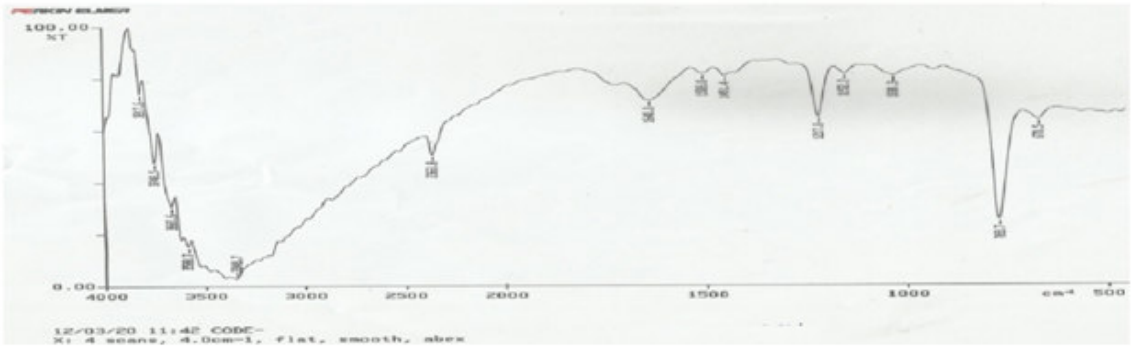

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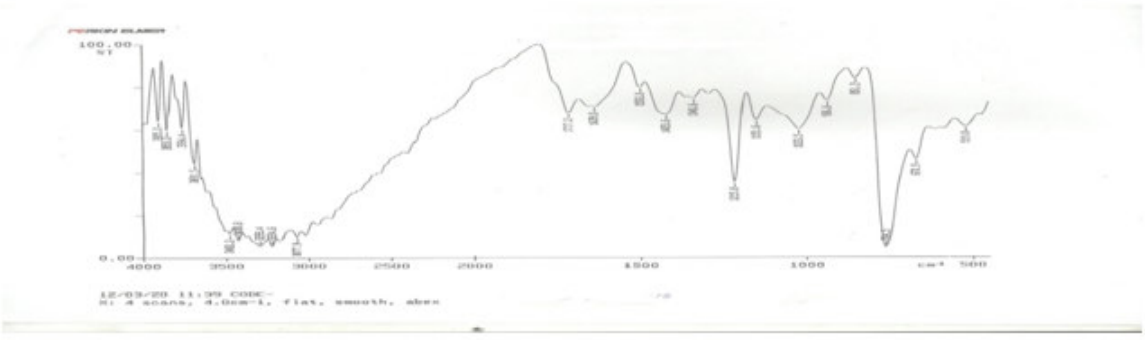
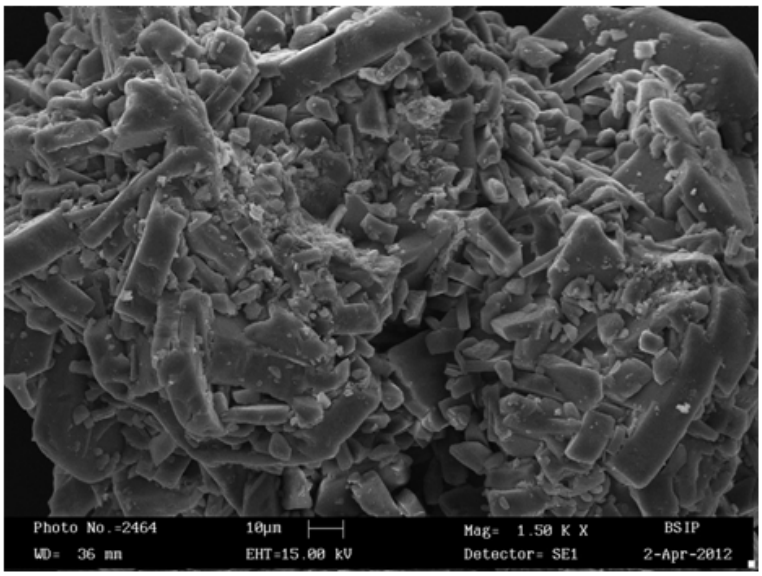


(C)

Figure 5
IR graph showing no interaction A: ACF, ACF- β-CD-PVP ternary complex; C: ACF- β-CD-SCMC ternary complex

Scanning electron microscopy (SEM)

ACF was observed to have rectangular shaped crystals with smooth surface and parallel arrangements. Even if there is a clear difference in crystallization state of raw materials and the products, this study is inadequate to affirm inclusion complexation but nevertheless helps to assess the existence of a single component in the formulations employed. Microscopic evaluation of ACF-β-CD binary kneaded inclusion complex containing PVP showed the presence of ACE crystals mixed and adhered on the surface of β-CD particles, revealing no apparent interaction between species in solid state. In the kneaded ternary systems, it was possible to differentiate ACE crystals as agglomerates on the surface of β-CD particles that had lost their original shape (Figure 6).



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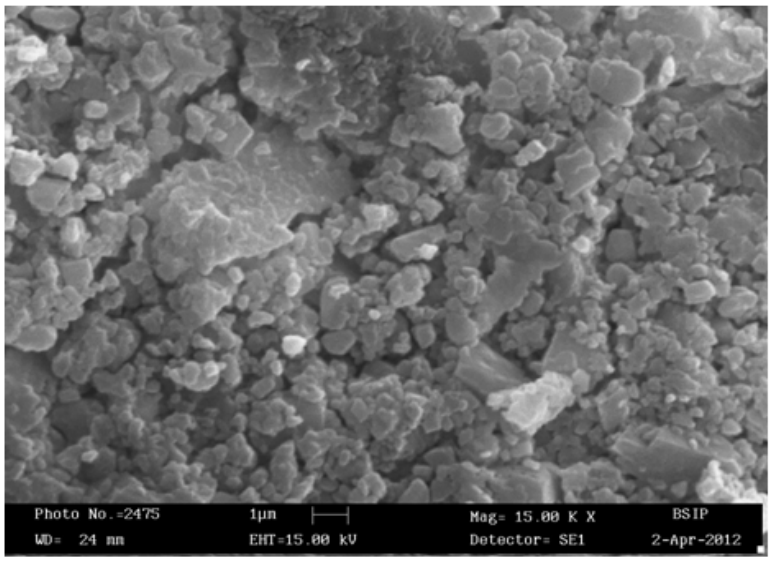

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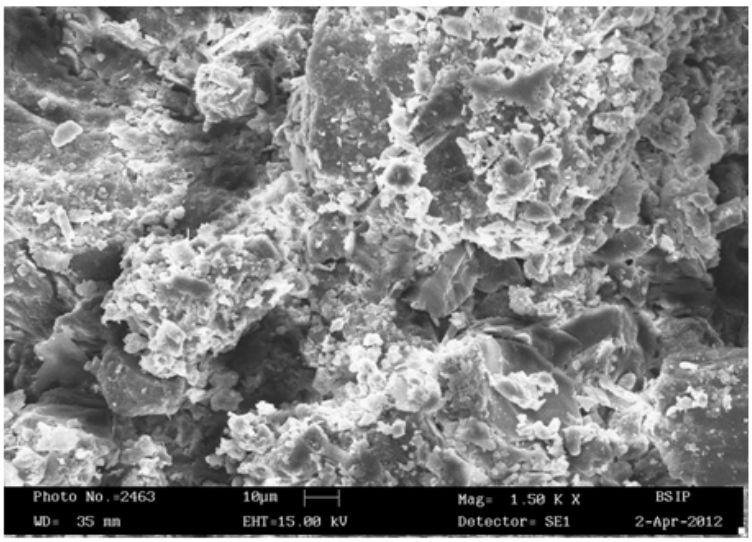

(C)

Figure 6:
SEM A: Aceclofenac B: Beta Cyclodextrin
C: Kneaded Ternary Complex Containing PVP

CONCLUSION

An inclusion complex of ACF was formed using βCDs as complexing agent through kneading method. Efforts were made to enhance the complexation efficiency and stability constant of ACF-βCD inclusion complexes using polymers. The optimized concentrations were 0.2% (w/v) for HPMC, PVP and Na CMC and 0.1% (w/v) for EC. PVP was adjudged as the best polymer owing to its superior effects on CE and stability constant of the kneaded ternary inclusion complex of ACF as compared to other polymers. EC was highly effective in reducing the number of CDs for forming inclusion complex but due to its hydrophobic nature it was not able to enhance the solubility of ACF. The formation of inclusion complex was further substituted with characterization of ACF-βCD ternary complexes. The study suggested the use of hydrophilic polymers for improving the CE and stability constant which will further decrease the toxicity and improve the potency of ACF. The study purports the quantification of ACF- βCD ternary complexes in blood by pharmacokinetic studies.

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CONFLICT OF INTEREST

Conflict of interest declared none.

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