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Amino Acid as Co-Crystal Coformer for Ebastine Solubility Enhancement

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ABSTRACT

Background: Ebastine (EB) is a selective, nonsedating H1 antihistamine belonging to Class II(BCS); its insufficient water solubility limits its oral bioavailability. Cocrystal is one of the most modern techniques used to increase the solubility and dissolving rate of a medicine, among other physicochemical properties.

Aim: The primary purpose of this study was to construct and assess EB cocrystal as an experiment to improve its solubility.

Methods: Various processes, such as solvent evaporation and liquid asset grinding with varying molar ratios of amino acid as a co-former, have been used to produce cocrystals. The produced formulations were evaluated by yield %, drug content, saturation solubility, in vitro dissolution tests, Powder X-ray Diffraction (PXRD), and scanning electron microscopy.

Results: Increased solubility by 364 times in distilled water with an improved dissolving profile.

Conclusion: Due to its ability to enhance physicochemical and mechanical qualities, co-crystallization is a promising method for solid formation. Using unique hydrogen bond synthon motifs, co-crystals have been successfully produced from several medications and co-former

Keyword: Ebastine,l-prolin ,l-histidin ,asparagine ,solvent evaporation ,liquid assist grinding.

INTRODUCTION

Recent researches in pharmaceutical formulations aimed to improve material, dissolution, and storage stability of active pharmaceutical ingredients [(1)].

The Food and Drug Administration (FDA) defines typical co-crystal as "multi-component solid crystal supermolecular complexes comprised of two or more constituents inside a crystals lattice where the constituents are in the neutral state and interact through non-ionic bond [(2,3,4)]

Co-crystals are often classified into two types, which are both molecular and ionic co-crystals. Molecular co-crystals consist of two or more different neutral components and are kept together by hydrogen or halogen bonds .On the other hand, ionic co-crystals have at least one ionic component and were maintained by coordination bonds or charge-aided hydrogen bonds in the case of the presence of metal cations [(5)].

Cocrystallization was defined as the modification of a compound molecular structure and altering its physical properties. This modification can be used industrially to minimize the need for additional additives and allowing the physicochemical properties of drugs to be improved[(6)].

Amino acids are natural zwitterionic molecules with relatively low toxicity compared to other coformers

In addition, research indicated that it was straightforward for amino acids to build charge-aided hydrogen bonding chains in crystalline stages and co-crystals. Amino and carboxyl groups of amino acids were good hydrogen bond donors and acceptors, making amino acids excellent candidates for zwitterionic coformers co-crystals [(7)].

Pharmaceutical co-crystals

A "pharmaceutical co-crystal" is created via hydrogen bonding or other non-covalent bond, such π-π interaction and van- der-Waals bond, between an active pharmaceutical ingredient (API) and a coformer in a specific stoichiometry ratio. Coformer is either ionic or a neutrally nontoxic inactive chemical selected from the (FDA) and (GRAS) list, or it is another active pharmaceutical ingredient. Co-crystal formation necessitates knowledge of the drug's target, selection of a suitable coformer, and many tests [(8)].

Co-crystal formation permits the modification of key physicochemical properties of pharmaceuticals, such as solubility, dissolution rate, temperature and humidity stability, and compressibility. The co-crystal synthesis of medicinal compounds a substantial occasion for the progress of pharmaceutical products with improved physicochemical qualities that do not alter their pharmacological effects. Due to this, there has been a significant push to generate cocrystals for a variety of applications, making cocrystallization the preferred approach in pharmaceutical sciences. [(9)].

Advantages of co-crystals

Improving the solubility

Solubility and dissolution rate played a significant influence in determining the pace and degree of absorption.

Co-crystals were believed to feature a mechanism that promotes solubility by changing the lattice and solvation energies, and increasing the solvent affinity due to presence of coformer[(8)].

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Curcumin- ascorbic acid cocrystals shown a remarkable increase in the water solubility of curcumin, particularly 576 folds in water, 10 folds in the buffer pH 1.2, and 9 folds in the buffer pH 6.8.[9]

Improving bioavailability

Co-crystals altering drug solubility, pharmacokinetics, and bioavailability has the possible to improve the transfer and clinical efficacy of therapeutic products.The higher solubility and dissolution in aqueous solutions resulted in enhanced bioavailability [10]. It was found that preparation of piroxicam co-crystals with sodium acetate coformer, co-crystallization increased solubility and demonstrated a faster dissolving rate, as evidenced by a 30% increase in the extent of dissolution. [11].

Taste masking

Co-crystallization could be a hopeful approach for taste masking by using sugar- based coformers [12]. Theophelline and saccharine were co-crystallized with a stoichiometric ratio of 1:1 using liquid-assisted grinding. According to the automated sweetness testing, the produced co-crystals exhibited both improved solubility and sweetness.[13].

Controlled release

Solubility and dissolution of API controlled by selection of coformer, low soluble coformers produced co-crystals with slow dissolving rates, whereas highly-soluble coformers produced co-crystals with quicker dissolution, Co-crystals of the antithyroid medication propylthiouracil with cinnamic acid as co-former displayed lower solubility and slowed dissolving rate[14].

Coformer selection

Coformer is a component that bind with the API in the crystal frame via non-covalent bonds, is normally nonvolatile, and is not a solvent (including water) [4] . Coformer should not be poisonous and have no negative side effects. Ideal co-crystal formers should be on the US FDA "Everything added to food in the United States" (EAFUS) list, which includes approximately 3000 compounds that are suitable as food additives, or GRAS-approved. However, due to the abundance of coformers, co-crystal screening is challenging[14,15] .There are many rules should be taken in consideration for selection of conformer, such as The Rule of pka , Gibbs free energy and ΔpKa, computational co-crystal design, supramolecular synthons approach, hydrogen bond donors and acceptors and flexibility of synthon-forming functional groups.

MATERIAL

Ebastine (EB)was purchased (remove space)from hyperchem,l-proline from Avonchem UK ,l-histidin Qualikemis india, and asparagine from Qualikemis india

METHOD

Theoretical rules for formation of Ebastine Co-crystals

1.**pKa rule**

This rule was used as a conformer to prepare cocrystal with EB (pka 8.19), since According to the"pKa rule",

$\Delta pKa = pKa(\text{acceptor (EB)}) - pKa(\text{donor (BENZ)})$[16,17,18]

According to FDA Δ pKa is considered as a threshold for distinguishing between co-crystals and salt. FDA indicates, the formation of salt will happen in the components having Δ pKa ≥ 1, whereas if the components having Δ pKa < 1 it will result in co-crystal formation [19].

2. Gibbs free energy and ΔpKa

$$\Delta G^{\circ}_{\text{ion-water}}{}^{\text{HA·B}} = -RT \ln K^{\text{HA·B}}_{\text{ion-water}} = -2.3RT \log K^{\text{HA·B}}_{\text{ion-water}} = -2.3RT\Delta pK_a$$

Knowing that At 298 K $\Delta G^{HA.B}_{ion-water} = -5.71\ \Delta pK$

So, positive ΔpKa resemble negative $\Delta G^{HA.B}_{ion-water}$ and thus favor proton transfer from donor to acceptor, which results in salt formation, whereas negative ΔpKa resemble positive $\Delta G^{HA.B}_{ion-water}$ and hence favour cocrystal formation [16].

Different methods including solvent evaporation and liquid asset grinding with different molar ratio (Table 1) were used for preparation of EB co-crystals.

1-Preparation of co-crystals by solvent evaporation (SE)

Two ratios were created using1:4 and 1:8(EB:coformer) molar ratios (Asparagine, L-prolin and L-histidin) (Table), the drug and conformer were dissolved in 50 ml of methanol wih stirring at 1000 rpm for one hour, then the lid was removed and the cocrystals were exposed to assess ment by slow evaporation at room temperature , The co-crystals were collected and stored for evaluation [20]

2-Preparation of co-crystals by Liquid-assisted grinding (LAG)

Two molar ratios of 1:4 and 1:8 (EB:coformer) molar ratios(Asparagine, L-prolin and L- histidin) molar ratio accordingly by grinding with mortar and pestle for 45 minutes with addition of drop of methanol every ten minutes during grinding[21,22] . The substance is then dried at 40 degrees Celsius. Dry cocrystals were collected and kept for evaluation reasons[23].

Table (1): Composition of EB Co-crystal Formulation by Slurry

Method	Coformer	Formula symbol	Ratio	Volume of solvent (methanol)	Time (hr)
Solvent evaporation	Asparginin	EB1	1-4	50ml	1hr
		EB2	1-8	50ml	1hr
	L-prolin	EB3	1-4	50ml	1hr
		EB4	1-8	50ml	1hr
	L-Histadin	EB5	1-4	50ml	1hr
		EB6	1-8	50ml	1hr

Table (2): Composition of EB Cocrystal Formulation by LAG

Method	Coformer	Formula symbol	Ratio	Volume of solvent (methanol)	Time (min)
Liquid assist grinding	Asparginin	EB7	1-4	5ml	45min
		EB8	1-8	5ml	45min
	L-prolin	EB9	1-4	5ml	45min
		EB10	1-8	5ml	45min
	L- Histadin	EB11	1-4	5ml	45min
		EB12	1-8	5ml	45min

Characterization of EB co-crystal

1-Determination of percentage yield

Using the following equation, the prepared co-crystal's yield was determined (1)

$$\%yeild = \frac{\text{Weight of cocrystal}}{\text{wt of drug+wt of coformer}} \times 100\% \text{.....Eq(1)}$$

2- Determination of drug content

EB co-crystals 10 mg equivalent after a proper dilution and 30 minutes of stirring, EB in 10 ml of methanol was dissolve. The drug concentration was then considered by quantifying the absorbance of the resulting solution at 253 nm [24]. The behind equation was used to determine the percentage of drug content in the cocrystal.

$$\text{Drug content} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100 \ldots \text{Eq(2)}$$

3- Solubility study

By introducing excess quantities of co-crystals to a plane test tube holding 10 ml of water and placing it in a water bath shaker (Memmert, Germany) at 50 rpm and 25 oC for 48 hours, it was possible to evaluate the solubility of EB-co-crystal. Following an appropriate dilution, the material was filtered using Whatman filter paper before being subjected to UV spectroscopic analysis at 257 nm [25] This research was done in three copies..

4-In vitro dissolution study

For EB-co-crystal formulations with the maximum solubility, the USP type II equipment (paddle dissolution vessel) (Copley dissolution 8000, UK) was utilized for dissolution testing. Co-crystals corresponding to 10 mg of EB were dispersed in 1000 mL of 0.1 N HCl for dissolution (pH 1.2). The rotation speed was 100 rpm, and the heat was set to 37 0.5 °C. At 257 nm, spectrophotometric (Carry win UV, Varian, Australia) measurements were made of the released EB concentration [26].

2-Scanning electron microscopy

The surface morphology of the manufactured cocrystals is examined using a scanning electron microscope (VEGA3Tuscan). It is a type of electron microscope that makes images by scanning a specimen with a high-energy electron beam. It is used to determine the surface characteristics of the co-crystal [27] .

2- Powder x-ray diffraction

Powder X-ray diffraction (PXRD) analysis was conducted to analyze changes in the drug's crystalline structure. in addition to detecting the creation of a new crystalline structure. (27)(28). The samples were bombarded with monochromatic CuK radiation using an X-ray diffractometer (XRD-6000 Shimadzu, Japan) and evaluated at 2theta between 10° and 90° [28] .

Selection of the optimum formula

The optimal formulation was chosen based on the solubility studies and dissolution profile of EB from co-crystals.

Ethical Approval: The study was approved by the Ethics Board of college of pharmacy/University of Baghdad and informed written consent was taken from each participant in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical

Association (Declaration of Helsinki) for studies involving humans..

RESULTS

Characterization of Ebastine co-crystal

1-Percentage of yield

High percentage yield was obtained from all the co-crystal formulas that ranged between (88%-98%).

2-Drug content

The percent drug content of all formulas was in the range (96%-103%), indicated that there was minor loss of drug throughout co-crystallization process.

3- Solubility and dissolution

The solubility findings are presented in Table (2). Preparing EB as co-crystals resulted in a considerable p0.05 increase in its solubility, which increased as the ratio of drug to conformer rose.

This result can be related to the features of co-crystals, which are thought to contain a process that increases solubility by altering the lattice and solvation energies and by raising the solvent affinity owing to the presence of coformer [29].

On the other hand, it was discovered that the solubility of EB was not substantially increased p>0.05 by utilizing the same ratio while making co-crystals by different ways, showing that the coformer type and ratio, and not the method, impacted the solubility of EB.

Dissolution study in the present investigation, all formulas were dissolved to investigate the influence of coformer ratio and production technique on the dissolving profile of EB. Figure (2) and demonstrate that the release of all formulations was distinct and quicker than that of the pure medication.

Due to the enhanced solubility of EB, the dissolution rate of the produced cocrystals has risen. The outcome is explicable by the Noyes and Whitney equation,

$\frac{dm}{dt} = \frac{DA\,(Cs-C)}{h}$ …. Eq (4) where the saturation solubility of the drug in the diffusion layer (Cs) at experiment temperature is proportional to the dissolving rate [30].To utilize the potential biopharmaceutical advantages of highly soluble co-crystals, disproportionation, i.e. precipitation of the less soluble parent API, must be avoided during co-crystal dissolution. as an alternative, avoided [31].

Utilizing a crystallization inhibitor or excess coformer is a typical method for resolving the co-crystal disproportionation issue [32] . When using an excessive amount of coformer, the coformer's dissolution in the diffusion layer may reduce the cocrystal's solubility, hence diminishing the thermodynamic motivating force for the precipitation of the parent API.

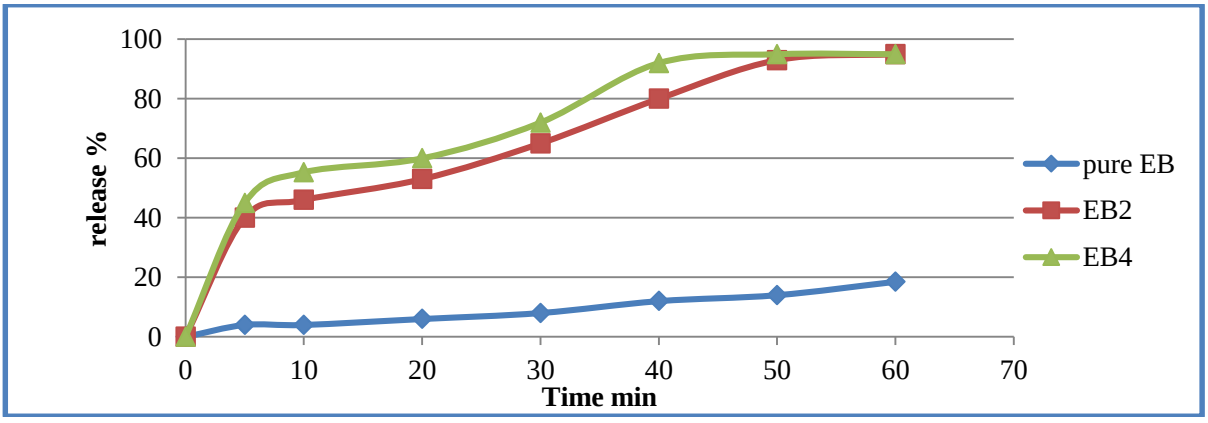

Figure (1) Release of EB co-crystal

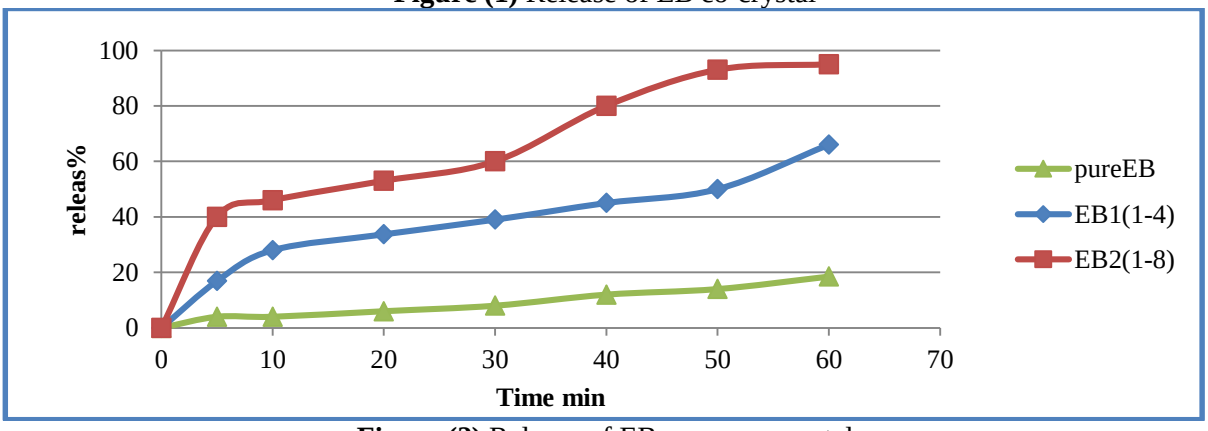

Figure (2) Release of EB asparg cocrystal

Table (3) EB percent of yield, Drug Content and Solubility of slurry prepared Formulas

Method	Coformer	Formula symbol	Yield %	Drug content %	Solubility mg/ml
Solvent evaporation	Asparginin	EB1	97%	98%	0.6±0.03
		EB2	95%	102%	1.186±0.03
	L-prolin	EB3	92%	103%	0.116±0.01
		EB4	90%	98%	0.22± 0.02
	L-Histadin	EB5	92%	101%	0.196 ± 0.015
		EB6	96%	101%	0.21 ±0.015

Table (4) EB percent of yield, Drug Content and Solubility of LAG prepared Formulas

Method	Coformer	Formula symbol	Yield %	Drug content %	Solubility mg/ml
Liquid assist grinding	Asparginin	EB7	98%	96%	0.52±0.025
		EB8	96%	101%	1.13±0.02
	L-prolin	EB9	95%	101%	0.13±0.015
		EB10	92%	103%	0.23±0.02
	L- Histadin	EB11	88%	98%	0.21±0.015
		EB12	92%	101%	0.36±0.01

Characterization of selected formula

1-Scanning electron microscopy (SEM)

Using a scanning electron microscope (SEM), the surface morphology of the produced co-crystals were compared to those of the EB , Asparagine and selected formula.

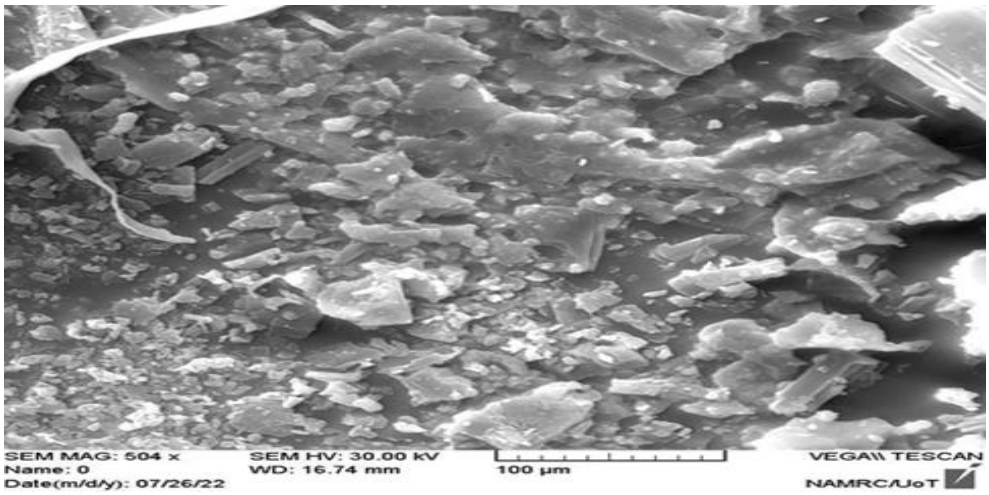

Figure (3) SEM for EB

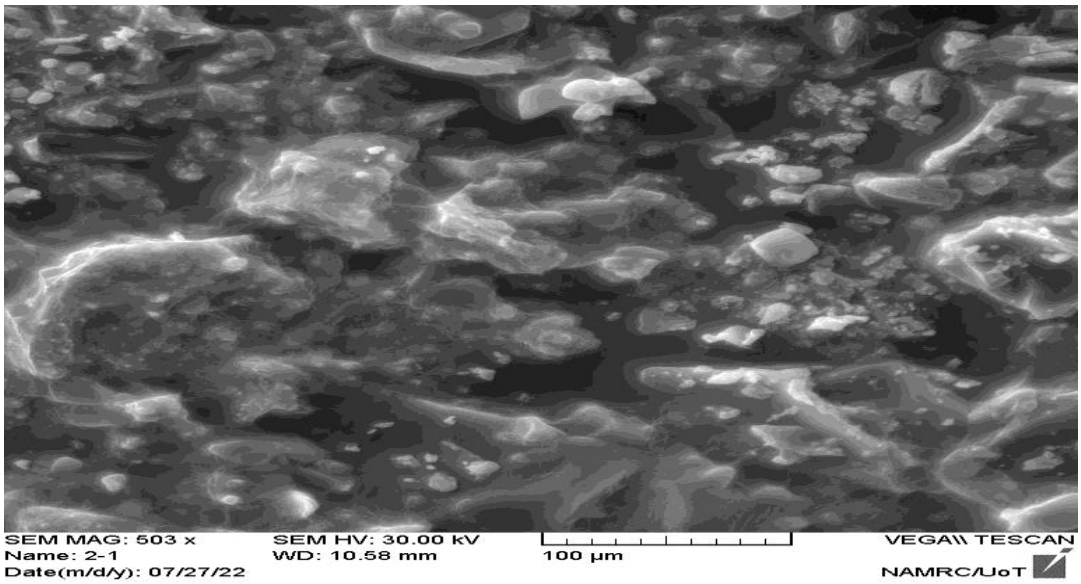

Figure (4) SEM for Asparagine

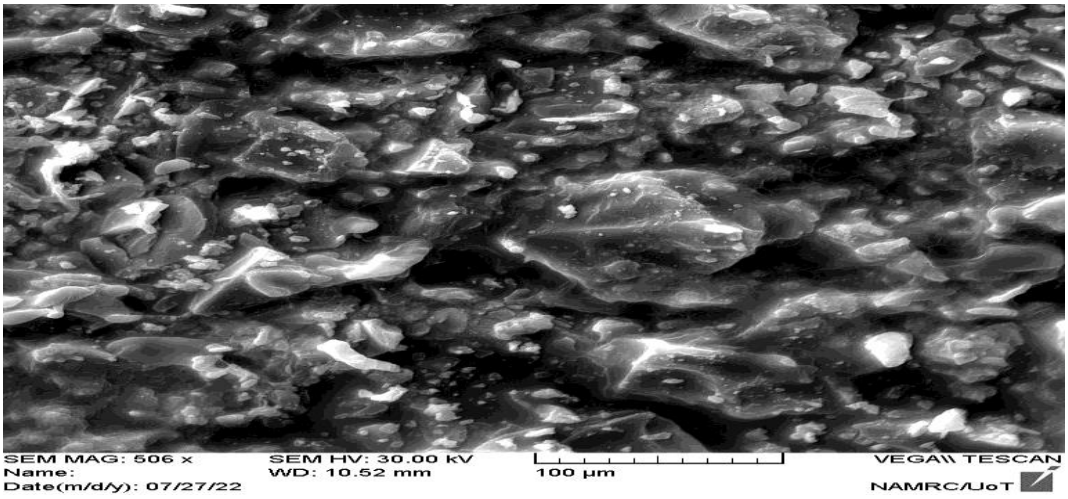

Figure (5) SEM for EB2

2-Powder x-ray diffraction

Powder X-ray diffraction (PXRD) study was performed to evaluate changes, in the crystalline nature of the drug .and to detect the formation of new crystalline form [33,34].

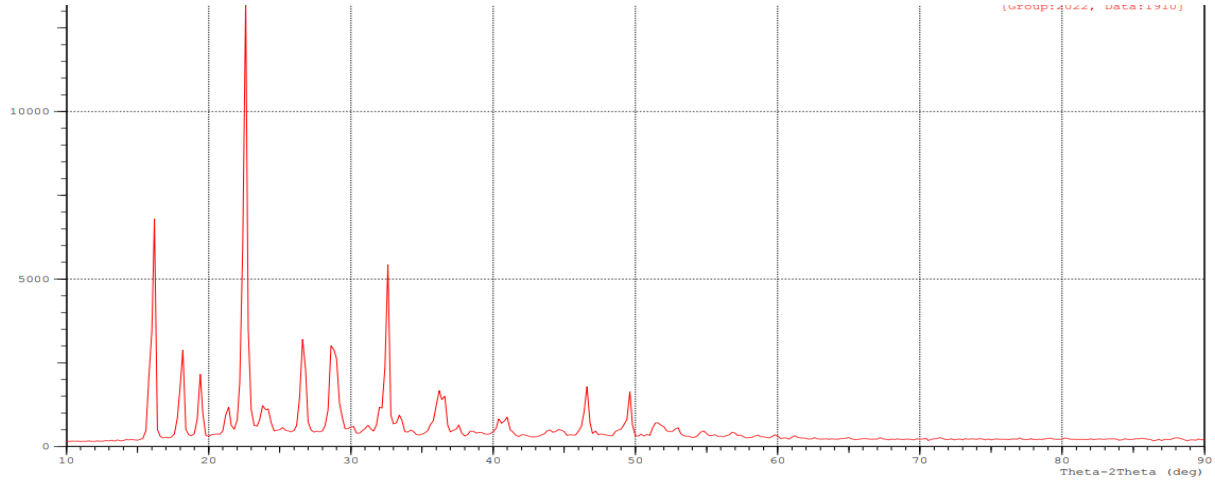

Figure (6) PXRD of Ebastine

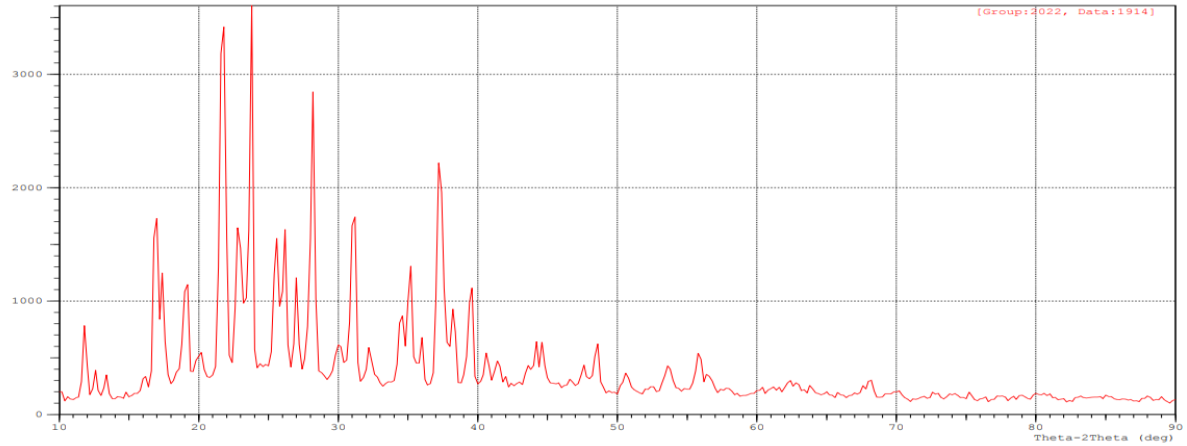

Figure (7) PXRD of Asparagine

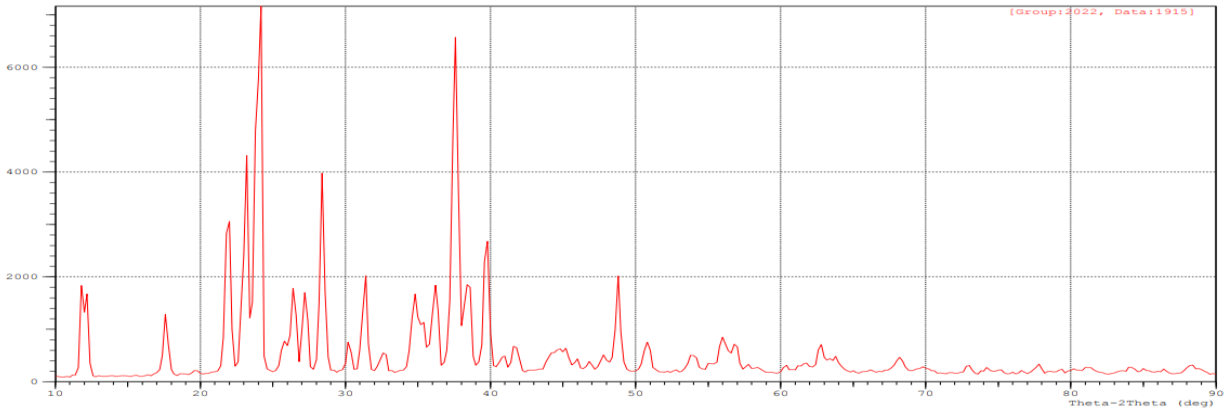

Figure (8) PXRD of EB-asparagine physical mix

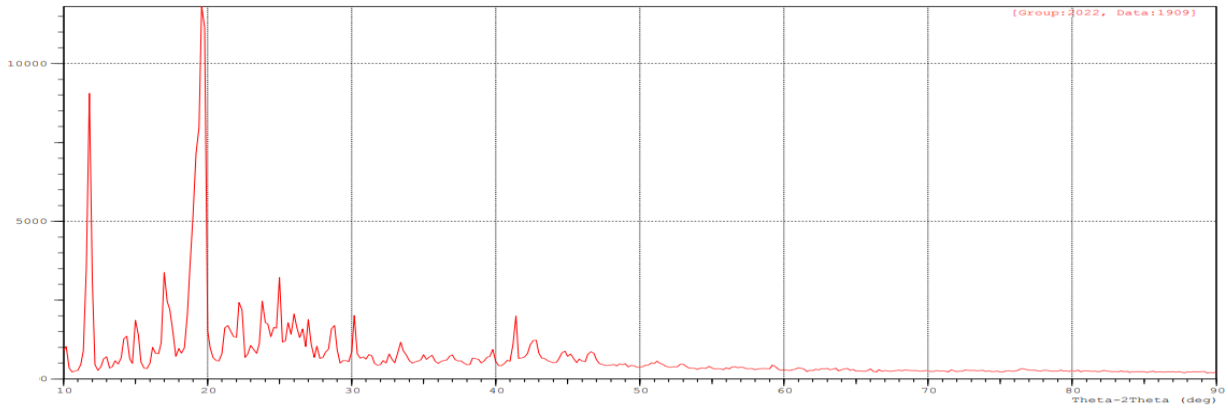

Figure (9) PXRD of EB2

DISCUSSION

1-solublity and dissolution

1-Morphology

SEM (Figure 3) scans revealed the change in the surface morphology of co-crystals compared to the pure EB and coformer .

2-Powder x-ray diffraction

Each crystalline form of a drug has a characteristic PXRD pattern. The diffractograms of EB, aspargenin and its physical mixture. The major diffraction peaks of EB are shown at 2 Ɵ of 16.8º, 18.5 º, 23.5 º,33 º,37 º,40 º,48 º and 50 º with high intensities as shown in(Figure 6), while the major diffraction , the Asparagine peaks of 11.85°, 17.70°, 18.23°, 19.91°, 27.84°, and 43.15°[35].

Moreover the PXRD of EB2 showed a new intense peak at 2Ɵ of 12º, (Figure 9) This result indicated the formation of new crystal lattice [34]. This peak was also found in the physical mixture (Figure 8) but with lower intensity compared to that found in the diffractogram of the selected formula, indicating the possibility of formation of co-crystals even by simple mixing .

CONCLUSION

Introduction and discussion of pharmaceutical cocrystals with an emphasis on physical characterisation and quality control. Pharmaceutical cocrystals provide various applications in the creation of novel chemical entities and the enhancement of products comprising previously recognized active pharmaceutical ingredients. A greater comprehension of intricate physical characteristics

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