RESEARCH ARTICLE

Studies on Spectral Characterization, Dissolution and Solubility of Aceclofenac Multicomponent Inclusion Complex using Different Auxiliary Agent

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ABSTRACT

Current research was designed to examine how aceclofenac interacted with cyclodextrin and its derivatives. The different auxiliary agents such as mannitol, L-arginine and citric acid were also evaluated for enhancement solubility of aceclofenac and selected as third component for preparing multicomponent inclusion complex. In direction to increase bioavailability and solubility of the poorly soluble medication aceclofenac, a complex was created that belongs to BCS CLASS-II. The multicomponent inclusion complex was created by using physical mixing and kneading techniques. The distinct concentrations of L-arginine were tested for the ternary systems. Interactions between the solid and liquid phases were studied using FTIR, DSC, XRD, and 1H-NMR. A study on phase solubility proved that L-arginine significantly affected the methyl-β-cyclodextrin complexation with aceclofenac. Saturation solubility study and in-vitro study state that prepared complex shows expansion of solubility similarly bioavailability of poorly water-soluble aceclofenac.

Keywords: Aceclofenac, methyl-β-cyclodextrin, multicomponent inclusion complex, auxiliary agent, L-arginine.

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INTRODUCTION

Aceclofenac is ACF or (2-[2-[2-(2,6-dichlorophenyl) amino phenyl] acetyl] oxy acetic acid, C. The NSAID is used for the relief of pain and inflammation.[1,2] ACFC is BCS CLASS-II,insoluble in water (0.058 µg/ml) but has good permeability. Low aqueous solubility of ACFC results in rate limiting step for dissolution leads to poor bioavailability and therapeutic effect of drug.[3-5] A number of methods exist for refining solubility of drugs that are not very water-soluble. These include solid dispersion technique, salt production, surfactant use, size reduction, nanomization, and inclusion complex formation.[6-10] The inclusion complex is made using cyclodextrin or its derivatives, which are essential for making drugs water-soluble. However, there are a few drawbacks to this method, such as the fact that it's expensive, has a high molecular weight, and requires a lot of it to get the desired effect due to its poor complexation efficiency.[11-15] This problem is overcomed by using different auxiliary agents (AUXAs) such as hydroxyl acids, sugar alcohol, amino acids, and polymer by forming Multicompoent inclusion complex with drug and cyclodextrin/its derivatives. The auxiliary agent shows synergistic outcome on solubility and complexation efficiency of drug- cyclodextrin inclusion complexes.[16] Aim of present investigation is to prepare multicomponent inclusion complex of ACFC drug, cycloextrin/its derivatives with different auxiliary agents, these enhance the rate of dissolution and bioavailability of ACFC.

MATERIALS AND METHODS

Materials

Aceclofenac (ACFC), Beta-cyclodextrin, Methyl-betacyclodextrin, Hydroxy-propyl-beta-cyclodetrin (HP-β-CD), Citric acid(CTA), L-Arginine (L-ARN), D- Mannitol (D-MNT) was purchased from Yarrow Chem Products, Mumbai, India.

Methods of Functionalization of MWCNTs

Screening of Auxiliary Agent

Various auxiliary agents such as amino acids, hydroxy acids and sugar alcohol namely L-arginine (L-ARN), citric acid (CTA) and D- Mannitol (D-MNT), were screened by ACFC, in absence of CD and its derivatives to select suitable AXA and to evaluate for their solubility improvement possessions towards ACFC.[17,18]

Fortitude of Concentration of Auxiliary Agent

Concentrations of through an experiment selected AUXAs, namely L-ARN, were measured in the ternary complex. Saturation solubility tests were conducted after five solutions ranging from 0.1 to 0.5% were produced in water.[17,18]

Phase Solubility Studies

In order to find out how binary and ternary systems dissolve in water, researchers followed the steps laid out by Higuchi and Cannors. For the binary system, a 50 mL volumetric flask was utilised, and 10 mL of distilled water holdingvarious concentrations of M-β-CD,β-CD, and HP-β-CD solutions (0.001-0.01 M) was introduced. Using a

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Table 1: Binary and Ternary System Phase solubility study

Parameters	ACFC-B	ACFC-T
Slope	0.0042	0.0472
R^2	0.9912	0.9984
CE	0.0042	0.0495
$K_C(M^{-1})$	403.84	4720.00

rotary flask shaker, all of the solution-containing flasks were vigorously shaken for 48 hours at 37°C. A 2401-PC UV spectrophotometer was used to measure absorbances at 274 nm. If necessary, the solutions were diluted before filtering them using Whatman filter paper no. 42.[19,20] The phase solubility of the ternary system was investigated using the same methodology as that of the binary system. The M-β-CD that was selected for the experiment was combined with 10 mL of distilled water that had an extra of ACFC. As a third component, a fixed amount of the AUXAs agent, specifically 0.4% L-ARN, was added.[19,20]
For both ternary systems, stability constant (Kc) was determined by analyzing phase solubility graph in water.
From initial straight section of phase solubility map, apparent stability constant (S0), intrinsic solubility of medication, was computed using equation:

$$Stability\ Constant = \frac{\text{Slope}}{\text{S0}\ (1-\text{Slope})} \ldots (1)$$

The following formula was used to generate CE values for CDs; these values are useful for selecting complexation conditions.[19, 21]

$$Complexation\ Efficiency\ = \frac{Slope}{(1-Slope)} \ldots (2)$$

Preparation of Multicompoent Inclusion Complex of ACFC
The physical mixing and kneading methods were used to create ACFC with M-B-CD inclusion complexes.
The ACFC-PM-B binary inclusion complex was made using the physical mixing approach. It was readily made by evenly mixing ACFC and M-β-CD in a glass mortar with a 1:1 molar ratio. A glass mortar was used to mix ACFC and M-β-CD in a consistent 1:1 molar ratio. MCIC (ACFC-PM-T) was then made by adding L-ARN in the appropriate proportions during trituration, with 1:1:0.4% . The last step was to dry the complexes and strain them through a 100-mesh sieve. After preparation, the complexes were transferred to glass vials for future research.[22]
By putting the necessary amounts of ACFC and M- β-CD (1:1)into glass mortar, the binary inclusion complex (ACFC-IC-B) was produced using the kneading method. It was mixed with water, ground into a paste, and then kneaded for approximately an hour to create a slurry. To keep the product's consistency just right, the necessary

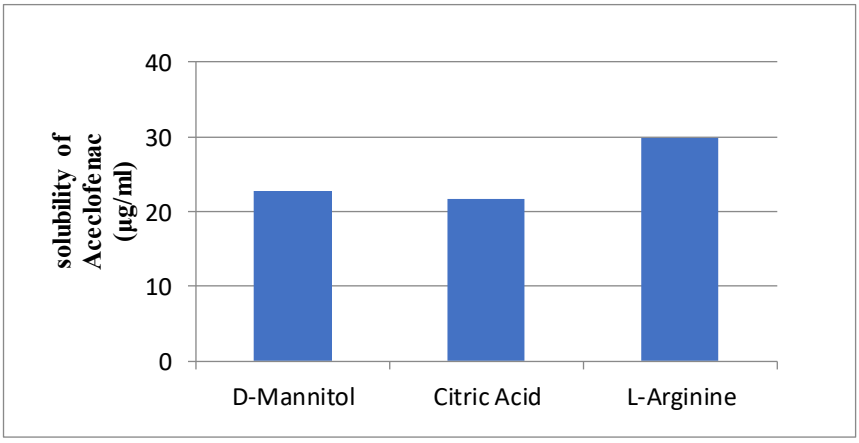

Figure 1: Solubility of ACFC in several AXAs

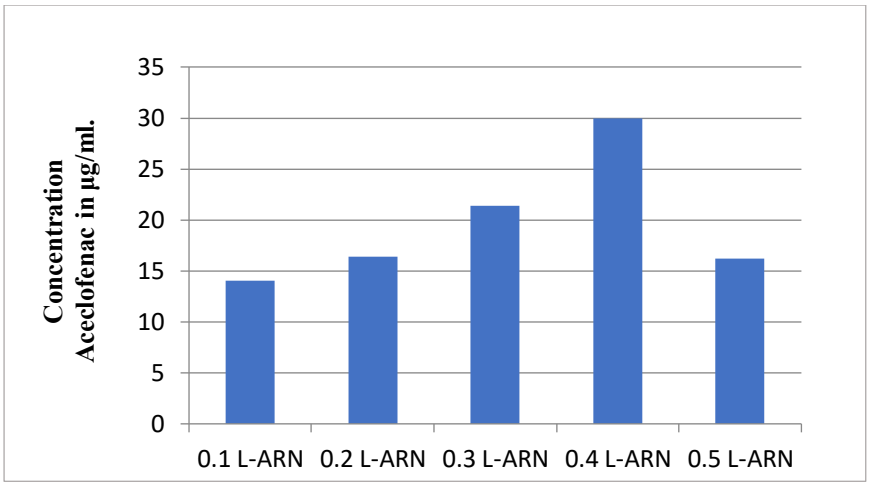

Figure 2: Various Concentration of L-Arginine

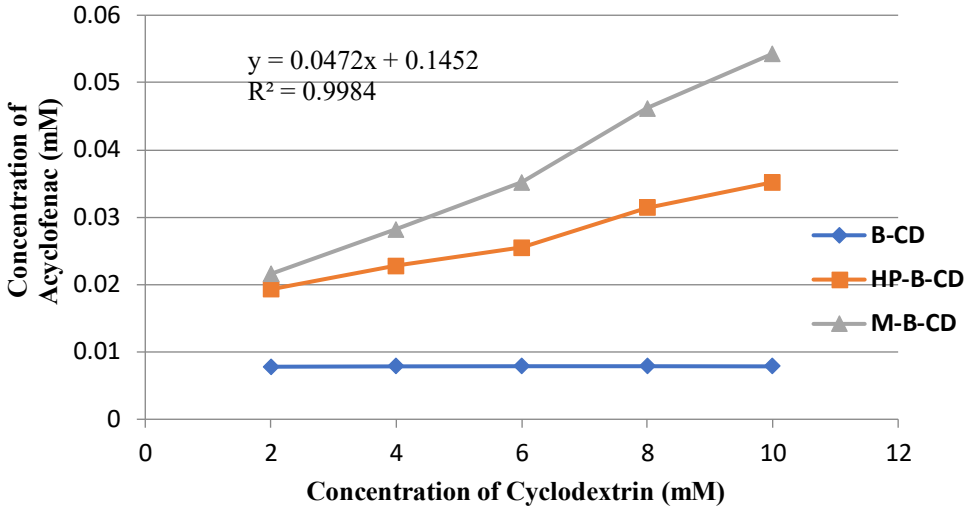

Figure 3: Phase solubility diagram with ACFC

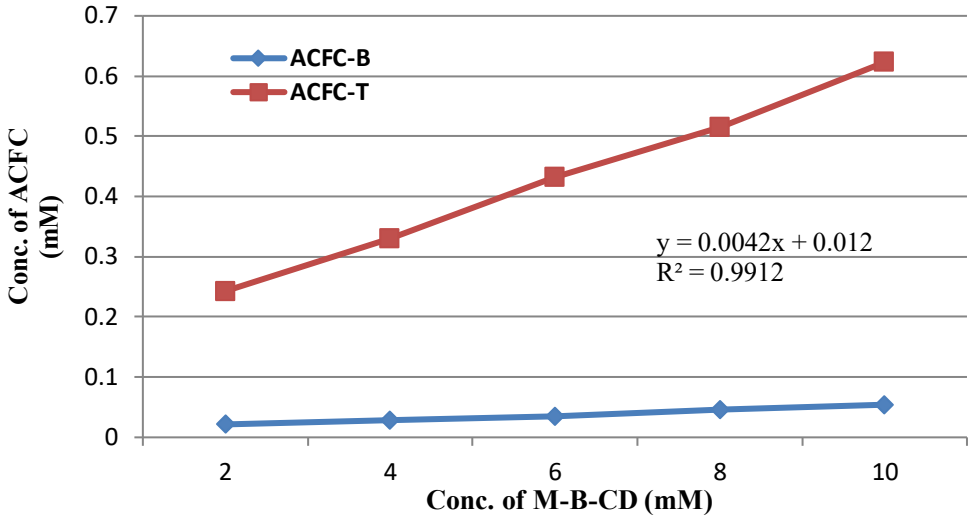

Figure 4: Phase solubility diagram for ACFC-B (Binary System of ACFC and M-β-CD) and ACFC-T (Ternary system of ACFC, M-β-CD with Citric acid)

amount of solvent was added while kneading. Before being stored in the desiccator for future use, the goods were dried and passed through #100 sieves.

The MCIC (ACFC-IC-T) was prepared by adding to this required quantity of L-ARN gradually with 1:1:0.4% Molar ratios.[23-25]

Characterization of MCIC

Saturation Solubility

The saturation solubility technique was used to define aqueous solubility of ACFC, Binary system, and MCICs in water. Vials containing 10 ml of water (solvents) were supplemented with an excess of the ACFC pure medication and various MCIC, namely ACFC-IC-T and ACFC-PM-T. After 24 hours of being shaken at 25°C and 100 rpm, the sealed vials were emptied and the contents filtered using Whatman filter paper No.42. Appropriate dilutions of the samples were then used for estimate.[17,18,26]

Fourier Transform Infrared Spectroscopy

FT-IR spectra of ACFC (pure medication) and all MCIC (4000-500 cm -1) by using FTIRspectrophotometer[27].

Differential Scanning Calorimetry

Pure drug and MCIC generated by various methods were subjected to DSC tests in order to assess drug-carrier compatibility. DSC investigationby using an SDT Q600 from TA Instruments USA, in a nitrogen surroundings, by a heating 10°C/min. Temperature sort that we utilised was 0-400°C.[28,29]

X-Ray Diffraction Studies

A drug and all MCIC samples were subjected to XRD. The Singaporean firm PAN Analytical SpectrisPvt. Ltd. used the method, which involves a copper target, a current 40 mA, and voltage 45 kV. Scanningprogression was implemented in a 2θ range of 1° to 40°.[30]

Nuclear Magnetic Resonance Spectroscopy

In order to verify presence of complexes, the ACFC and MCIC samples were analysed using 1H NMR. A DMSO was utilised as the solvent.[27]

In-vitro Dissolution Studies

USP type-II equipment was used to conduct an in-vitro dissolution study of ACFC. One hundred milligrammes of the medicine, or the MCIC, was dissolved in nine hundred millilitres of 6.8 phosphate buffer for testing. A temperature

of 37 ±5°C was maintained while spin speed 50 rpm. Five millilitres (mL) of dissolving medium was taken every five minutes.[30,31] Volume of dissolving fluid was accustomed by adding 5 ml of new dissolution medium after every sample. Solutions were diluted and filtered using Whatman filter paper before being measured for absorbance at 274 nm using a UV-visible spectrophotometer.[32,33]

RESULTS

Screening of Auxiliary agents and its Concentration

The screening of different AXAs for ACFC was shown in Fig-1. The maximam Solubility for ACFC was 29.93 µg/ml with L-ARG observed.The Optimization of the concentration of AXAs was shown in the fig.2. Figure 2 shows that ACFC solubility increases linearly with increasing L-ARN concentrations up to 0.4%, but thereafter it stopped increasing significantly. Therefore, in order to conduct phase solubility investigations and create ternary complexes, 0.4% L-ARN was utilized as the third component.

Phase Solubility Studies

Binary system

ACFC Phase solubility diagram with cyclodextrin and its derivatives as shown in fig-3. This study helps to select suitble cyclodextrin to form best inclusion complex. Results suggest that HP-β-CD and M-β-CD have a solubility curve that is similar to AL type, indicating first order reaction with formation of water-soluble complex. ACFC is more soluble in M-β-CD with its increasing concentration and selected for establishment of inclusion complex(1:1).

Phase solubility for Binary also Ternary system

Based on slope of straight line in AL kind solubility figure, stability constant (Kc) for 1:1 complex of ACFC-B was determined to be 125.00 M^{-1}, while for ACFC-T it was 200.93 M^{-1}. increasedKc value of ternary system indicates the enhanced solubility of ACFC than the binary system due to the intermolecular interaction between the ACFC, M-β-CD with Citric acid.

Saturation Solubility Study

Saturation solubility tests were performed on ACFC, binary, & ternary complexes in water, and results are displayed in Figure 5. ACFC has low solubility in water 2.2307 µg/ml. The solubility is observed in the order as ACFC < ACFC-PM-B < ACFC-IC-B < ACFC-PM-T < ACFC-IC-T. The ternary complexes with M-β-CD and L-ARN improved aqueous solubility of ACFC. Solubility was observed to increase in all cases, according to data (Figure 5). However, inclusion complexes formed by M-β-CD and L-ARN (1:1:0.4%) by kneading method showed the largest rise, 16 times higher than pure drug.

Fourier Transform Infrared Spectroscopy

The FTIR spectrophotometer was used to take FT-IR spectra of ACFC (pure medication), M-β-CD, physical mixes, and all MCIC. Spectra were scanned in range of 4000-500 cm-1. This study explains interaction between the drug and different AUXAs. FTIR spectrum of ACFC and multicomponent inclusion complex (ACFC-IC-T) was as shown in as shown in Fig-6 and Fig-7. There are several peaks observed in the ACFC spectrum, such as those at 3315.73 $cm^{-1}$for N-H stretching, 1588.17 cm^{-1} for aromatic C-C stretching, 1759.48 cm^{-1} for C-O stretching, 1504.70 cm^{-1} for in plane bending for N-H, 1279.62 cm^{-1} for C-N aromatic amine, 1342.28 cm^{-1} for O-H in plane bending, 897.88 cm^{-1} for O-H out plane bending, and 748.21 cm^{-1} for out plane bending for N-H. The ACFC-IC-T multicomponent inclusion complex is comprised of the distinctive peaks observed at 2359.15 (C-O stretching), 1153.79 cm^{-1} (C-N aromatic amine), 3412.31 (N-H stretching), 1557.15 cm^{-1} (aromatic C-C stretching), 864.93 cm^{-1} (O-H out plane bending), and 750.59 cm^{-1} (out plane bending for N-H). Strength of various peaks, including N-H and O-H, is reduced in the ACFC inclusion complex. Because ACFC-IC-T's FTIR spectra have not changed noticeably, we can rule out the possibility of a drug-AXA interaction.

Differential Scanning Calorimetry

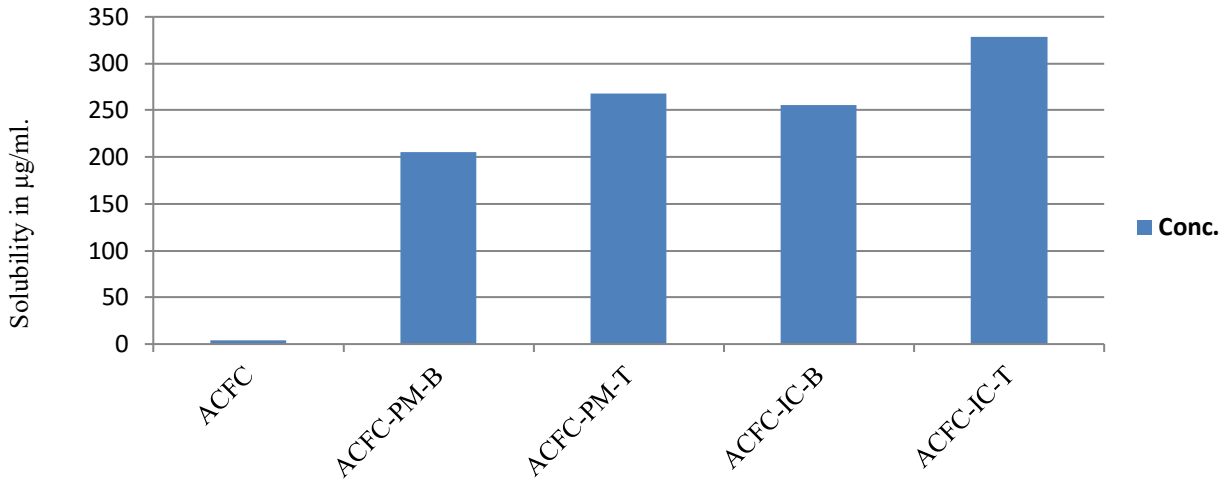

Figure 5: Solubility of ACFC and its compounds in water at 25 ± 2°C, in cooperation binary and ternary. ACFC-PM-B: Binary inclusion complex by physical mixing method, ACFC-PM-T: Ternary Inclusion complex by Physical mixing method, ACFC-IC-B: Binary inclusion complex by kneading method, ACFC-IC-T: Ternary enclosure complex by kneading method

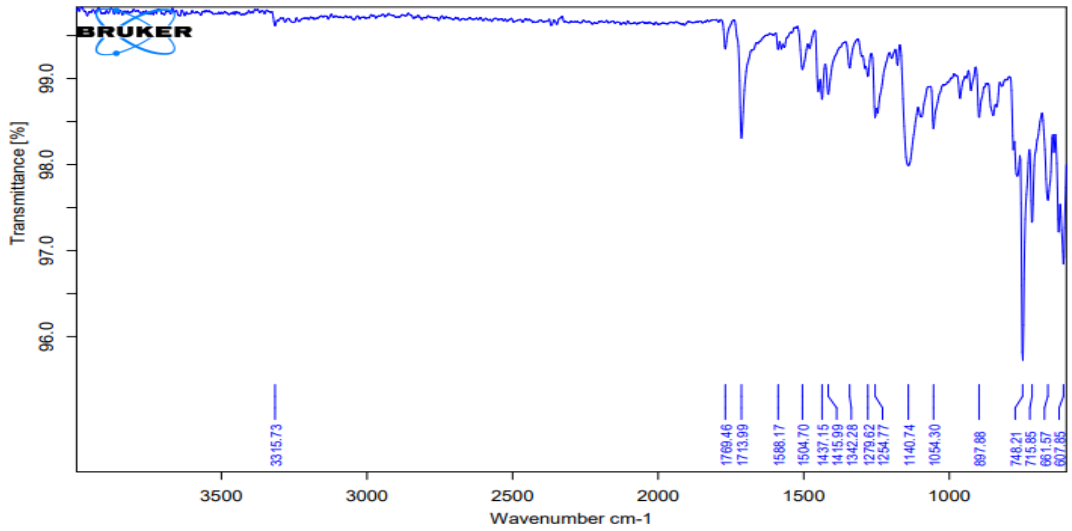

Figure 6: FTIR of Pure Drug ACFC

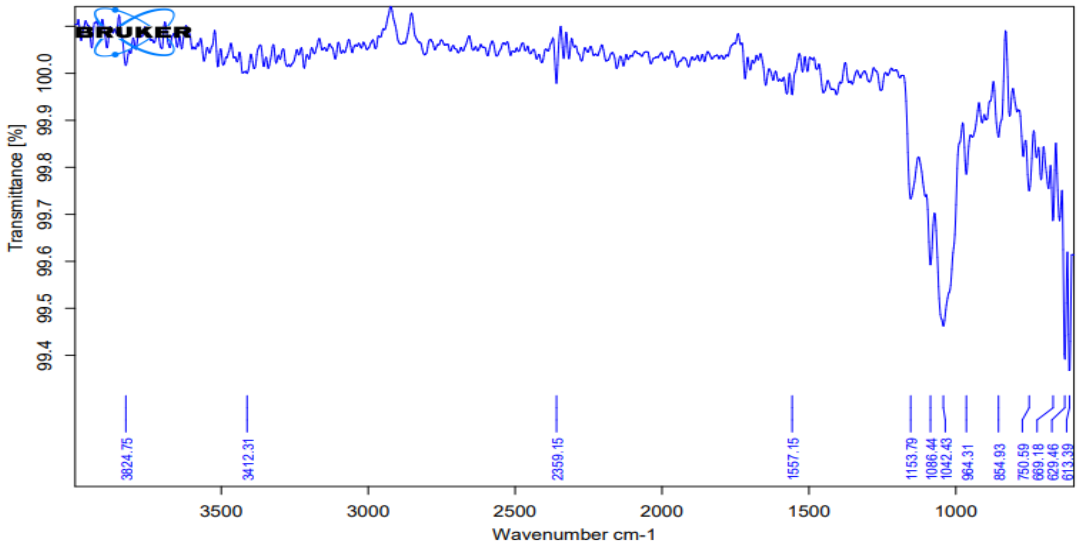

Figure 7: FTIR of ACFC-IC-T

Figure 8 shows that at 155°C, the pure ACFC exhibited a pronounced endothermic peak. The presence or lack of an endothermic peak at 370°C in the M-H-CD indicates the development of robust multicomponent inclusion complexes, as demonstrated in Figure 9, in contrast to the multicomponent inclusion complexes created by the kneading approach.

X-ray Diffractometry Studies

Crystalline nature of ACFC, M-β-CD and L-ARN was evaluated by X-ray diffraction studies. ACFC shows sharp and less diffused characteristic peak in diffraction pattern of drug which indicates crystallite nature of drug (Fig: 10). DSC of multicomponent inclusion complex (ACFC-IC-T) shows less sharp and highly diffused characteristic peak. The decreased intensity of characteristic peak in diffraction pattern of ACFC-IC-T shows the decreased in crystalline nature of ACFC (Pure) and formation of amorphous multicomponent inclusion complex formation.

1H NMR

^{1}H NMR spectra of ACFC as shown in Fig. 12 and gave the data, ACFC δ 3.476 (2H, CH2), δ 6.544–6.56 (H C4-H), δ 6.989 (4H),δ 2.07 (1H NH), δ 7.114 (2 H C3-H, C5-H). ^{1}H NMR spectra of ACFC-IC-T as shown in Fig. 13 and gave the data, δ 6.522–6.542 (H C4-H), δ 7.120 (2 H C3-H, C5-H), δ 3.589 (2H, CH2)), δ 6.939 (4H),. An increase in ACFC solubility is caused by the creation of an inclusion complex among ACFC and M-β-CD, as indicated by change in chemical shift, which also suggests existence of an auxiliary agent.

In-vitro Dissolution Studies

Figure 14 displays the in-vitro dissolution profile of ACFC and various inclusion complexes. Dissolution rate of ACFC (Pure drug) lower than ACFC-PM-T but ACFC-IC-T shows the higher dissolution rate than that of ACFC-PM-T. The rate of dissolution at 10 min for pure ACFC, ACFC-PM-T and ACFC-IC-T was found to be 9.11, 28.35 and 42.02, at 60 min dissolution rate was found to be 23.15, 74.59 and 83.74. Ternary complexes that included L-arginine and were made using the kneading approach outperformed other complex in terms of drug release and rate of dissolution of ACFC. Solubilizing activity of M-β-CD is improved by adding AXAs.

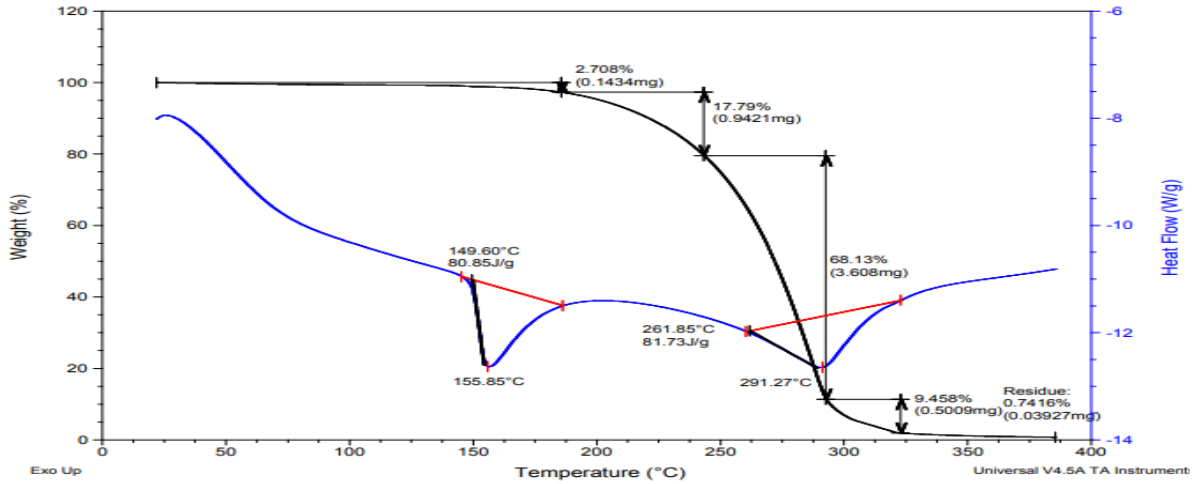

Figure 8: DSC of ACFC (Pure)

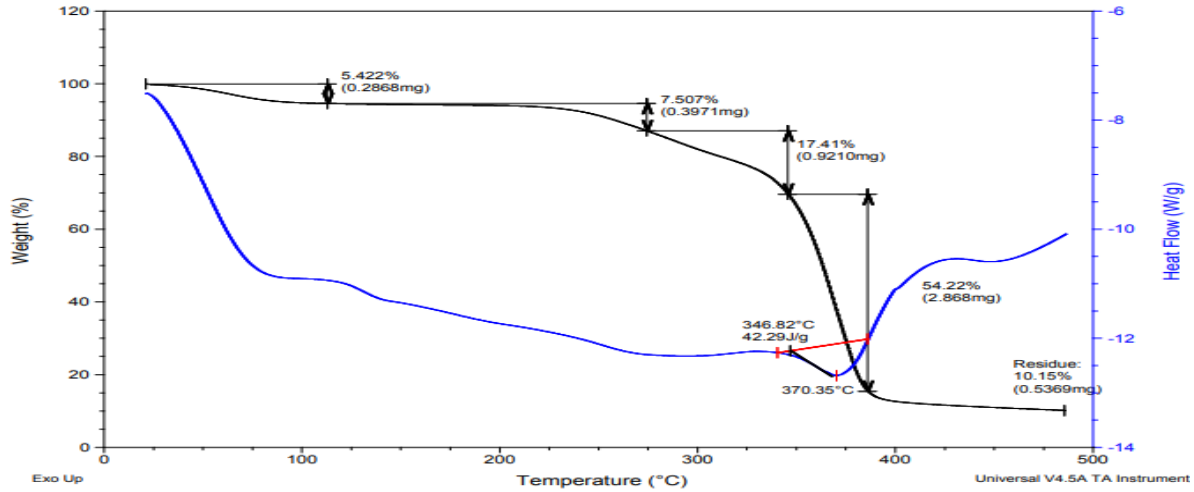

Figure 9: DSC of ACFC-IC-T

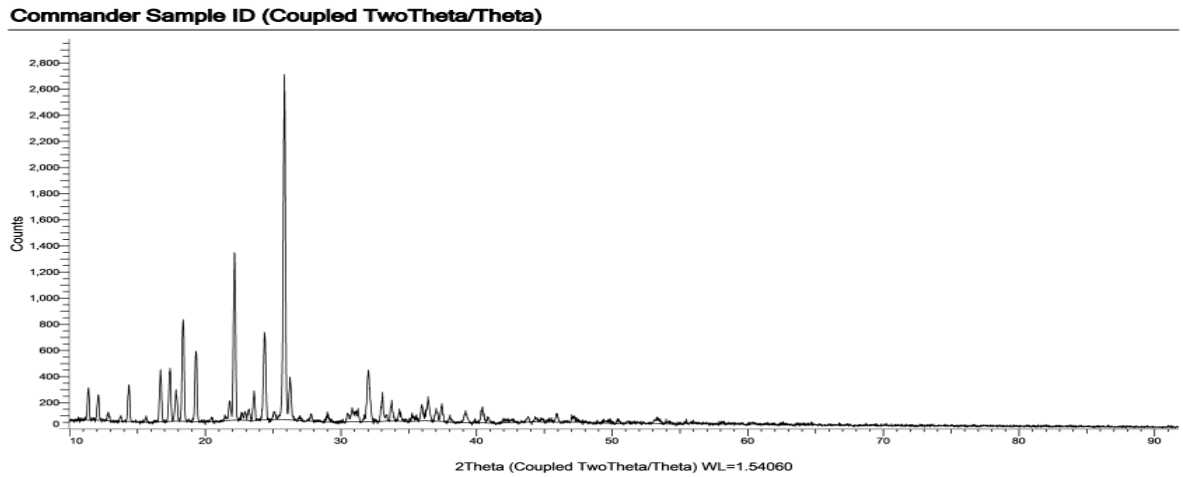

Figure 10: XRD of ACFC (Pure)

CONCLUSION

The study focuses on the solubility of ACFC in various AXAs and L-Arginine concentrations. The maximum solubility for ACFC was 29.93 µg/ml with L-ARG observed. The optimization of the concentration of AXAs was shown, and ACFC solubility increased linearly with increasing L-ARN concentrations up to 0.4%. To conduct phase solubility investigations and create ternary complexes, 0.4% L-ARN was utilized as the third component.Phase solubility studies were conducted on ACFC with cyclodextrin and its derivatives, with results suggesting that M-β-CD and HP-β-CD have a solubility curve similar to AL type, indicating first order reaction with

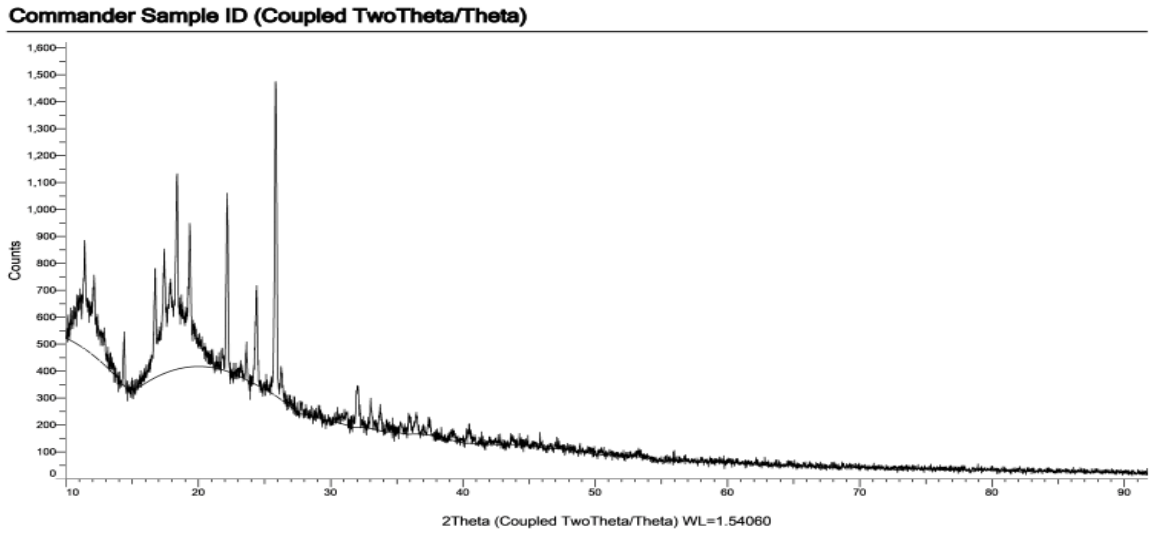

Figure 11: XRD of ACFC-IC-T

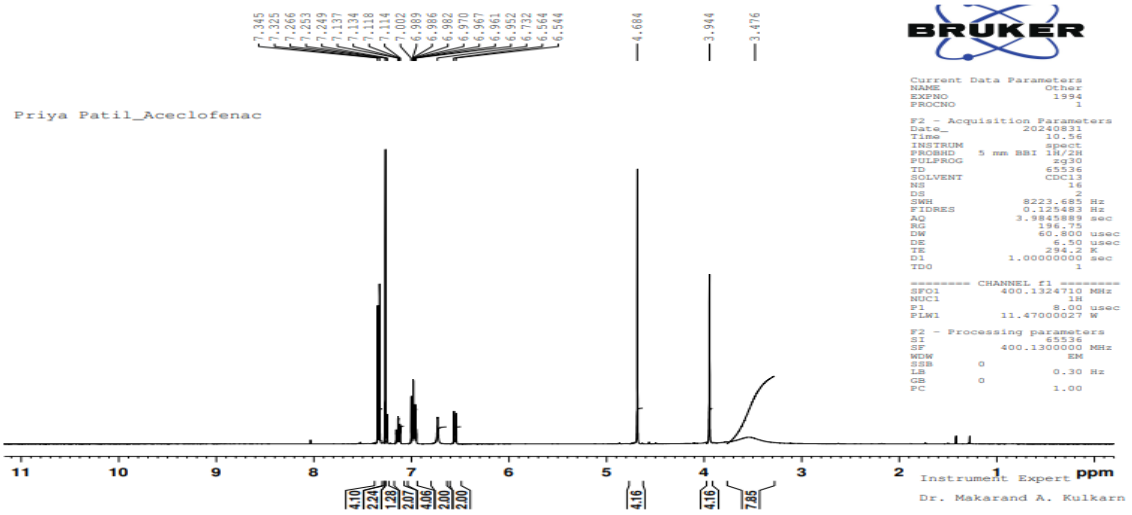

Figure 12: NMR of ACFC

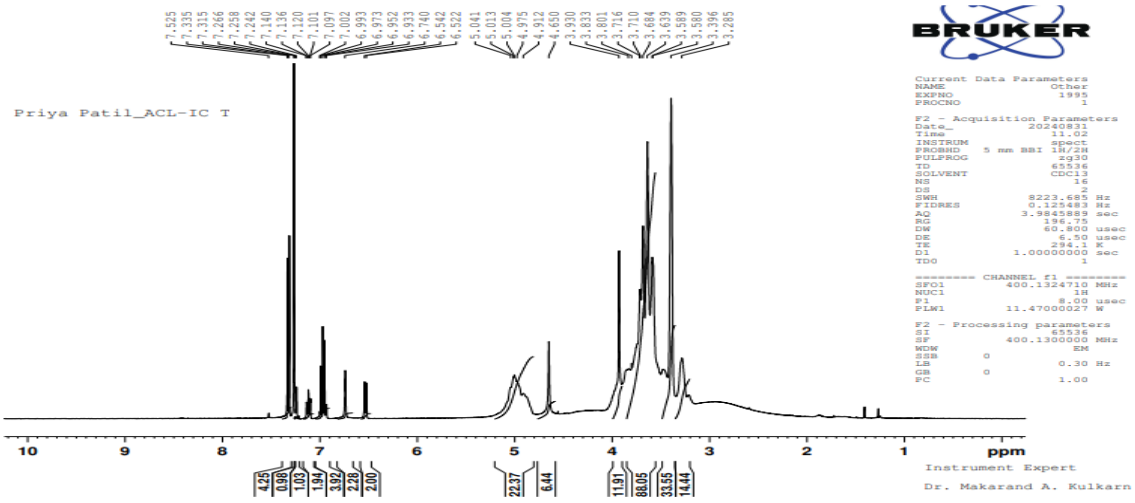

Figure 13: NMR of ACFC-IC-T

formation of water-soluble complex. ACFC is more soluble in M-β-CD with its increasing concentration and selected for establishment of inclusion complex in 1:1 molar ratio.

Saturation solubility tests were performed on ACFC, binary, and ternary complexes in water at 25 ± 20C. The ternary complexes formed by M-β-CD and L-ARN in

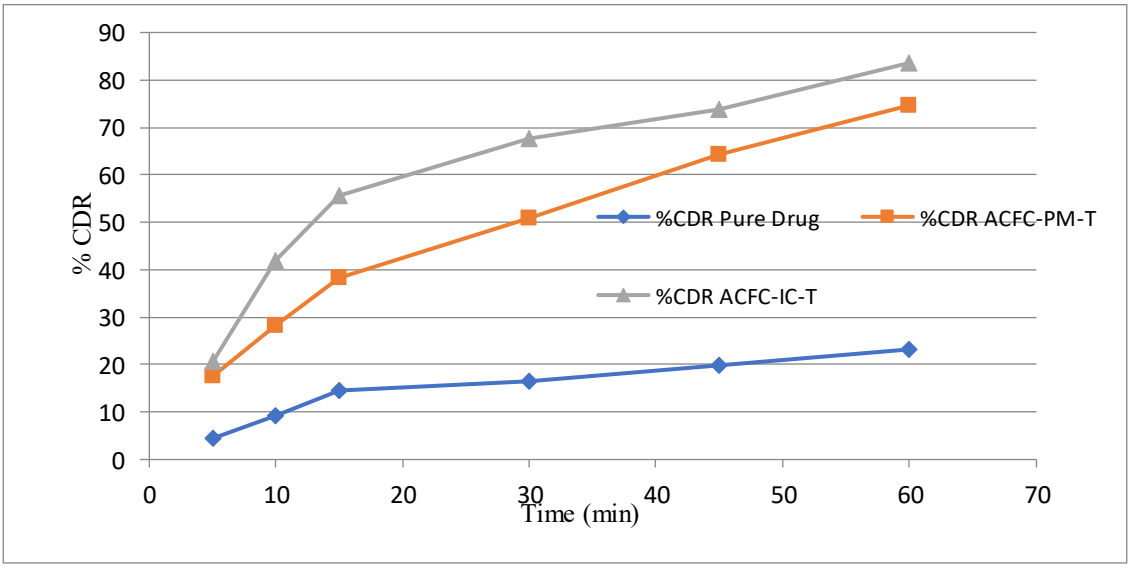

Figure 14: ACFC and complexes in-vitro dissolution pH 6.8 Phosphate buffer

1:1:0.4% ratios by kneading method showed the largest rise, 16 times higher than pure drug. FTIR spectrum of ACFC and multicomponent inclusion complex (ACFC-IC-T) showed various peaks for out plane bending for N-H.X-ray diffractometry studies evaluated the crystallite nature of ACFC, M-β-CD, and L-ARN, with ACFC showing a sharp and less diffused characteristic peak in diffraction patterns. 1H NMR spectra of ACFC showed an increase in solubility due to creation of an inclusion complex among ACFC and M-β-CD, suggesting existence of an auxiliary agent.

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