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Original Article

DEVELOPMENT OF BINARY AND TERNARY COMPLEX OF CEFUROXIME AXETIL WITH CYCLODEXTRIN FOR IMPROVING PHARMACEUTICAL CHARACTERISTICS

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ABSTRACT

Objective: The current research objective is systematic development and characterization of binary and ternary inclusion complexes of cefuroxime axetil with β-cyclodextrin to improve its pharmaceutical characteristics by using the kneading method.

Methods: Phase solubility study was carried out using Higuchi and Connors method. Based on its result, binary complexes of cefuroxime axetil with different ratio of β-cyclodextrin were developed and characterized using differential scanning calorimeter (DSC), fourier transform infrared spectroscopy (FT-IR) and X-ray powder diffractometry (XRD). Then, binary complexes were analyzed for *in vitro* dissolution testing. The ternary complexes were developed using different ratio of PVP K-30 as a ternary component and evaluated for *in vitro* dissolution testing and *in vitro* taste masking.

Results: Binary complex of cefuroxime axetil with β-cyclodextrin (1:1) showed better drug release than pure drug. During the development of the ternary complex, β-cyclodextrin (1:1) and 1% w/v PVP K-30 as a ternary agent resulted in an optimized ternary complex. The DSC, FT-IR and XRD studies clearly revealed the formation of binary and ternary complexes. The ternary complex showed better drug release of>85% within 30 min. in comparison to binary complex. The *in vitro* taste-masking study revealed the taste masking efficiency of the ternary complex of cefuroxime with β-cyclodextrin.

Conclusion: The developed binary and ternary complex of cefuroxime axetil based on β-cyclodextrin with PVP K-30 showed improved *in vitro* dissolution rate and taste masking in comparison to pure drug. The drug release was better in ternary complexes. The present research work successfully shows the utility of binary and ternary complexes for improving pharmaceutical characteristics of cefuroxime axetil.

Keywords: Cefuroxime axetil, Inclusion complex, Binary complex, Ternary complex, Cyclodextrin, Kneading method, Bioavailability, Beta-cyclodextrin

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INTRODUCTION

The main goal of oral drug delivery systems is to modulate the solubility of active pharmaceutical ingredients (APIs) that improve the absorption of the drug and its bioavailability also. About 40% of the new chemical entity (NCEs) in the pipeline and 60% of newly developed APIs are associated with low solubility that results less assimilation and bioavailability. The problem of low solubility is mainly related to the BCS (Biopharmaceutical Classification System) class-II and IV drugs. These drugs show low absorption that leads to inconsistent *in vitro-in vivo* correlation and poor bioavailability. The dissolution step is the rate-limiting factor for the assimilation of BCS class II drugs, whereas dissolution and permeability both are rate-limiting factors for BCS class IV drugs. Pharmaceutical researchers are constantly working on various approaches for improving the drug solubility and dissolution rate of BCS class II drugs, which improve the therapeutic responses and overcome the toxic effects owing to high dose [1-4]. The currently applied approaches for improving the dissolution rate of poorly soluble drugs are micronization, nanoformulations, salt formation, prodrug and drug derivatization, co solvency, use of surfactants, cyclodextrin complexes, change in crystal habit or co-crystals, self-emulsifying drug delivery systems, solid dispersions etc [5, 6]. Each technique has its own merits and demerits regarding solubility enhancement and the selection of suitable one mainly depends on the type of drug, polymers, therapeutic, and targeted delivery of drugs which to be obtained [7, 8].

Inclusion complexes have emerged as a viable and fruitful alternative for solid dispersions and other techniques for the development of solid state forms to improve pharmaceutical characteristics such as solubility, chemical stability, bioavailability and efficiency. Low toxicity and different cavity sizes of cyclodextrins (CDs) make it an important tool for enhancement of solubility and bioavailability of drugs [9], besides diminishing gastric irritation caused by several medicaments and improvement of bitter taste [10, 11]. Various methods are reported in the literature, such as co-precipitation, neutralisation, ball-milling, spray drying, kneading, freeze-drying, sealed-heating and solvent evaporation [12]. In the present investigation, the kneading technique was employed since it is an efficient technique for protecting medicament from chemical decomposition, lessening loss of potential because of low processing temperature and decline water content level [13].

These complexes were earlier known by some other names such as “occlusion compounds, adducts and clathrates” then Schlenk, a scientist, named the complexes as “inclusion compounds”. The size of the guest molecule is an important parameter in this technique such as the formation of a stable complex with desired physicochemical properties, the size of the guest molecule should be comparable to the host molecule so that it can easily entrap into the cavity of the host molecule [14].

Cyclodextrin complexes have attracted the researcher’s focus for the development of inclusion complexes due to several advantages accompanied by these formulations. Various technologies have been used for the synthesis of cyclodextrin complexes formation such as kneading, co-precipitation, solvent evaporation, lyophilization, spray drying etc [15, 16].

Cefuroxime axetil (CFA) is a β-lactamase-stable 1-acet-oxyethylester that is a prodrug of cefuroxime cephalosporin which is used for treatment of respiratory tract infection, pharyngitis, tonsillitis, acute bacterialotitis, urinary tract infections and simple skin infection. It consists of 1-acetoxymethyl ester that helps it in intestinal assimilation [17, 18]. It has less aqueous solubility with the bioavailability of 30%-60%. It belongs to BCS II class drug with of oral bioavailability of 37% on an empty stomach, upto 52% if taken after food with half-life of 1.2-1.6 h [19].

CDs are macrocyclic oligosaccharides capable for improving the solubility and bioavailability for poorly soluble molecules by encapsulating guest molecule in its inside void that is lipophilic in nature [20-23].

For BCS II, the rate-limiting step is medicament discharge from the dosage form and its solubility in the GI fluid and not the assimilation; thus by improving solubility, bioavailability also improves. Thus, the primary objective of the present research is to develop binary and ternary inclusion complexes of cefuroxime axetil with β-CD and PVP K-30 for improving its pharmaceutical characterization.

This investigation mainly focused on analysis of physicochemical features of the inclusion complexes of CFA with β-CD in the presence of PVP K-30 as a ternary component. The complexes were developed by kneading technique and characterized by differential scanning calorimetry (DSC), FT-IR and X-ray powder diffractometry (XRD).

MATERIALS AND METHODS

Materials

Cefuroxime axetil was obtained as a gift from Sun Pharmaceutical laboratories, Gurugram, India. β-CD was purchased from Central drug house Ltd, Delhi, India and PVP K-30 from Loba Chemie Pvt. Ltd. Mumbai, India. All chemicals and reagents of analytical grades were utilized.

Methods

Phase solubility studies

It is mostly employed technique for the investigation of inclusion complexation. Its profiles do not authenticate the development of inclusion complexes but only depict how the increment in CDs concentration influences the solubility of medicament. It also helps in the determination of the stoichiometry ratio for drug and cyclodextrin [24].

According to Higuchi and Connors method, the excess quantity of CFA was incorporated to 20 ml of aqueous solutions containing various concentrations of β-CD (2-10 mmol. L^{-1}) without the addition of PVP K-30. Whatman filter paper was used for the filtration of samples which were obtained after shaking of suspension on a rotary shaker for 48h at 125 rpm until equilibrium is attained. Then, filtered solutions were appropriately diluted and investigated under spectrophotometrically (UV–vis spectrophotometer) at 281 nm [25-27].

Equation (1) and (2) are used for the determination of association constant (Ks) of complex and CE of β-CD, respectively.

$$K_{D:CD} = \frac{\text{Slope}}{S_0\,(1-\text{Slope})} \quad \ldots\ldots (1)$$

S ° is the solubility of CFA in absence of β-CD.

"S ° is the intercept and slope is obtained from the phase solubility diagram constructed by plotting concentration of drug on y-axis and concentration of β-CD on the x-axis."

It provides information regarding the stoichiometry for the formation of complex.

$$CE = K_{D:CD}S_0 = slope/(1-slope) \quad \ldots. (2)$$

The primary purpose behind the phase solubility study was to determine the stability constants and complexation efficiency, to find out which complex is stable among different ratio of CDs in the binary complex [28, 29].

Formulation of binary inclusion complexes

A fixed amount of the drug and β-CD were weighed as shown in table 1. First, β-CD was incorporated to the mortar; a minute amount of methanol was also incorporated during trituration to obtain slurry-like consistency. Cefuroxime axetil (drug) was incorporated slowly into the slurry and triturated for a half-hour. The obtained paste was dried in a hot air oven for 24 h at 40 °C, stored in desiccators over fused calcium chloride and then, the dried paste was passed through sieve no. 60 and packed in the container. Similarly, the preparation of the binary complex of molar ratio 1:3 and 1:5 was prepared and packed in the container for further analysis [30].

Table 1: Formulation of binary and ternary complexes

S. No.	Inclusion complexes	CFA (mg)	β-CD (mg)	PVP K-30 (%w/v)
1.	Binary complex (1:1)	1.021	2.270	-
2.	Binary complex (1:3)	1.021	6.810	-
3.	Binary complex (1:5)	1.021	11.350	-
4.	Ternary complex (0.25%w/v)	1.021	2.270	0.25%
5.	Ternary complex (0.50% w/v)	1.021	2.270	0.5%
6.	Ternary complex (1.0 %w/v)	1.021	2.270	1.0%

Characterization

FT-IR analysis

FT-IR study of drug, excipients and complexes were carried out with (FT-IR Alpha Bruker 1206 0280, Germany) by KBr disc method to identify the functional groups present in them. The spectra were recorded over the 4000-400 $cm^{-}1$ range and analyzed [31, 32].

DSC study of binary complexes

DSC measurements were carried out on DSC Q10 V9.9 Build 303 to investigate the thermal behavior of samples. This technique is used to study the thermal transition of a polymer. For example, the melting point of a crystalline polymer, glass transition and crystallization temperature. The samples (2 mg) of individual substances i.e. CFA, β-CD and complexes, were weighed and thematically sealed in flat bottomed aluminum pan with crimped on the lid. The pan was placed on the sample holder and an empty pan was placed on the reference pan holder of DSC apparatus. The samples were heated in an atmosphere of nitrogen gas bypassing it at 60 ml/min flow rate over a temperature range from 40-300 °C [33, 34].

XRD analysis of binary complexes

This study was performed at PW1710 X-ray diffractometer with Cu as anode material and graphite monochromator, operated at a voltage of 35kV, current 40 mA in the 2θ angle range of 10-70 °C with scan time of 0.5s. The X-ray diffractogram showed narrow and broad peaks reflecting the nature of drugs, excipients and complexes [35].

Dissolution studies

This study was conducted in the dissolution test apparatus-II paddle (Disso2000 Tablet dissolution test apparatus, Lab India, Mumbai, India). 1025 mg of pure CFA/complexes were incorporated into a vessel that contained 900 ml of 0.1N HCl, maintained at 37±0.5 °C at

50rpm. 5 ml of aliquots were collected at predetermined time intervals and filtered through Whatman filter paper, suitably diluted and investigated spectrophotometrically (Shimadzu UV–vis spectrophotometer 1800, Japan) at 281 nm [36, 37].

Preparation and characterization of ternary inclusion complexes

Binary complex of molar ratio 1:1 showed 85.53% release, which was more significant than rest two complexes. The formation of ternary inclusion complexes of the drug and β-CD in the molar ratio of 1:1 was selected for the formulation of a ternary complex with PVP-K30. The formulations of ternary complexes is shown in table 2 and characterized for phase solubility, FT-IR, DSC, PXRD and % CDR as performed for binary complexes [38-42].

***In vitro* taste evaluation study**

The objective of taste masking is the reduction/inhibition of the interaction between the drug and the taste buds. Dissolution testing should be conducted for confirmation of the slow discharge of drug in the oral cavity, which is crucial for taste masking of the drug. Molecules with high bitter levels have a lower acceptable range of drug discharge and vice-versa, thus there is no range for acceptable drug release. Slow discharge of the drug results into taste-masking due to drug is present in minimal and below the bitterness threshold in the oral cavity. In this analysis, the drug is analyzed from the dissolution media of phosphate buffer (pH 6.8) at concentrations below its bitterness threshold [43-47]. Threshold bitterness concentration is the lowest concentration that had a bitter taste. In the present study, the bitterness threshold concentration was taken from reported literature on cefuroxime axetil [48].

A quantity of optimized inclusion complex equivalent to 100 mg of cefuroxime axetil was incorporated to a volumetric flask containing 10 ml of phosphate buffer. The mixture was vortexed for 30s, filtered and analyzed for cefuroxime axetil concentration at 281 nm by UV-Visible spectrophotometer and that was compared with the threshold value. For acceptable taste masking, the quantity of solubilized medicament within 30s should not be greater than the threshold bitterness concentration of the medicament [49].

RESULTS

Phase solubility studies

The phase solubility diagrams of CFA in aqueous β-CD solution in the presence or absence of PVP K-30 demonstrated AL type of solubility curve with linear increment in CFA solubility upon increment in concentration of β-CD as shown in table 2 and fig. 1.

Table 2: Solubility of cefuroxime axetil with increasing concentration of β-CD

S. No.	β-CD(mmol. L-1)	CFA/β-CD(mmol. L-1)	CFA/β-CD/PVP K-30 (mmol. L-1)
1	2	0.78**±0.05**	0.94**±0.06**
2	4	1.03**±0.03**	1.38**±0.03**
3	6	1.49**±0.07**	1.79**±0.06**
4	8	1.72**±0.08**	2.2**±0.12**
5	10	1.93**±0.10**	2.61**±0.04**

(n=3) with mean±SD.

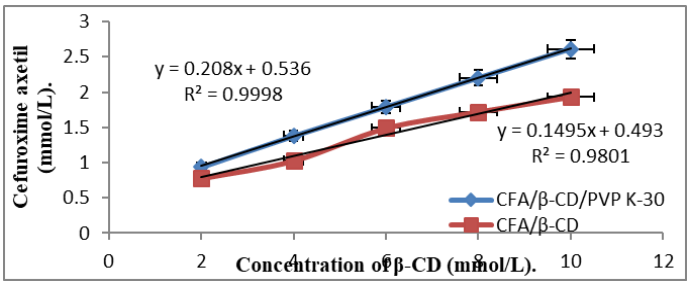

Fig. 1: Phase solubility study of binary and ternary complex, (n=3) with mean±SD value

Its slopes were found to be less than 1 which indicates that 1:1 stoichiometry developed water-soluble complexes [13, 25]. The values of S_0, slopes, Ks, and CE of complex enhanced with the addition of PVP-K30 to the complexation media, demonstrating better efficacy of ternary over the binary complex. This may be due to electrostatic/hydrogen bonding interaction and salt formation of PVP K-30 with β-CD and CFA. Apart from this, molecular interactions such as hydrophobic bonding, van der waals dispersion forces, which are based on solubilization of the medicament that promote the release of high-energy water molecules exist in the cavity, might also have responded to valuable effects of PVP-K30 as a ternary component. This data showed that the system released energy upon complexation and the presence of PVP-K30 makes it more favorable, signifying its importance as a ternary component for the development of ternary complexes. Jagtap *et al.,* also obtained similar results in their research [50].

FT-IR analysis

FT-IR analysis of model drug CFA revealed various characteristics peaks such as peaks at 1798.40 cm^{-1} corresponding to amide cefum ring, 673.96 cm^{-1} corresponding to–C-S stretching, 1156.82 cm^{-1} corresponding to–C-N stretching, 1332.76 cm^{-1} corresponding to–C=O stretching, 3476.72 cm^{-1} corresponding to–N-H stretching (primary amide) and 1601.1 cm^{-1} for carboxylic C=O stretching for carboxylic bond. While β-CD showed its characteristics peaks at 3420.02 cm^{-1}corresponding to-O-H stretching, 2956.08 cm^{-1} corresponding to aliphatic-C-H stretching, 1077.10 cm^{-1} corresponding to–C-O stretching. PVP K-30 revealed its characteristic peaks at 3278.25 cm^{-1} corresponding to stretching vibration of–O-H, 2924.59 cm^{-1} corresponding to–CH stretching, 1643.28 cm^{-1} corresponding to–C=O stretching, 1252.18 cm^{-1} corresponding to-C-N stretching. FT-IR spectrum is demonstrated in fig. 2.

After the formation of complexes, the peaks describing functional groups of the drug disappeared or shifted left or right, evidencing the entrapment of drug into the cavity of β-CD.

In FT-IR spectra of binary complexes, alterations in shift, shape and extinction of peaks were found that showed the development of satisfactory inclusion complex as shown in fig. 2. Among observed shifts, it is feasible to list for guest: loss of the peaks at 3420 cm^{-1} (OH stretch), 2924 cm^{-1} and 2834 cm^{-1} (CH sp^3), which authenticate the presence of inclusion in host cavity. Moreover, these outcomes recommend that a molecule enters in the host by means of the

condensed rings A and C, portions with the lowest polarity. The intense shift and enhanced intensity of band in 3320 cm^{-1} also confirmed localization of guest in host cavity. In addition, existence of 1021 cm^{-1} peak demonstrates that no chemical interaction occurred on the external host face. Similar results were obtained by Sapte *et al.,* in their study [51].

DSC analysis

This technique helps in investigating the interaction between a guest and host molecules during the formation of the binary complexes. Alteration in melting points occurs due to the embedment of guest molecules in the cavity of β-CDs. The thermogram of CFA, β-CD and binary complexes are demonstrated in fig. 3. The DSC curve of CFA exhibited glass transition temperature (Tg) at 81.90 °C that indicated its amorphous nature. The presence of a wide endothermic peak at 137.52 °C in curve of β-CD was recognized due to losing water from β-CD cavity. In DSC of the physical mixture, the band has been shifted toward right but showing two endothermic peaks evident of no complex formation. The binary complexes had wide peaks at 147.18 °C and assignable to loss of water content and loss of Tg of CFA confirmed entrapment of CFA inside β-CD cavity with water molecules as a substitution. These results justify the presence of strong physical interaction between CFA and β-CD and the fabrication of stable binary inclusion complexes in solid-state [52]. The results obtained are in agreement with the similar study by Ding *et al.,* showing the justification of the results obtained [53].

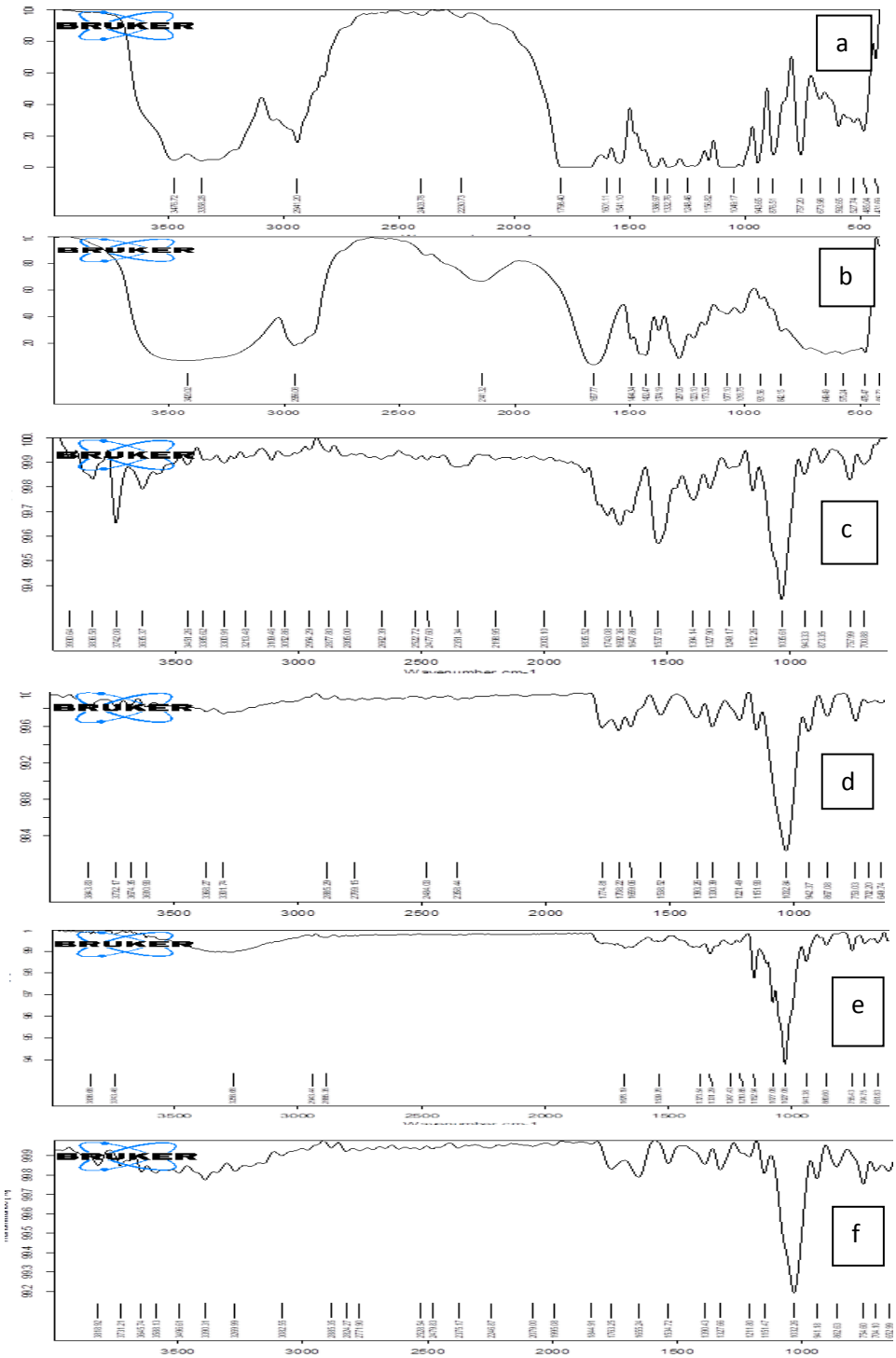

Fig. 2: FT-IR analysis of a) CFA, b) β-CD, c) physical mixture, d) Binary complex 1:1, e) Binary complex 1:3 and f) Binary complex 1:5

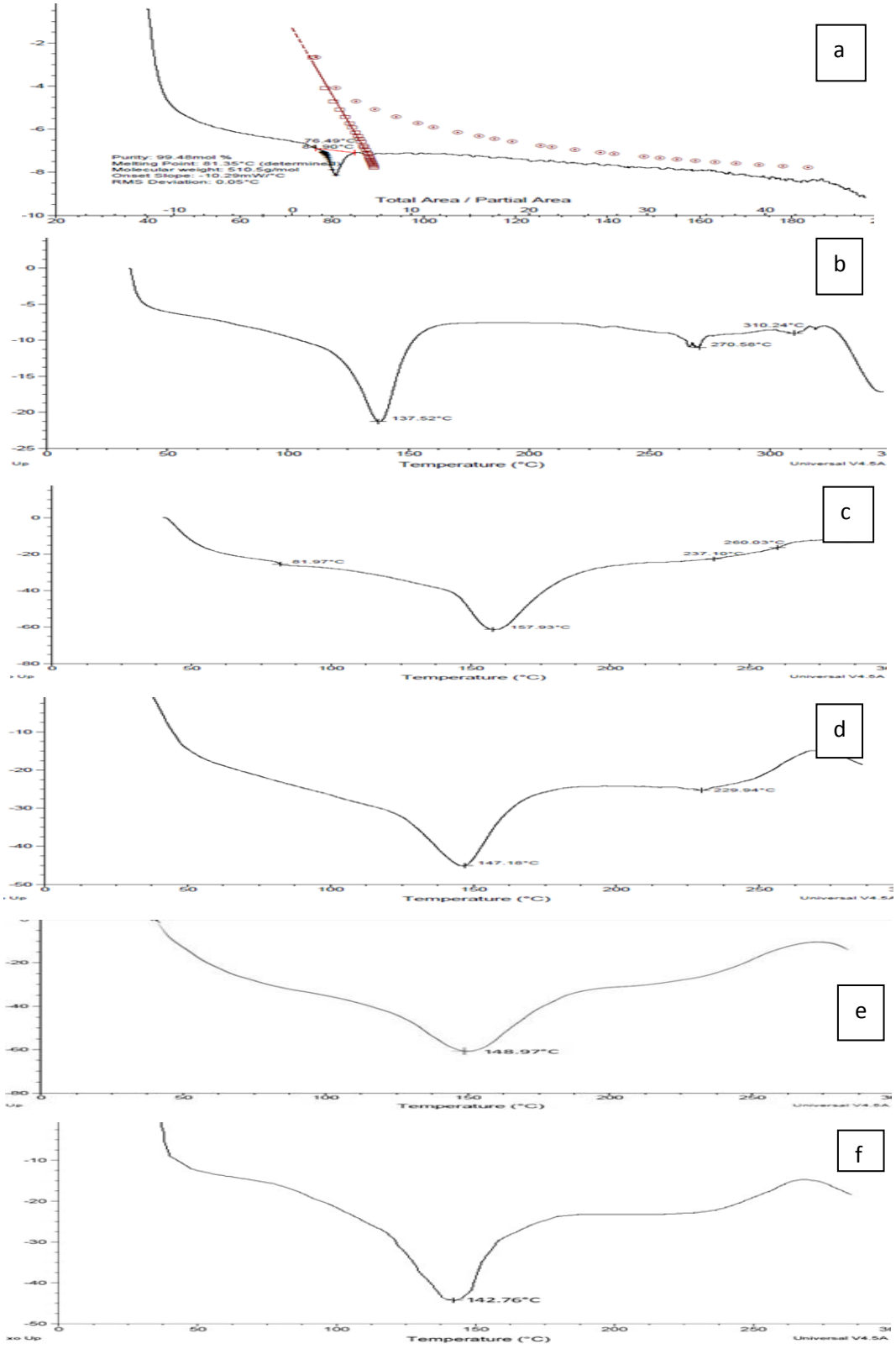

Fig. 3: DSC spectrum of a) CFA, b) β-CD, c) Physical mixture, d) Binary complex 1:1, e) Binary complex 1:3 and f) Binary complex 1:5

XRD analysis

The physical state of pure drug and its binary complexes could be evaluated by investigating their XRD spectrum, as depicted in fig. 4. The diffractogram of CFA showed diffused peaks that confirmed its amorphous nature. The diffractogram of β-CD showing peaks at 2θ value of 11.94, 12.57, 15.29, 17.07, 19.05, 20.74 and 22.56. The diffractogram of the complexes showed no diffused maxima, such as the formation of sharp, narrow peaks indicating the crystalline nature of complexes due to entrapment of amorphous drug into crystalline cavity of cyclodextrin.

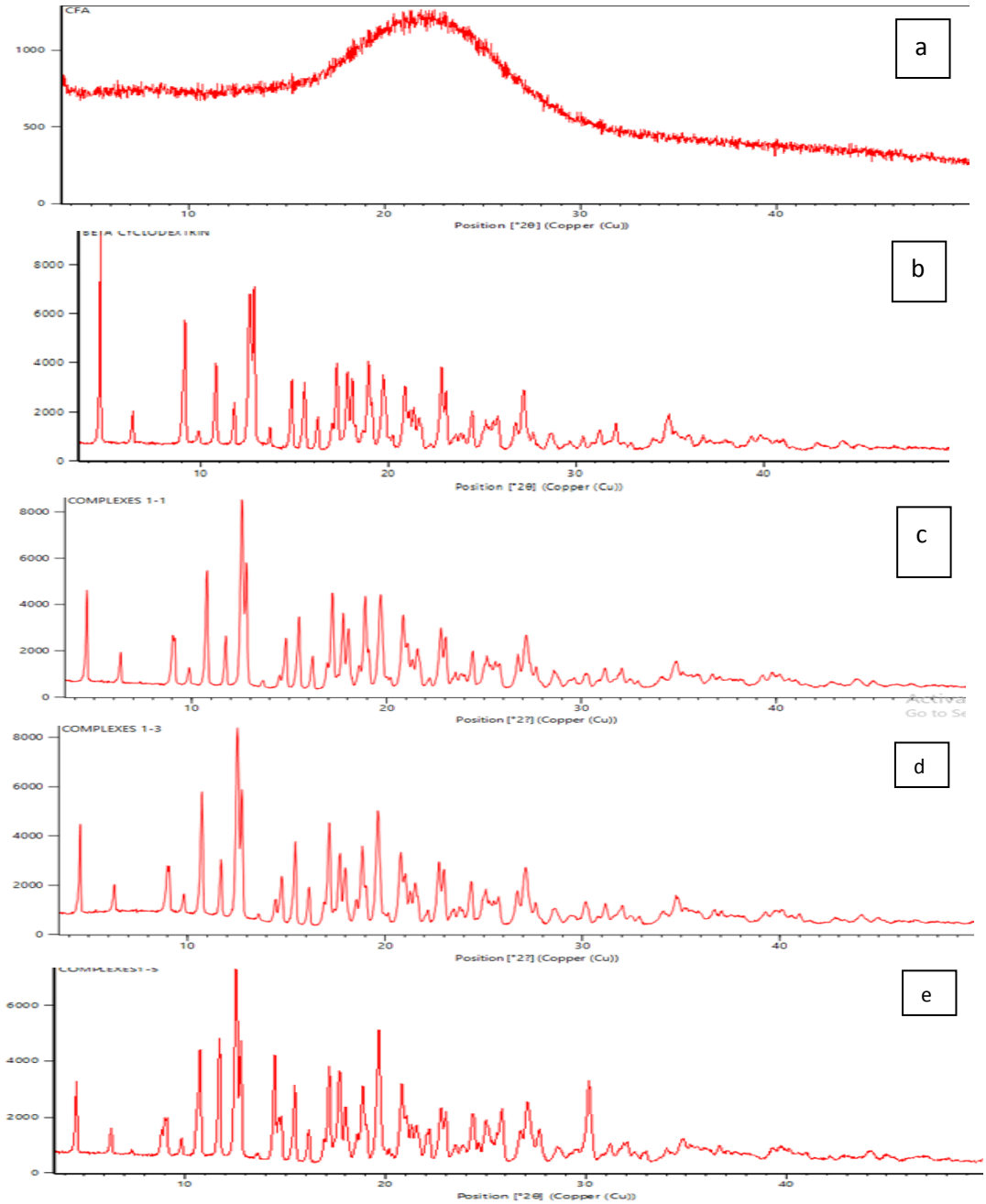

Fig. 4: XRD spectrum of a) CFA, b) β-CD, c) Binary complex 1:1, d) Binary complex 1:3 and e) Binary complex 1:5

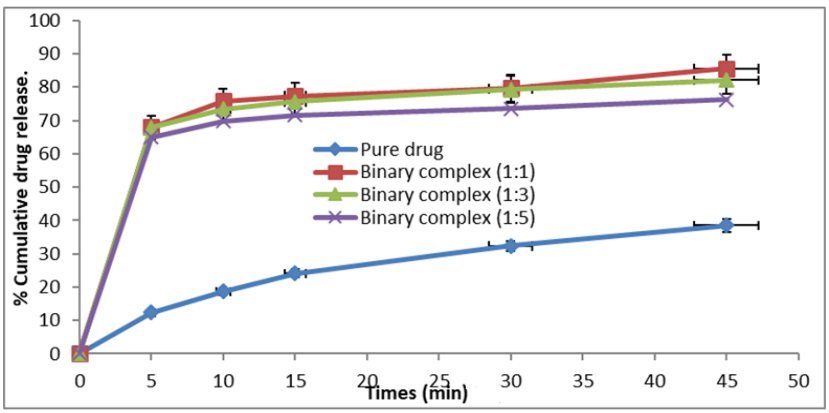

Fig. 5: Comparative % CDR of pure drug and binary complexes, (n=3 with mean±SD)

Evaluation of ternary inclusion complexes

FT-IR analysis of ternary complexes

In inclusion complex formation, no covalent bond is formed as demonstrated in fig. 6. Only dipole-dipole interaction, van der waal forces and hydrogen bonding are formed. In the complexes, some peaks of functional groups of cefuroxime axetil were absent and some were shifted from the original range indicating entrapment of cefuroxime inside the cavity of beta-cyclodextrin [51].

DSC study of ternary complexes

The complexes showed the shifting of the endothermic peak in all the thermogram, confirming the development of inclusion complexes. The sharp endotherm got converted to broad endotherm and shifted to its right as shown in fig. 7 [51].

XRD analysis

In ternary complexes, overlapping of β-CD and PVP K-30 crystalline peaks was observed as shown in fig. 8. However, peaks of PVP K-30 were dimmed to a certain extent because of solid-state interaction during the development of ternary complexes [50].

***In vitro* % cumulative drug release studies of ternary complexes**

This study was conducted in 0.1N HCl using the USP-II apparatus at 37±2 °C and at 50 rpm for ternary complexes. Results of *in vitro* % cumulative drug release of ternary complexes with different concentrations of PVP K-30 are shown in fig. 9.

In vitro % cumulative drug release studies of ternary complexes showed the best dissolution in complex having 1% w/v PVP K-30. The release is much higher because of the hydrophilic nature of polyvinylpyrrolidone. As the concentration of PVP K-30 increases, the dissolution of complexes also gets increased. But, there was no role of PVP K-30 to mask the bitterness of cefuroxime axetil. Prabhakaran *et al.*, also found similar results that authenticate the accuracy of the results [51].

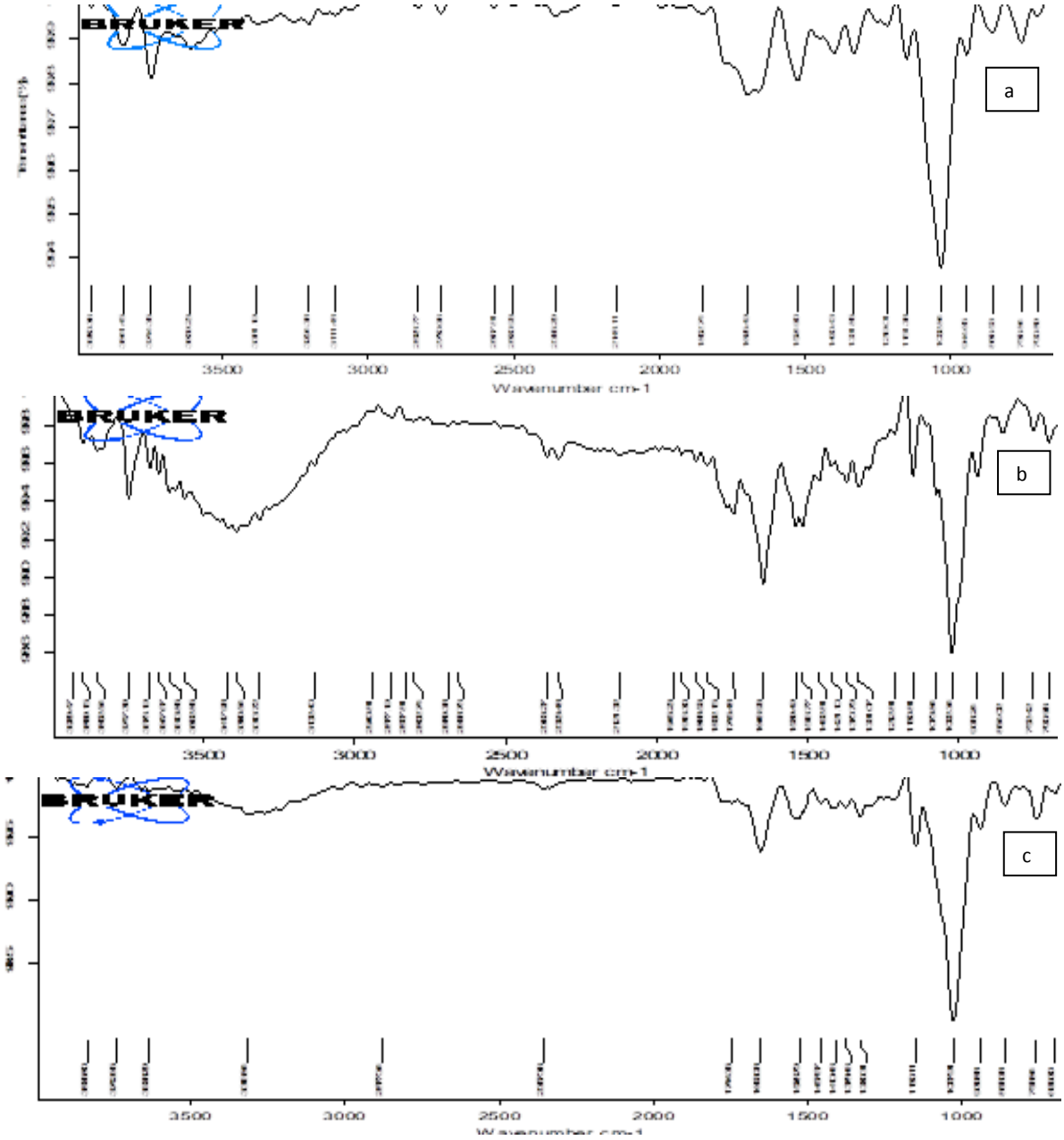

Fig. 6: FT-IR spectrum of a) Ternary complex with 0.25% PVP, b) Ternary complex with 0.5% PVP and c) Ternary complex with 1% PVP

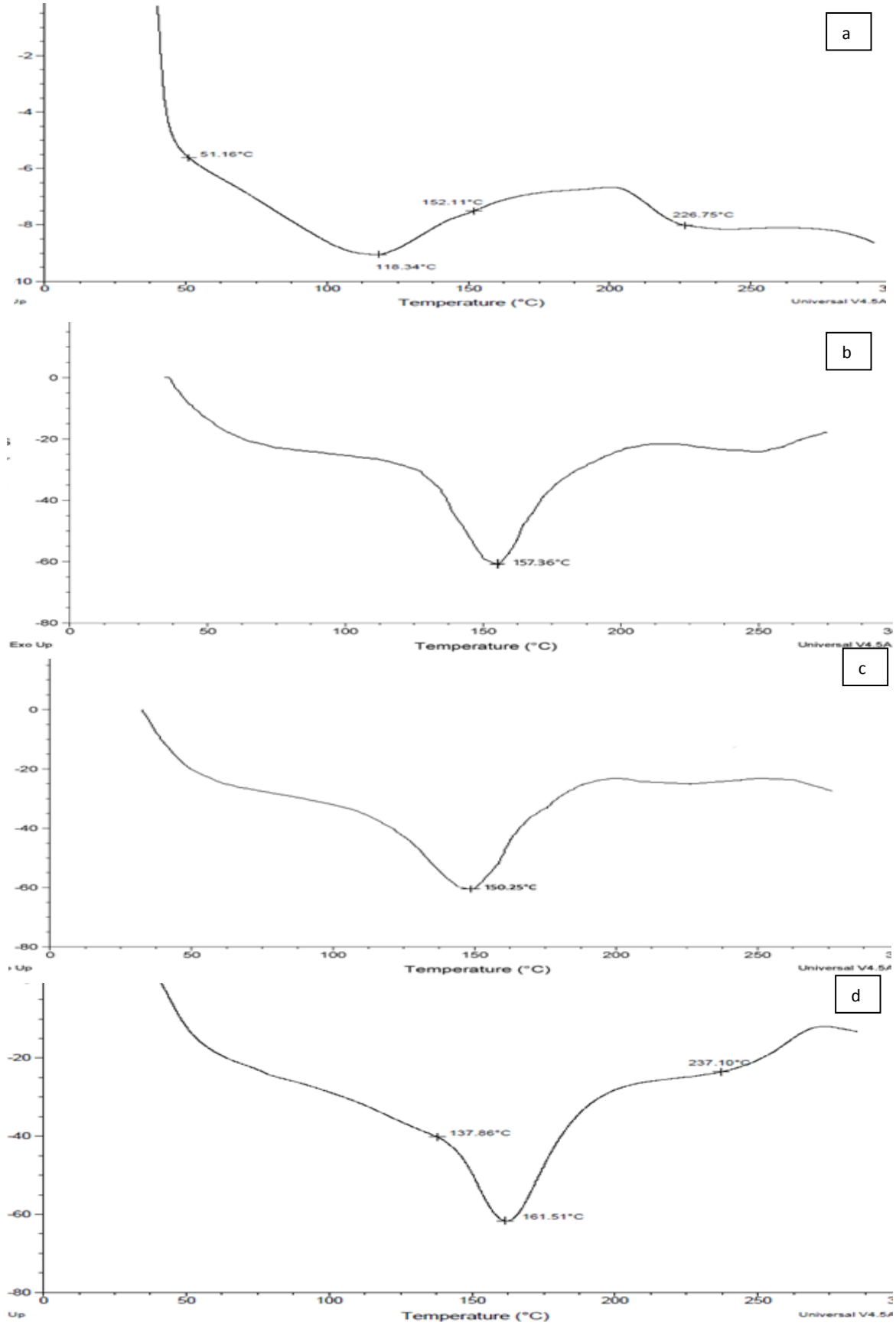

Fig. 7: DSC spectrum of a) PVP-K30, b) Ternary complex with 0.25% PVP, c) Ternary complex with 0.5% PVP and d) Ternary complex with 1% PVP

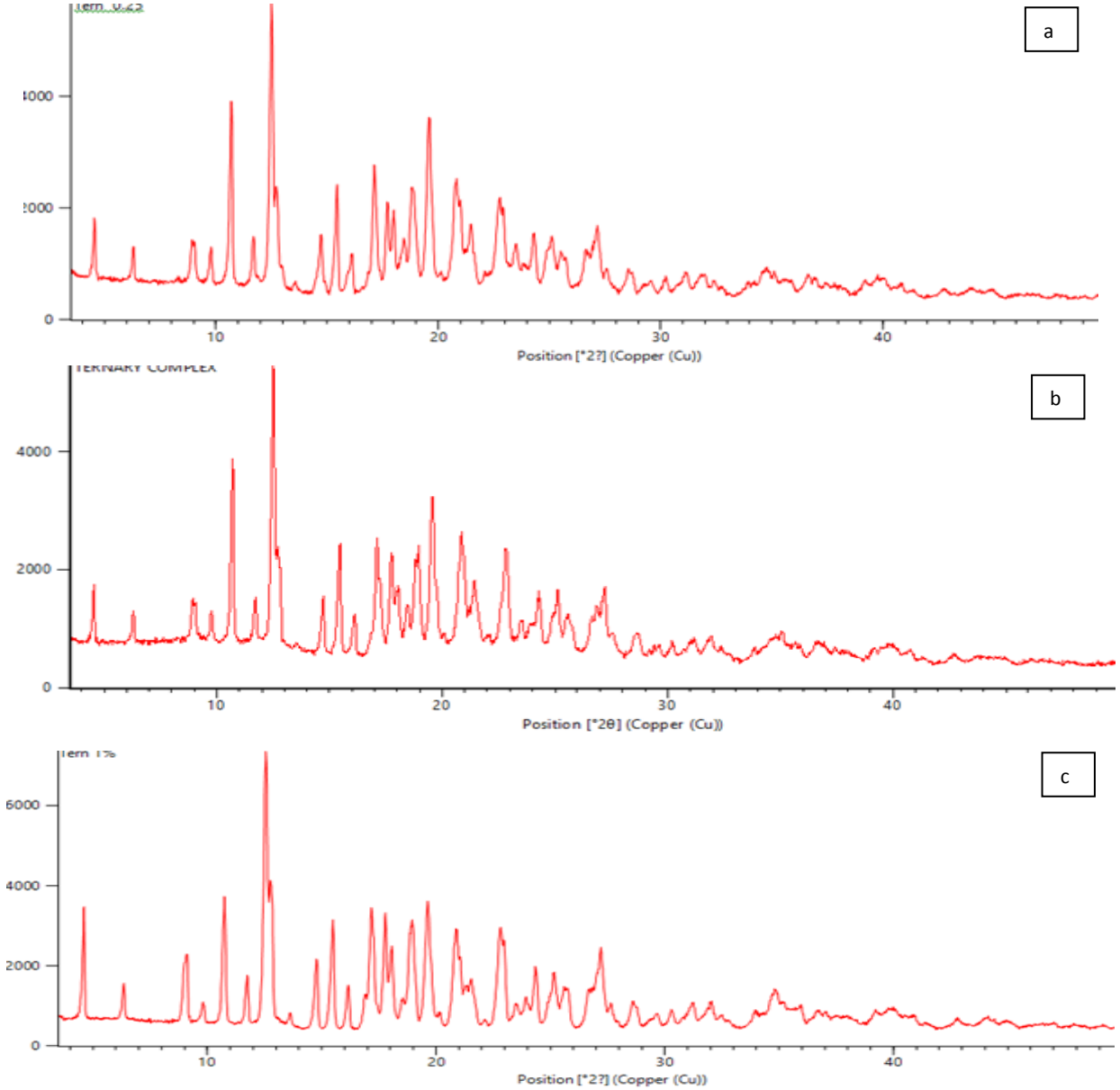

Fig. 8: XRD spectrum of a) Ternary complex with 0.25% PVP, b) Ternary complex with 0.5% PVP and c) Ternary complex with 1% PVP

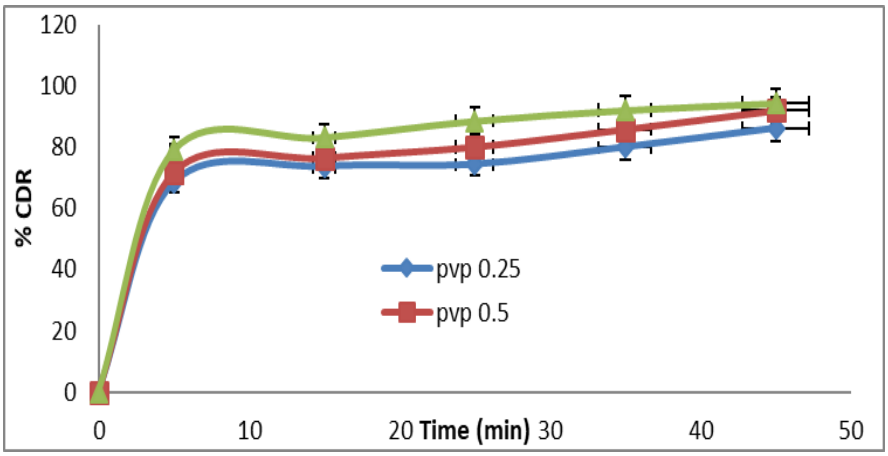

Fig. 9: % CDR of ternary complexes with different concentration of PVP K-30, (n=3 with mean±SD)

***In vitro* taste evaluation study**

The reported bitterness threshold value of CFA is 40µg/ml [49]. A quantity of prepared ternary inclusion complex equivalent to 100 mg of CFA was incorporated to a volumetric flask consisting of 100 ml of 6.8 phosphate buffer. The mixture was vortexed for 30s, filtered and analyzed. The amount of CFA dissolved in the phosphate buffer was detected to be 37.23µg/ml, which is below the threshold value at the end of 30s, indicating the masking of the bitter taste of the drug [54].

CONCLUSION

In this study, the binary and ternary complexes of cefuroxime axetil were prepared by the kneading method. It was concluded that PVP K-30 can act as a ternary component for improving the pharmaceutical characteristics of CFA with β-CD. Ternary complexes resulted in a better dissolution profile than binary complexes with>85% drug release within 30 min owing to the positive effect of incorporation of basic PVP K-30, which drastically improved phase solubility parameters like Ks and CE, interacting simultaneously both with β-CD (via H-bonding) and CFA (via electrostatic interactions and salt formation). The *in vitro* taste-masking study also revealed that the ternary complex was able to mask the bitter taste of the drug. Thus, it can be concluded that ternary systems of CFA with β-CD and PVP K-30 is a viable method for improving the pharmaceutical characteristics of cefuroxime axetil.

Ethics approval and consent to participate

Not Applicable.

Human and animal rights

No humans/animals were used for studies for this research investigation.

Availability of data and material

The authors confirm that the data supporting the results and findings of this study are available within the article and its supplementary materials.

Consent for publication

Not Applicable.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Authors declare no conflict of interest financial or otherwise.

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