RESEARCH ARTICLE

Preparation and Evaluation of Pharmaceutical Cocrystals for Solubility Enhancement of Dextromethorphan HBr

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ABSTRACT

Purpose: To study the cocrystal formation between dextromethorphan HBr and a selected conformer, tartaric acid, as a method of improving the physicochemical properties especially the solubility of dextromethorphan HBr which was selected as a model drug.

Methods: Different methods were used to prepare cocrystals of dextromethorphan HBr such as co-grinding; liquid assisted grinding, and solvent evaporation methods at different molar ratio (1:1, 1:2 and 1:3). Characterization of the prepared formulation was done using saturation solubility, drug content, Fourier transform-infrared (FTIR) spectroscopy, differential scanning calorimeter (DSC), *In vitro* dissolution study, Powder X-ray diffraction (PXRD), and scanning electron microscopy (SEM).

Results: Saturation solubility study revealed an increase in the solubility of drug dextromethorphan HBr, especially in F_9 prepared by the solvent evaporation method. FTIR studies confirm the formation of hydrogen bonds in the selected formula, F_9, with a noticeable shift in the vibration bands.

Thermal analyses by DSC demonstrated the formation of new species, a cocrystal having melting points that is different from its components. The formation of cocrystals was also confirmed by PXRD denoting the crystallinity of formed cocrystals through the observation of new intense peaks with 2θ value difference. The formulations containing the prepared cocrystals showed an improvement in the dissolution rate with marked enhancement in the drug solubility. Also, SEM analyses exhibited micrographical variation typical to cocrystals, suggesting the generation of a new solid phase.

Conclusion: The study showed that the described solvent evaporation method can be used as a simple method to prepare cocrystals at molar ratio 1:3 to enhance the solubility of sparingly soluble drug represented by dextromethorphan HBr.

Keywords: Cocrystal, Dextromethorphan HBr, Solvent evaporation-method, Solubility enhancement.

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INTRODUCTION

Active pharmaceutical industries (APIs) can be present in various individual solid forms, such as solvates, hydrates polymorphs, salts, amorphous solids and cocrystals. Each system can have exclusive physicochemical properties that can affect many attributes of the drug such as drug bioavailability, stability, purification, manufacturability, purification, and performance.[1]

Numerous approaches have been pursued to improve solubility and dissolution rate of poorly soluble drugs, such as salt preparation,[2] solid dispersion,[3,4] microemulsification,[5,6] self-nanoemulsification,[7] cosolvency,[8] inclusion complex formation with cyclodextrin,[9,10] choosing the right polymorphs,[11] and nanoparticles formation.[12,13] Cocrystals can be defined as molecular crystals that contain more than one of different molecules typically a drug and a cocrystal former "coformers" in the same structure of crystal lattice which exists as solids at ambient conditions, bonded together by weak intermolecular interactions such as hydrogen bonding, van der waals forces, and π–π stacking.[14,15] In pharmaceutical systems, the most popular bonds that form the foundation of molecular recognition phenomena are 'hydrogen bonds' and were responsible for the production of families of molecular networks in the crystalline molecules.[16]

These crystalline solids (cocrystals) have gathered a renewed concern in the previous decades for modification a variety of material properties.[17] Many of the published reports on cocrystals have shown their positive contribution to the field of pharmaceutical and medical sciences because of their ability to improve the physicochemical properties of drugs, like solubility, dissolution, hygroscopicity, stability, crystallinity, and melting point without affecting the main drug pharmacological activity.[18] Cocrystals of many organic compounds have been described in the past years where they

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were named differently such as addition compounds, molecular complexes and heteromolecular cocrystals. Irrespective of terminology a multi-component crystal is a crystal in which there is no covalent chemical bond between components that may arise consequently after the crystal formation.

The selection of coformers is a critical step in pharmaceutical cocrystal development where they should be compatible with a particular active pharmaceutical ingredient (API) and capable of the formation of hydrogen bonds.[19] Many cocrystal formers can be used especially in the field of pharmaceutical sciences such as tartaric acid, ascorbic acid, gallic acid, nicotinamide, citric acid, aglutamic acid, histidine, urea, saccharine, glycine, succinic acid, sucrose, and alpha ketoglutaric acid.[20]

In the process of cocrystallization, a coformer molecule should be chosen from a wide range of compounds that is capable to form hydrogen bonds, so it can produce a stable supramolecular synthon with the active molecule. Both the active ingredient and selected coformer should have desired properties that include safety and not be converted to a toxic product when consumed by humans. Most of organic acids or molecules with amino groups are selected because of their abilities to form stable cocrystals.[21]

In the current study, certain approach known as "supramolecular synthon" is used for coformer selection which ensures the formation of hydrogen bonding between the API, dextromethorphan HBr and the coformer to find the complementary functional groups for API which are capable of forming a hydrogen bonds. The previous research studies showed an increase in solubility when tartaric acid was used as a conformer.[22] Therefore, L-tartaric acid was selected as a conformer. Tartaric acid contains 4 donors of hydrogen bond and 6 hydrogen bond acceptors as shown in (Figure 1B).

Dextromethorphan HBr (DXM) is a non-narcotic antitussive agent generally used as an ingredient in cough and cold remedies.[23] DXM belongs to class II of biopharmaceutics classification system (BCS), where drugs of this class exhibit low solubility and high permeability.[24] Chemically, it can be defined as a salt of the methyl ether of the D-isomer of levorphanol, a narcotic analgesic. Physically, DXM appears as white crystals in color, it is sparingly soluble in water and freely soluble in alcohol. It has a molecular weight of 370.32 g/mole, a molecular formula of $C_{18}H_{25}NO{\bullet}HBr{\bullet}H_2O$, and the chemical structural is shown in (Figure 1 A):

Formation of cocrystal is carried out using co-grinding, solvent evaporation and liquid assisted grinding methods. This study aims to explore the formation of cocrystal between DXM and a selected coformer as a method to improve the physicochemical properties especially solubility of DXM which was used as a model drug to represent a class of sparingly soluble drugs.

The formulated cocrystals are to be characterized using solubility studies, FTIR spectroscopy, thermal analysis such as DSC, PXPD spectroscopy, SEM, and *In vitro* dissolution study.

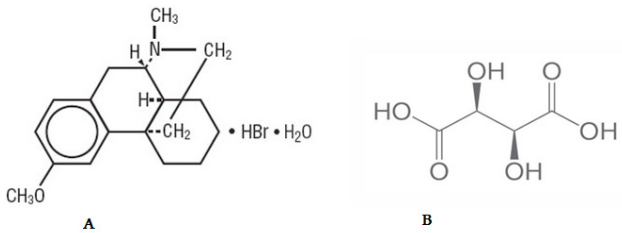

Figure 1: Chemical structure of dextromethorphan HBr (A); tartaric acid (B)

MATERIALS AND METHODS

Materials

Dextromethorphan HBr was provided as a gift from the Middle East Laboratories Co. Ltd, Iraq. Tartaric acid was obtained from HiMedia, India. All of the ingredients used in this study were of analytical grade.

Preparation of Cocrystal

Three methods were employed to prepare cocrystals of dextromethorphan HBr as described below:

Dry Grinding Method

Three formulas were prepared at different stoichiometric ratio (1:1, 1:2, and 1:3) of DXM HBr and tartaric acid as a conformer as shown in table 1. Drug and coformer were mixed in a mortar using pestle and ground for 45 minutes to form cocrystals. These cocrystals have dried overnight at ambient temperature, then stored in tightly closed containers.[25,26]

Solvent Evaporation Method

Dextromethorphan HBr and tartaric acid were carefully weighed at different stoichiometric ratio (1:1, 1:2, and 1:3) as shown in Table 1. Each compound was dissolved in ethanol separately. The two solutions were mixed and sonicated for a few minutes, and then the solution of both components was poured into a Petri dish. The prepared solution was allowed to evaporate at room temperature until the solution is completely dry. The obtained cocrystal solids were stored in a tightly closed container for further evaluation.[27,28]

Liquid Assisted Grinding

Liquid assisted grinding technique was used to prepare cocrystals using tartaric acid as coformer. The formation of DXM cocrystals was performed in the same molar ratio (1:1, 1:2, and 1:3) as shown in Table 1. Grinding of a mixture of DXM and tartaric acid was carried out in mortar and pestle for 30 minutes with the addition of 2.5 mL ethanol dropwise, and then the wet crystals were dried in an oven and stored for further analyses.[29] In this technique, ethanol acts as a promoter, either as "media" that enables molecular diffusion or as an essential element that forms multi-components inclusion framework and has been used to enhance supramolecular selectivity in crystalline systems. It can be described the effect of the solvent as a catalytic, so that it is not part of the final product, because of its small amount used.

Characterization of Cocrystal DXM-tartaric Acid

Saturation Solubility

An excess quantity of DXM and the formulated cocrystals was added to 10 mL vials containing distilled water to

determine the saturation solubility. The vials were immersed in shaker water bath, subjected to agitation and allowed to stand for equilibration for 24 hours. Then, the Filtration and dilution of samples were done, and the concentration of DXM was determined from the absorbance measurement at λmax 278 nm by using an ultraviolet-visible light double beam spectrophotometer (Cary, Australia).[30]

Drug Content

An accurate weight of cocrystal powder equivalent to 10 mg of pure drug was taken and dissolved in a 60 mL of 0.1 N HCl and the volume was completed to 100 mL in a volumetric flask. The resulting solution was filtered using Whatman filter paper 41 and the absorbance of the solution was measured at λ_{max} 278 nm using an ultraviolet Cary spectrophotometer.[31]

Fourier Transform-infrared (FTIR) Spectroscopy Analysis

The FTIR spectrophotometer (Lambda 7600, Australia) was used to observe and confirm the formation of hydrogen bonds and to eliminate any chemical interaction between the drug and the coformer. Dry potassium bromide (KBr) was mixed with the sample at a constant ratio of (1:10), and this mixture was compressed into pellets. The spectrum of samples was recorded between 4000 cm^{-1} and 400 cm^{-1}. The analysis was accomplished for pure drug, coformer, physical mixture of drug and tartaric acid at ratio (1:1) and the selected cocrystals.[32]

Differential Scanning Calorimeter (DSC) Analysis

The thermodynamic characteristics of DXM, tartaric acid, and the selected cocrystal formula were measured using a DSC-60 plus apparatus (Shimadzu, Japan). Approximately 4 mg of each sample was placed in an aluminum pan, and the temperature was increased from 25 to 300˚C at a rate 10˚C/min, with nitrogen flow at rate of 50 mL/min. An aluminum pan filled with alumina was used as reference material.[33]

In vitro Dissolution Study

Intrinsic dissolution study was performed using USP apparatus II dissolution vessel (Faithful, China) containing 500 mL 0.1 N HCl (pH 1) at 37°C and a rotation of 50 rpm was used. Dissolution studies of pure powder and the selected cocrystal (equivalent to 10 mg) were carried out. Samples (n = 3) were withdrawn at 5 minutes time intervals (5, 10, 15, 20, 25, 30, 35, 40 and 45 minutes) and replaced with fresh dissolution media.

Table 1: Compositions of DXM-tartaric acid cocrystals in molar ratios

Formula	*DXM: tartaric acid molar ratio*	*Cocrystallization methods*
F_1	1:1	Co grinding
F_2	1:2	Co grinding
F_3	1:3	Co grinding
F_4	1:1	Liquid assisted grinding
F_5	1:2	Liquid assisted grinding
F_6	1:3	Liquid assisted grinding
F_7	1:1	Solvent evaporation
F_8	1:2	Solvent evaporation
F_9	1:3	Solvent evaporation

The samples were diluted appropriately and the absorbance was measured by using (UV-visible) Cary spectrophotometer at 278 nm.[34]

Powder X-ray Diffraction (PXRD) Studies

Powder X-ray diffractograms of pure drug, the coformer, and the selected formulated cocrystal were obtained using analytical XRD instrument (XRD-6000, Shimadzu, Japan). The scanning range was from 10 to 70˚ at 2θ scale at scan speed of 10 degree/min. The voltage and strength of the electric current were 40 KV and 30 mA, respectively.[35]

Scanning Electron Microscopy (SEM)

The surface morphology and shape of prepared cocrystals in comparison with pure drug and coformer were observed by using a scanning electron microscope. For SEM measurement, DXM, tartaric acid and selected cocrystal formulation were fixed at metal stubs using double-sided adhesive tape. Drying of those samples in a vacuum chamber is necessary, then sputter-coated with a gold layer of 10 nm thick and viewed under a high-resolution scanning electron microscope (Tescan, vega 2, Czech Republic) by using different magnifications.[36]

RESULTS AND DISCUSSION

Saturation Solubility

The saturation solubility of pure DXM in 0.1N HCl (pH 1) at 37°C was found to be 0.8 mg/mL after 24 hours. On the other hand, the cocrystal forms of DXM with tartaric acid at the molar ratio 1:1, 1:2 and 1:3 prepared by co-grinding, liquid assisted grinding and slow evaporation methods showed an increase in DXM solubility (as shown in Figure 2) after 24 hours under the same conditions as the pure drug. Cocrystals of DXM and tartaric acid prepared by solvent evaporation method at ratio 1:3 showed the highest improvement in dynamic solubility (1.6 mg/mL). This result can be attributed to desirable noncovalent interaction between DXM and tartaric acid conformer where this hypothesis can be approved by further studies, specially FTIR study as shown in the coming sections of this paper.

Drug Content

The drug content of all formulation was found satisfactory and ranged from 90% ± 0.2 to 98% ± 0.4 as shown in Table 2.

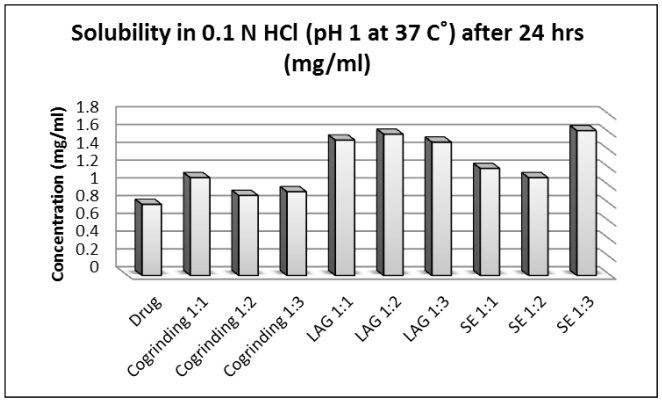

Figure 2: Solubility of dextromethorphan HBr and prepared cocrystals in 0.1 N HCl (pH 1) at 37˚Cand after 24 hours equilibration

The values indicate good content uniformity for the cocrystal formulations.[37]

Fourier Transform-infrared (FTIR) Spectroscopy Analysis

Fourier transformation spectroscopies are commonly used as a tool for letting recognition of molecular modification in cocrystal lattice by hydrogen bond formation. Drug spectrum (Figure 3) showed noticeable absorption bands at 2165.67 and 2586.07 cm^{-1} corresponding to the NH^+ stretching vibration in the tertiary amine group of the drug. The spectrum also showed a strong band for DXM at 3287.1 cm^{-1} corresponding to aromatic C–H stretching,[38] 1612 cm^{-1} corresponding to C=C stretching, and at 2927 cm^{-1} corresponding to methoxy (CH_3–O–) stretching.[39] The FTIR spectrum of tartaric acid (Figure 4) has a typical peak at wave number 3404.71 cm^{-1} indicating the stretching vibration of a hydroxyl function group, wave number 1738.51 cm^{-1} indicating the C= O carboxylic acid bond, and wave number 1131.05 cm^{-1} indicating C-O bond. The spectrum of physical mixture (Figure 5) of drug and tartaric acid at a ratio of (1:1) shows the characteristic peaks for both compounds indicating there is no chemical interaction has occurred between them.

The FTIR spectroscopy is used to confirm cocrystal formation because of its ability to detect differences in the chemical structures of samples indicative of the formation of hydrogen bonding. FTIR spectrum of the formulated cocrystals by solvent evaporation method F_9 at molar ratio 1:3 (Figure 6) showed a reduction in the intensity and disappearance of NH^+ stretching vibration of DXM and a reduction in the intensity of hydroxyl functional group vibration of tartaric acid indicated formation of hydrogen bonds. The lowering of frequency is the function of degree and strength of hydrogen bonding.

Table 2: Percent of drug content for formulated cocrystals

Formula	*Percent of drug content ± SD (n=3)*
F1	90 ± 0.2
F2	96 ± 0.1
F3	94 ± 0.4
F4	98 ± 0.33
F5	95 ± 0.15
F6	97 ± 0.7
F7	98 ± 0.76
F8	98 ± 0.6
F9	98 ± 0.32

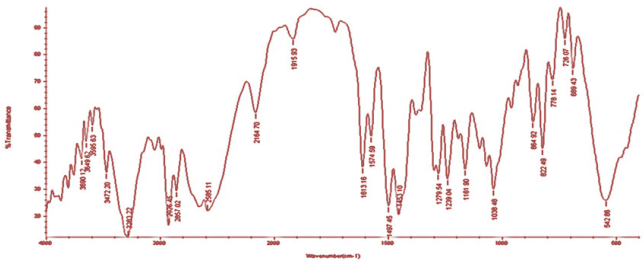

Figure 3: FTIR spectrum of pure dextromethorphan HBr

Differential Scanning Calorimeter (DSC) Analysis

Differential scanning calorimetry provides valuable information about cocrystals, such as their melting temperature, enthalpy of fusion, thermal transition temperature, crystallinity. The DSC thermograms of DXM, tartaric acid and their cocrystals prepared by solvent evaporation method at molar ratio of 1:3 are shown in Figures 7–9, respectively. Dextromethorphan HBr showed a sharp peak with melting point of 130.35°C indicating its purity and crystallinity,[40] while DSC thermogram of tartaric acid showed a melting point of 174°C. However DXM- tartaric acid cocrystals showed a distinctive endotherm where two endothermic peaks at temperatures lower than the melting points of DXM and tartaric acid alone were observed. The first endothermic peak occurs at 79°C, perhaps due to the melting of the eutectic mixture. The second endothermic peak at 151.45°C represents the melting of cocrystals.[41]

The appearance of an exothermic peak immediately after the endothermic is characteristic of cocrystallization of physical mixtures components under heating to form

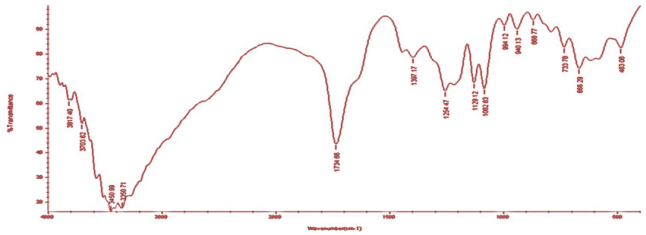

Figure 4: FTIR spectrum of tartaric acid

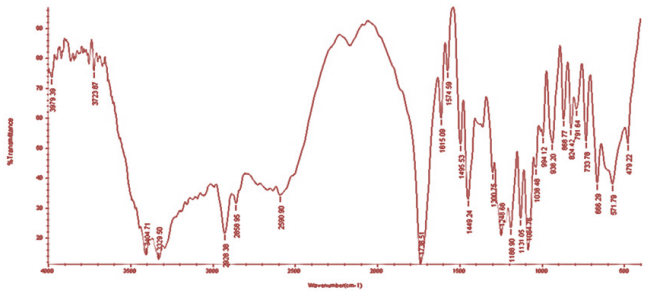

Figure 5: FTIR spectrum of physical mixture of dextromethorphan HBr and tartaric acid at 1:1 ratio

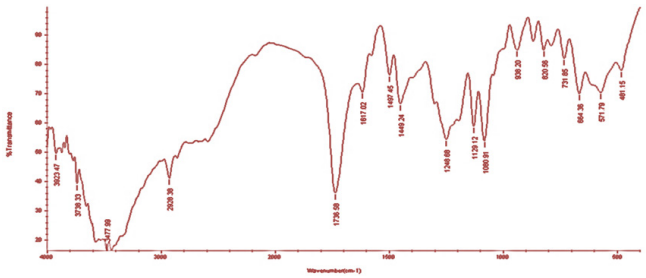

Figure 6: FTIR of dextromethorphan HBr–tartaric acid solvent evaporation–prepared cocrystal (F_9) at molar ratio of 1:3

cocrystals.[42] The "W-shaped" thermogram such as the one obtained for F_9 prepared by solvent evaporation method proved to be characteristic of the cocrystals. On the contrary, "V-shaped" thermogram is considered as the characteristic endotherm of the eutectic mixtures.[43]

In vitro Dissolution Study

The dissolution study was performed on the pure DXM and the selected cocrystal (F_9). The dissolution profile of the pure drug and the selected solvent evaporation–prepared cocrystal at molar ratio 1:3 are shown in Figure 10. The pure drug showed 70% drug release at 15 minutes, whereas SE-prepared cocrystal of DXM showed 100% release at 15 minutes. The *in vitro* dissolution studies revealed a notable increase in the percentage of drug release from cocrystals when compared with the pure drug. The greater dissolution of DXM from cocrystal can be endorsed to the change in pattern of crystalline molecules, size and shape and crystal habit of cocrystal to eventually lead to enhancing the solubility of cocrystal and faster dissolution.[44]

Powder X- Ray Diffraction (XRD) Studies

Powder XRD can be used to examine the change in molecular structure of the crystal lattice. Compounds in the powder state showed distinctive peaks of varying intensities at certain positions. The XRD pattern for the pure DXM (Figure 11 A) showed sharp and distinctive peaks at 2˚θ of 21.8, 19.7 and 35.4 degree with high intensity indicative of the crystalline nature of the drug. In tartaric acid, the strongest 3 peaks at 2˚θ were 68, 30 and 21 degree with high intensity as shown in (Figure 11 B). The Distinguishable powder XRD pattern of the cocrystal from its components was obtained and some additional diffraction peaks appeared which did not exist in the DXM or tartaric acid as a coformer. The additional peaks of cocrystal F_9 at 2˚θ appeared at 20.98, 29.45 and 20.47 degree with the diffused pattern as demonstrated in (Figure 11 C).

The existence of new peaks in the cocrystal indicates the formation of a new crystal formation; this shows that the positions of the atoms occupying the lattice are now different.[45] Inter arrangement of molecules is indicated by different peak locations of the cocrystals concerning pure drug and thus, proves the construction of a new crystalline phase.[46]

Scanning Electron Microscopy (SEM)

Morphology and size have a great influence on the physical properties of cocrystal. The SEM micrographs of pure drug, tartaric acid and cocrystals (F_9) are shown in (Figure 12 A, B, C, and D). Crystal habit of DXM showed rod-shaped irregular particles with smooth surface morphology and particle size of 500 µm at 100 x magnifications. The coformer tartaric acid appeared as block-shaped irregular particles with smooth surface morphology. The prepared cocrystals (F_9) by a solvent evaporation method, the crystal habit appeared as irregular crystalline shape particles with rough surface in which the

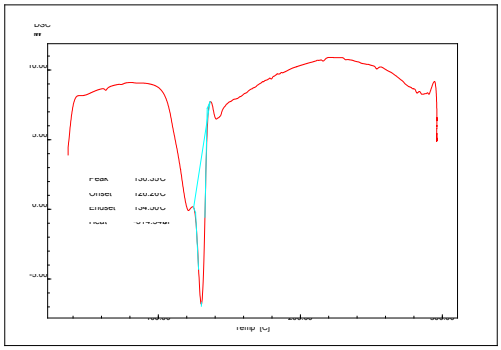

Figure 7: DSC thermogram of dextromethorphan HBr

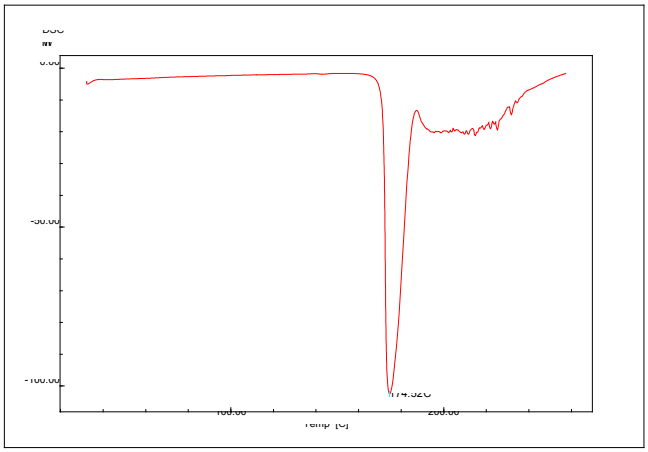

Figure 8: DSC thermogram of tartaric acid

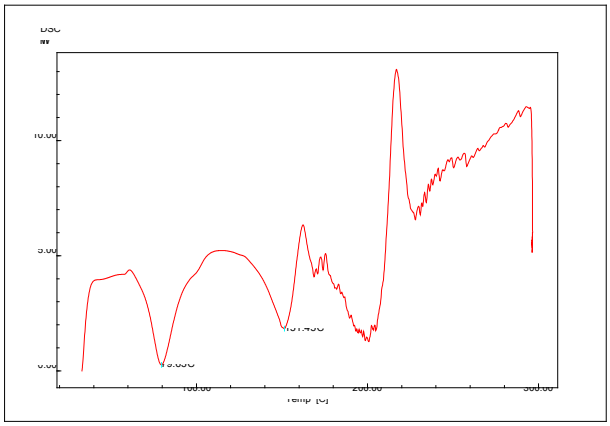

Figure 9: DSC thermogram of dextromethorphan HBr –tartaric acid solvent evaporation –prepared cocrystal (F_9) at molar ratio of 1:3

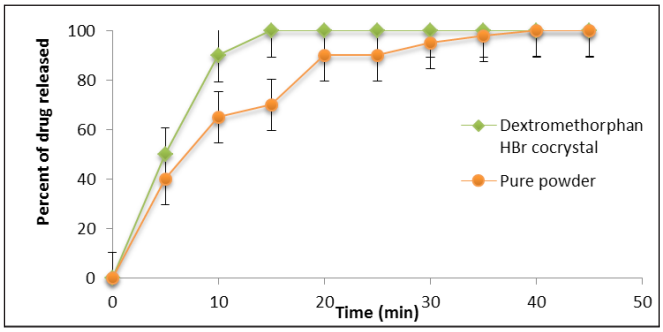

Figure 10: *In vitro* dissolution profile of dextromethorphan HBr cocrystal (F_9) and pure powder (mean ± SD)

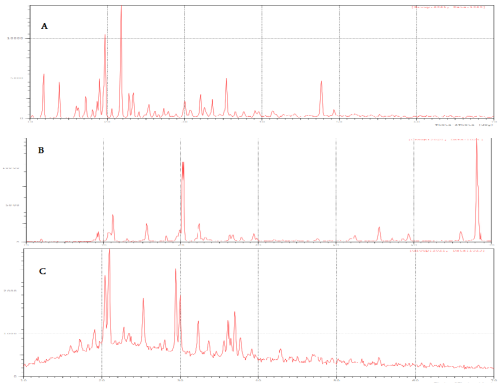

Figure 11: X-ray diffraction pattern of pure dextromethorphan HBr (A), pure tartaric acid (B), dextromethorphan HBr-tartaric acid cocrystals (F_9) prepared by solvent evaporation method (C)

original morphology of both components has disappeared and the particle size was decreased to 20 µm at 2 kx magnification. The differences in the size and shape of cocrystals suggest molecular interaction between cocrystal constituents. Thus, the morphology of the cocrystals was entirely different from those of DXM and tartaric acid, thus indicating the generation of a new crystalline material.[47]

CONCLUSION

The present study presented a great idea on cocrystal formulation and evaluation using simple and successful method for the preparation of cocrystals of a sparingly soluble drug dextromethorphan HBr. The simple solvent evaporation method can be considered a promising method to improve the physiochemical properties of the drug. Cocrystals of

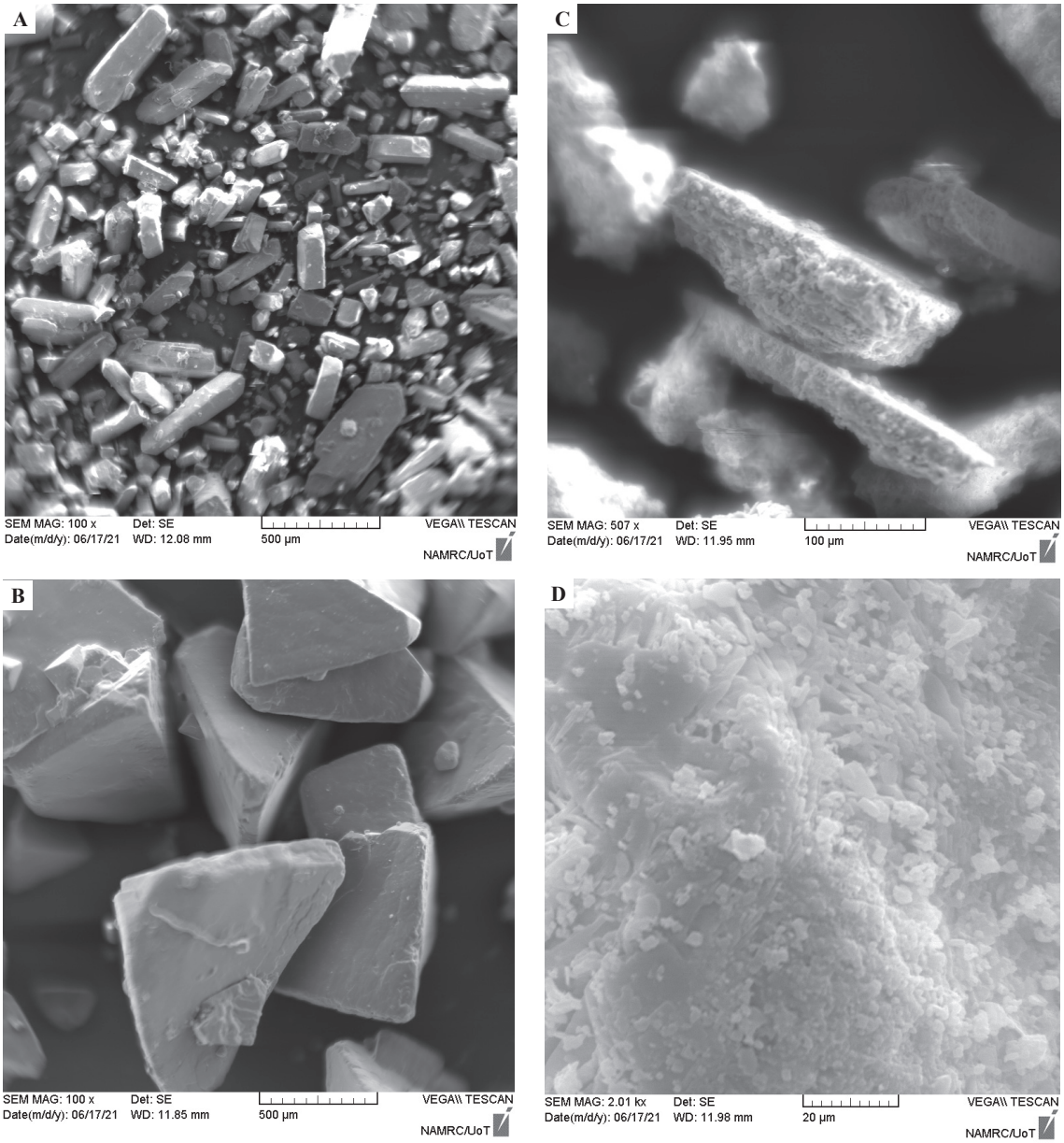

Figure 12: SEM images of pure powder at 100x magnification (A), tartaric acid at 100x magnification (B) and cocrystal (F_9) at 507 x and 2 kx magnification (C and D), respectively

Dextromethorphan HBr–tartaric acids as coformer were successfully prepared by solvent evaporation method at molar ratio of 1:3. The formation of the intended cocrystals was evaluated and confirmed through a set of highly specific analytical techniques including FTIR, DSC, and powder XRD. The solubility and dissolution rate of the prepared cocrystals were markedly increased compared to untreated pure drugs. The formula F_9 prepared by solvent evaporation method at a drug: coformer molar ratio of 1:3 was selected as a preferable one based on the evaluation parameters such as saturation solubility and FTIR that demonstrate the construction of hydrogen bonds between DXM and tartaric acid.

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