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Research Article

THEOPHYLLINE ASCORBIC ACID COCRYSTALS BY SONOCRYSTALLIZATION METHOD: FORMULATION AND CHARACTERIZATION STUDIES

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ABSTRACT

Objectives: The objective of the current research work was to develop theophylline ascorbic acid cocrystals by sonocrystallization method. The approach is a coadministrative approach to provide drug–drug cocrystals in chronic obstructive pulmonary disorder.

Methods: The cocrystals were formulated in 3 stoichiometric ratios of 1:1, 1:2, and 2:1 using the sonocrystallization-induced evaporation method. Methanol was used as a solvent. The cocrystals were evaluated for visual morphology, melting point, Fourier-transform infrared studies, saturation solubility in water and simulated lung fluid (SLF) pH 7.4, *in vitro* drug release in SLF pH 7.4, differential scanning calorimetry (DSC) studies, X-ray diffraction (XRD) studies, scanning electron microscopy (SEM) studies, and Raman spectroscopy.

Results: Cocrystals were successfully developed in all 3 stoichiometric ratios by the sonocrystallization method. The cocrystal of theophylline with ascorbic acid in ratio of 1:1 was found to be most optimized with 10-fold increase in saturation solubility in water and 11.5-fold increase in solubility in SLF pH 7.4 and two-fold increase in *in vitro* drug release in SLF pH 7.4. The cocrystal was found to show a lowered melting point as confirmed by DSC studies thus confirming the formation of a new crystalline phase. XRD studies to be added. SEM and Raman spectroscopy studies were found to confirm the change in crystalline characteristics of the cocrystals by indicating the formation of a new crystalline phase.

Conclusion: Cocrystals were successfully developed by the sonocrystallization method. The sonocrystallization method can be used as a preferred method for the formation of drug–drug cocrystals for a coadministrative approach to drug delivery.

Keywords: Cocrystals, Sonocrystallization, Theophylline, Ascorbic acid, Drug–drug cocrystal.

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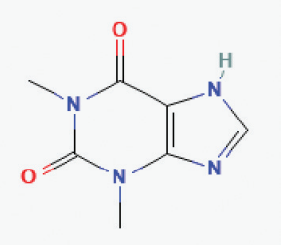
INTRODUCTION

The drug also known as an active pharmaceutical ingredient exhibits different forms in the solid state, namely salts, solvates, amorphous forms, polymorphs, cocrystals, etc. [1]. Crystal engineering encompasses several approaches to develop physical forms of solids with modified physicochemical attributes. One such approach is cocrystallization. Cocrystals comprise multicomponent pharmaceutical solid-state forms comprising of a drug which may be weakly acid or basic in association with an inert generally regarded as safe substance known as conformer in a stoichiometric ratio by means of hydrogen bonding [2,3]. These are molecular complexes in nature comprising more than one component in the same crystal lattice. Several non-covalent associations, such as hydrogen bonding, π-π stacking, and van der Waals forces may be involved in holding the drug and conformer together in the crystal lattice [4]. Cocrystallization may apply to a wide range of actives from weakly acidic to basic as well as neutral actives [2]. In addition to enhancing the physicochemical attributes of actives along with dissolution rate and bioavailability, cocrystals aid to create new paradigms for pharmaceutical companies in terms of intellectual property and patents affecting the life cycle of active pharmaceutical ingredients [5]. Cocrystals generate new realms in active drug designing and synthesis.

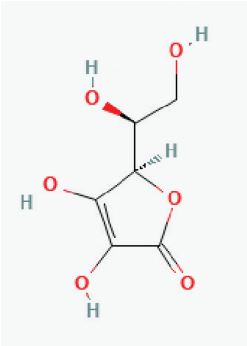
Several approaches have been attempted to cocrystallization, such as solvent evaporation, neat grinding, solvent-assisted grinding, hot melt extrusion, and slurry conversion. [6]. These approaches aim at tailor-making the drug crystal properties such as solubility and stability.



Theophylline as an antiasthmatic has many beneficial effects. It is used as a bronchodilator for treating breathing difficulties [7]. A methyl xanthine by nature, it is used in respiratory disorders, such as chronic obstructive pulmonary disease (COPD). Airflow limitation and respiratory symptoms are characteristic features of COPD [8]. It is a widely studied molecule in terms of solid-state chemistry and crystalline phase transformation behavior. Existing in four polymorphic forms, I, II, III, and IV, and a hydrate; its form I and hydrated form are stable in water [9]. Several studies on the cocrystallization of theophylline using coformers such as benzoic acid, salicylic acid, and nicotinamide have been attempted [10-12]. Several attempts have been made to develop novel forms of theophylline and studies on changes in physical and chemical properties have been conducted.

Coformers generally used for cocrystallization include water-soluble monocarboxylic acids, dicarboxylic acids, amides, and amines. [13].

Ascorbic acid as an antioxidant acts as a first line of defense in protecting the lung from delirious effects of oxidants and reactive



oxygen. Supplementation of ascorbic acid in chronic obstructive lung disease therapy has been found to be therapeutically beneficial in terms of lung function [14].

The objective of the current work was to formulate cocrystals of theophylline with ascorbic acid and thus design a coadministrative approach for COPD. The cocrystals were formulated by sonocrystallization and evaluated for various parameters to study the effect of cocrystallization such as visual morphology, melting point, saturated solubility, Fourier transform infrared (FTIR) spectroscopy, *in vitro* dissolution studies, differential scanning calorimetry (DSC), X-ray diffraction (XRD) studies, scanning electron microscopy (SEM), and Raman spectroscopy.

METHODS

Theophylline IP was generously gifted by Bajaj Healthcare Ltd., Masjid Bunder, Mumbai, India. Solvent methanol AR, coformers ascorbic acid, ferulic acid, mannitol, trehalose, xylitol, and leucine were purchased from LOBA chemicals. All other chemicals used were of analytical grade.

Screening of coformers using COSMO-quick software

Software-based screening of coformers was done using the COSMO-quick18 demo version. Coformers were ranked using COSMO-Quick software based on their compatibility to form cocrystals with the drug. Coformers such as mannitol, trehalose, ascorbic acid, ferulic acid, xylitol, and leucine were scrutinized for cocrystallization.

Preparation of theophylline cocrystals

Formulation of cocrystals using sonocrystallization

Drug theophylline (45.04 mg) and optimized coformer (44.3 mg) were weighed in the 3 different stoichiometric ratios of 1:1, 1:2, and 2:1 and were transferred in the beaker. 2 mL of methanol solvent was added to aid in the interaction between the drug and the coformer. The assembly was then subjected to bath sonication-induced evaporation of solvent for 15–30 min till a crystalline solid product was produced [15].

Characterization of theophylline cocrystals

Visual morphology

The visual appearance of theophylline, coformers, and cocrystals was studied. The images were recorded with a high-resolution camera.

Melting point

Theophylline, coformers, and cocrystals were filled in the capillary tube and tied to the thermometer. Subsequently, the thermometer was inserted into the thistle tube with constant heating. The temperature was raised gradually at a rate of 10°C every minute until the drug in the capillary tube melted, at which point the corresponding melting temperature was recorded. The melting point of the drug and developed cocrystals was determined using Expo Hi-Tech melting point apparatus (India).

FTIR

FTIR spectra of theophylline, coformers, and cocrystals were recorded using Jasco FTIR-4100 Fourier Transform spectrophotometer (Japan) using the KBr disc method over a scanning range of 400–4000 cm^{-1}. The sample was prepared by combining the drug with KBr in a 1:5 ratio and was compacted to form a disc [16].

Saturated solubility

Saturation solubility studies of theophylline and cocrystals were conducted in a simulated lung fluid (SLF) solution of pH 7.4 and distilled water. An excess amount of sample was taken in Eppendorf tubes containing 1 mL of solvent. These Eppendorf tubes were then sealed and subjected to shaking for 48 h at 37°C in a water shaker bath (Remi, CM 101, Mumbai, India). These were then centrifuged at 5000 rpm for 5 min and then filtered through a 0.45 µ filter. These samples were examined at 270 nm with an ultraviolet (UV) spectrophotometer. Respective blanks, i.e., SLF pH 7.4 or distilled water were used to eliminate the solvent effect [17].

In vitro dissolution studies

The type II USP Dissolution Apparatus (Paddle type) (LAB INDIA) was used to conduct i*n vitro* release studies of theophylline and cocrystals. A sample equivalent to 20 mg of the drug was weighed and filled in hard gelatine capsule size 1. The capsule was then placed in 900 mL SLF pH 7.4 media. According to USP, dissolution was carried out at 75 rpm and 37°C. 5 mL aliquots were collected at 5, 10, 15, 30, 45, and 60 min and analyzed at 230 nm using a UV spectrophotometer. The aliquots were then replenished with the same quantity of media to keep the sink condition [18].

Characterization studies on optimized cocrystal

DSC

DSC of theophylline and cocrystal with the highest solubility was conducted using Pyris-6 Perkin Elmer DSC with the aim to study their crystalline characteristics. 3–5 mg of the sample was placed in an empty DSC pan. This pan along with a blank pan was covered with a lid and crimped using a DSC crimper. These two pans were then heated from 50 to 300°C at the rate of 10°C/min and endothermic peaks obtained were studied [19].

Powder XRD (PXRD)

The PXRD analysis of the drug and cocrystal with the highest solubility was conducted using Bruker D8 ADVANCE DA VINCI (Germany). The sample was taken on a powder holder and was subjected to CuKα radiation, at a voltage of 40 kV and a current of 40 mA. The obtained signal pattern was recorded along with peak intensity and corresponding 2θ values [20].

SEM

The SEM images of the drug and cocrystal with the highest solubility were obtained using Carl Zeiss Supra 55 (Germany). Double-sided adhesive tape was used to attach the sample to the carbon. Under vacuum, a thin coating of gold was applied to the sample. After that, the sample stub was stored in a 10 kV SEM chamber. Various magnifications were used to acquire the images [21].

Raman spectroscopy

Raman spectroscopy was conducted for theophylline and cocrystal with the highest solubility. A Renishaw inVia Raman microscope was used for the procedure. A laser of intensity 785 nm was used. The amount of laser power employed was 50% (150 mW) (0.05%–0.15 mW per AU). The acquisition took 10 s. The spectra that were acquired were studied [22].

RESULTS AND DISCUSSION

Coformer screening

Coformer screening was done to check for compatible coformers for the targeted active theophylline (Table 1). The coformers were screened using Maestro software as well as by experimental approach.

Ascorbic acid was selected as the coformer due to its antioxidant properties [23].

Formulation of cocrystals

Sonocrystallization-induced evaporation of the solvent was found to successfully yield cocrystals of drug theophylline and coformer ascorbic acid in stoichiometric ratios of 1:1, 1:2, and 2:1. Sonocrystallization was used to induce evaporation of methanol and interaction between drug and coformer.

Visual morphology studies

There was a noticeable variation in the observed appearance of all cocrystals when compared with drug and coformer. The cocrystals in 1:1, 1:2, and 2:1 ratios were observed to be creamish white in color as compared to theophylline, which was found to be white dense whereas ascorbic acid was found to be white free flowing in nature (Fig. 1).

Melting point

The melting point of cocrystals of theophylline with ascorbic acid in ratios of 1:1, 1:2, and 2:1 was found to show a drastic decline in temperature as compared to plain theophylline and ascorbic acid (Table 2).

FTIR spectroscopy

FTIR spectroscopy of theophylline cocrystals was found to indicate distinct changes in the vibrational wavenumbers indicating changes in structural features.

The characteristic IR peaks of principal functional groups of theophylline were observed at 3120 cm^{-1} for N-H stretching of the amide group, 1750.75 cm^{-1} for C=O stretch of the amide group, 1560.28 cm^{-1} for N-H bending, 948.43 cm^{-1} for =C-H Bend, 666.04 cm^{-1} for C-H bend. The characteristic IR peaks for ascorbic acid were obtained at 3502.78 cm^{-1} for alcoholic OH stretch, 2916.60 cm^{-1} for carboxylic acid OH stretch, 1752.81 cm^{-1} for C=O ester stretch, 1657.26 cm^{-1} for C= O stretch for α, β unsaturated ketone, 1220.84, 1198.02, 1119.58 cm^{-1} for C-O stretch of carbonyl compound (Fig. 2 and Table 3).

The peak at wavenumber 3120 cm^{-1} for NH stretch was shifted to wavenumber 3401 cm^{-1} for cocrystals of drug and ascorbic acid in ratio of 1:1 and 1:2 and to 3408 cm^{-1} for ratio 2:1 thus indicating involvement in interaction in hydrogen bonding. The peak at 1752.61 cm^{-1} of ascorbic acid for C=O ester stretch was observed at 1752.81 cm^{-1}, 1748.54 cm^{-1}, and 1757.09 cm^{-1} for cocrystals in ratios of 1:1, 1:2, and 2:1 of theophylline and ascorbic acid. The mild shifts in the wavenumber indicate the interaction of the ester group in hydrogen bonding [24,25].

Saturated solubility studies

Theophylline: ascorbic acid cocrystal in 1:1 ratio by sonocrystallization was found to show a 10-fold increase in solubility in water as compared to theophylline alone whereas theophylline: ascorbic acid cocrystal in 1:1 ratio by sonocrystallization was found to show

Table 1: Maestro analysis report

API	Coformer	pKa difference	HBD	Energy	Interaction
Theophylline	Maltitol	−4.24	9	66.562	97
Theophylline	Trehalose	−3.31	8	66.562	71
Theophylline	Mannitol	−3.99	6	27.664	35
Theophylline	Leucine	6.27	0	13.732	32
Theophylline	Tryptophan	6.14	1	20.301	29
Theophylline	Isoleucine	−1.16	0	8.591	27
Theophylline	Ferulic acid	−4.9	1	46.346	19
Theophylline	Ascorbic acid	−3	4	16.75	19

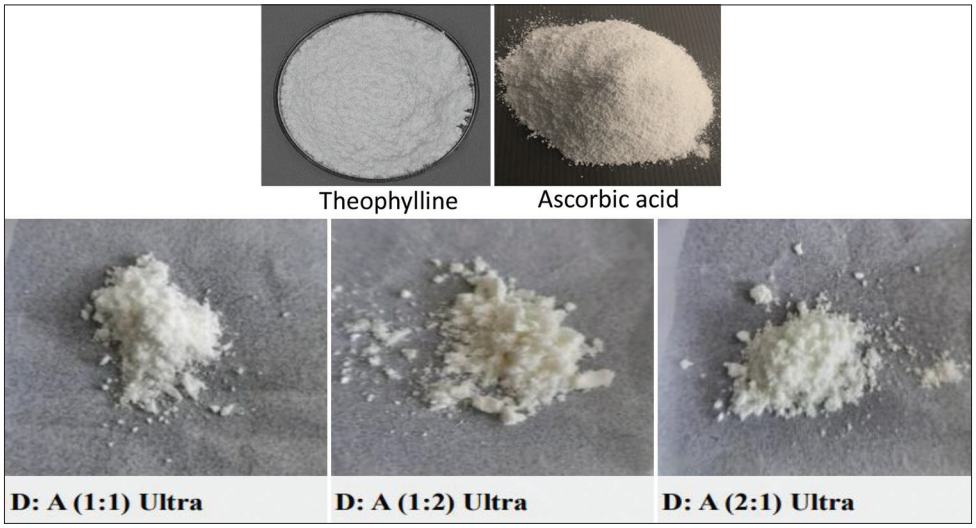


Fig. 1: Visual morphology of theophylline, ascorbic acid, and theophylline:ascorbic acid cocrystals in ratios of 1:1, 1:2, and 2:1, respectively

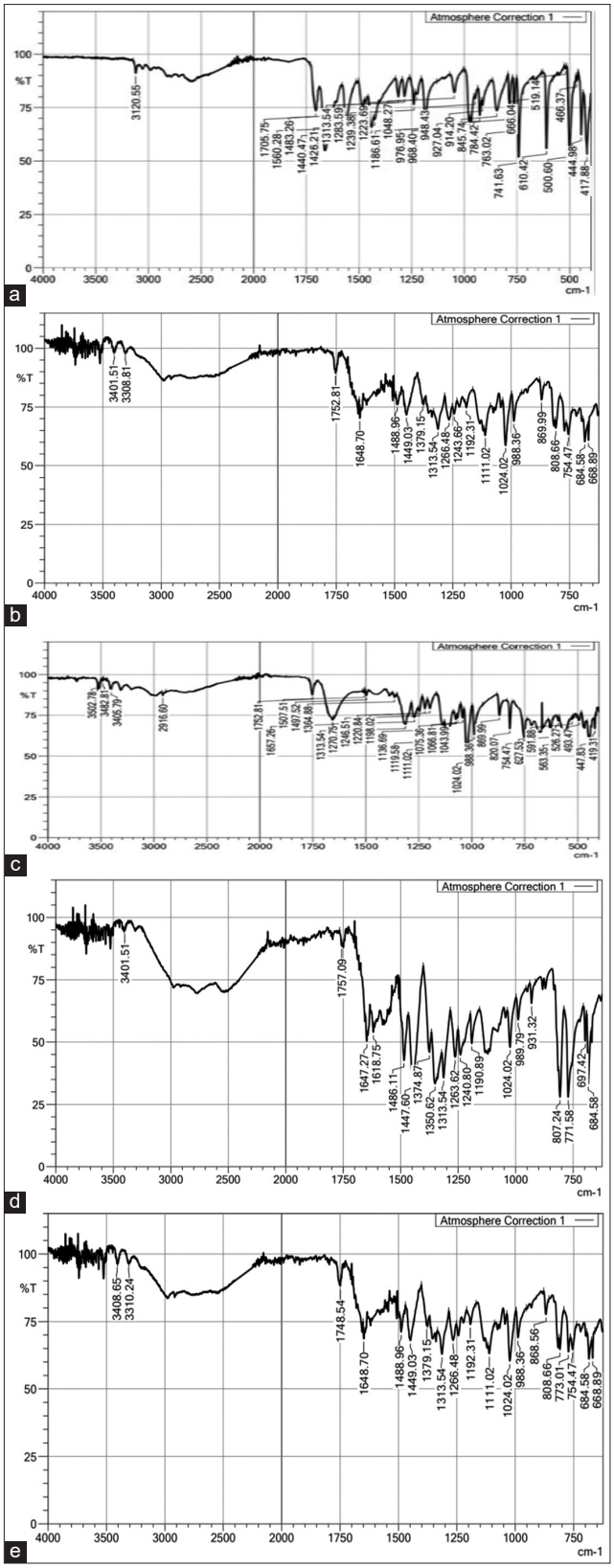


Fig. 2: Fourier transform infrared of (a) theophylline, (b) ascorbic acid, (c) theophylline:ascorbic acid in 1:1, (d) theophylline:ascorbic acid in 1:2, (e) theophylline: ascorbic acid in 2:1

11.5-fold increase in solubility in SLF as compared to theophylline alone (Table 4).

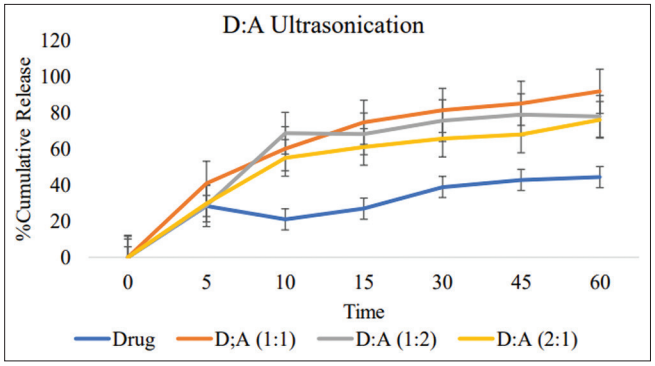


Fig. 3: Comparison of *in vitro* dissolution of drug and cocrystals formed by sonocrystallization method

Table 2: Melting points of theophylline, ascorbic acid, and cocrystals

Sample	Melting Point (°C)
Theophylline	272°C±0.45°C
Ascorbic acid	191°C±0.27°C
Theophylline: ascorbic cocrystal 1:1	173°C±0.5°C
Theophylline: ascorbic cocrystal 1:2	170°C±0.25°C
Theophylline: ascorbic cocrystal 2:1	176°C±0.15°C

In vitro dissolution studies

The Theophylline: ascorbic acid cocrystals in a 1:1 ratio were found to exhibit a 2-fold enhancement in *in vitro* release in SLF pH 7.4 as compared to theophylline alone (Table 5 and Fig. 3).

Based on the saturation solubility and *in vitro* drug release profile of cocrystals, the theophylline: ascorbic acid cocrystal in a 1:1 ratio was found to be most optimized and considered for further evaluation studies.

Characterization studies on optimized cocrystals

DSC

The cocrystallization of theophylline: ascorbic acid in a 1:1 ratio was confirmed by DSC studies (Fig. 4). The cocrystals of theophylline: ascorbic acid in a 1:1 ratio revealed a shift in the melting endotherm of theophylline, from 270°C to 175°C, indicating a decline in melting point and thus a decrease in crystallinity and thus confirming cocrystal formation with varying melting characteristics [26].

PXRD

The characteristic XRD signal for the theophylline drug was observed at a 2θ value of 12.7° and for ascorbic acid at 25°. However, new signals at 2θ values of 16° and 31° were observed in the XRD study of theophylline: ascorbic acid cocrystal of 1:1 ratio (Fig. 5).

SEM

The cocrystals TP: AA produced by sonocrystallization in a 1:1 stoichiometric ratio were observed to be in small irregular particulate form, whereas the drug and coformer displayed distinct geometries of small cubic rhombic crystals for theophylline and large cubic crystals for ascorbic acid (Fig. 6).

Raman spectroscopy

Peak shifts in the Raman spectra for functional groups such as the aromatic ring, C-N-CH3, and >C=O mixed with NH deformation confirmed the formation of cocrystals and changes in crystalline characteristics of the drug (Fig. 7 and Table 6) [27].

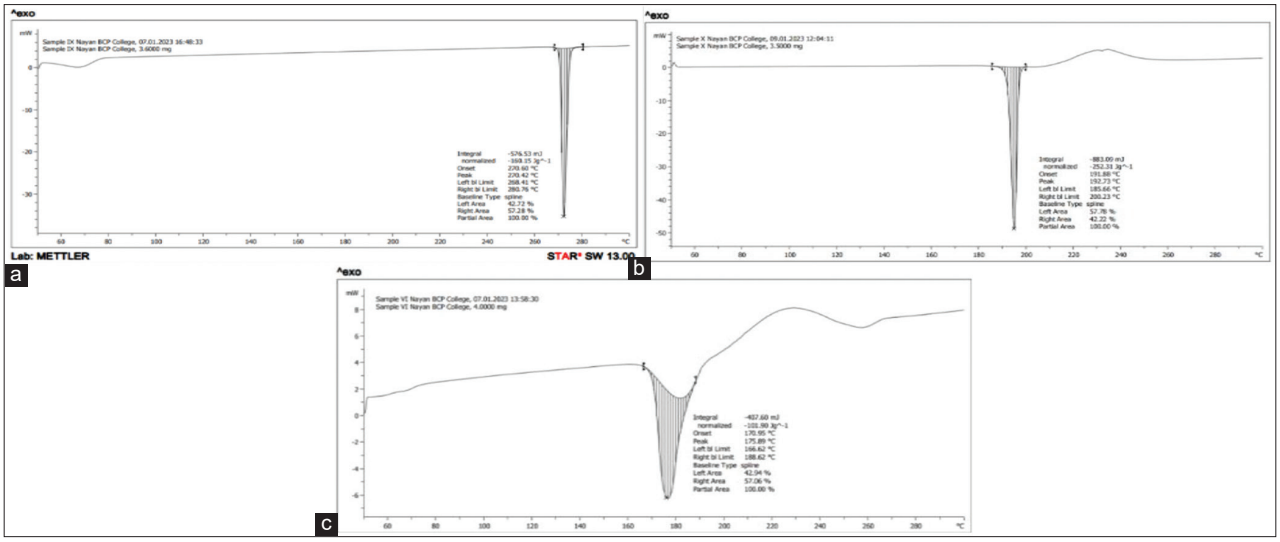


Fig. 4: Differential scanning calorimetry thermogram of (a) theophylline, (b) ascorbic acid, (c) theophylline:ascorbic acid in 1:1 cocrystal

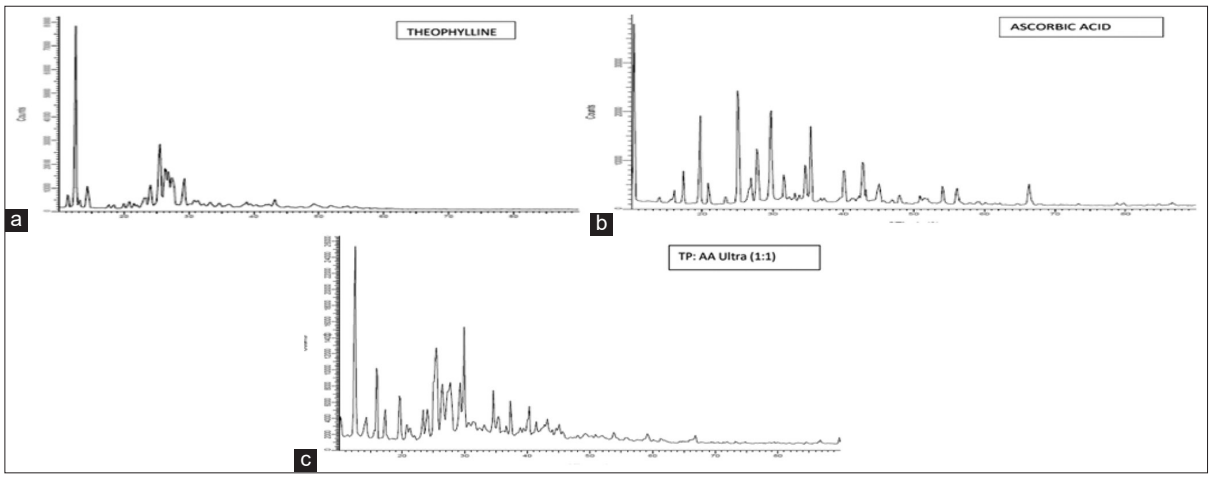


Fig. 5: Differential scanning calorimetry thermogram of (a) theophylline, (b) ascorbic acid, (c) theophylline:ascorbic acid 1:1 cocrystal

Table 3: FTIR comparative data for theophylline drug, ascorbic acid, and developed cocrystals

TP wavenumber (cm^{-1})	AA wavenumber (cm^{-1})	D: AA 1:1 wavenumber (cm^{-1})	D: AA 1:2 wavenumber (cm^{-1})	D: AA 2:1 wavenumber (cm^{-1})
3120	3502.78, 2916.60	Not observed	Not observed	Not observed
1750.75	1752.61	1752.81	1748.54	1757.09
1560.28	1657.26, 1220.84, 1198.02, 1119.58	1560 Not Observed	1560 Not Observed	1560 Not Observed
948.43		Not observed	Not observed	Not observed
666.04		668.89	668.89	Not observed

FTIR: Fourier transform infrared

Table 4: Saturated solubility in concentration per ml for theophylline and cocrystals developed by sonocrystallization

Compound		Concentration (mg/mL)
Theophylline	In distilled water	8.35±0.453
D: AA 1:1	In distilled water	86.23±0.297
D: AA 1:2		57.45±0.167
D: AA 2:1		38.76±0.346
Theophylline	In simulated lung fluid (pH 7.4)	5.84±0.256
D: AA 1:1	In simulated lung fluid (pH 7.4)	67.51±0.765
D: AA 1:2		34.05±0.145
D: AA 2:1		38.95±0.325

Cocrystals involve the synthon approach comprising of construction of a supermolecule using molecular fragments generating supramolecular synthon. Complementary functional groups from drug and coformer form a supramolecular synthon template [28]. The lowering of melting points of theophylline: ascorbic acid cocrystals in ratios of 1:1, 1:2, and 2:1 indicated a change in crystalline structure and a probable increase in solubility characteristics. The -NH and -C=O of the amide group of theophylline interact with the alcoholic -OH group of ascorbic acid through hydrogen bonding to yield cocrystals. The solubility of theophylline: ascorbic

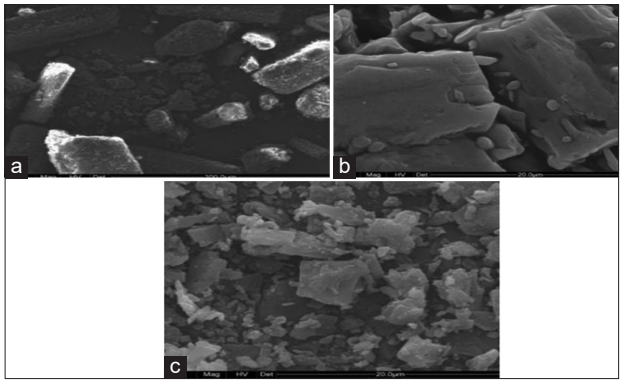


Fig. 6: Scanning electron microscopy of (a) theophylline, (b) ascorbic acid, (c) theophylline:ascorbic acid in 1:1 cocrystal

acid cocrystal by sonococrystallization in water and SLF was found to be enhanced by 10 and 11.5 folds, respectively. Thus, association of water-soluble ascorbic acid with theophylline by hydrogen bonding was found to impact the solubility of the drug in water and SLF. The decline in melting point of theophylline as confirmed by DSC studies confirmed the decrease in the crystalline nature of the drug and also supported the obtained results of enhancement in solubility and *in vitro* drug release of drug in water. The observed XRD signals at new 2θ values confirm the change in crystalline characteristics of the drug after cocrystallization i.e., association of the drug with coformer. Cocrystallization of theophylline was found to induce distinct changes in morphological characteristics as confirmed by SEM studies. Peak shifts for characteristic functional groups in Raman spectra were observed in cocrystals thus confirming the change in crystalline characteristics.

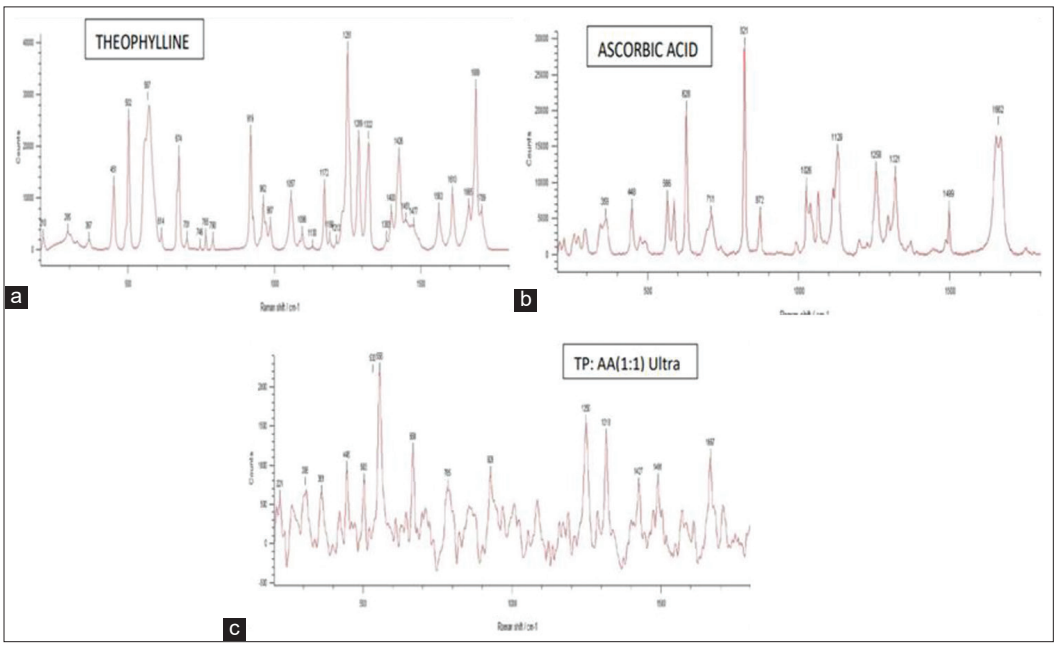


Fig. 7: Raman spectra of (a) theophylline, (b) ascorbic acid, (c) theophylline:ascorbic acid in 1:1

Table 5: Cumulative release of theophylline and cocrystals in ratios of 1:1, 1:2, and 2:1 in simulated lung fluid pH 7.4

Time (min)	±Cumulative release (%)			
	Theophylline	Theophylline: ascorbic acid 1:1	Theophylline: ascorbic acid 1:2	Theophylline: ascorbic acid2:1
0	0	0	0	0
5	28.42±0.234	40.98±0.372	28.61±0.532	29.77±0.179
10	21.03±0.767	60.15±0.138	68.78±0.154	55.06±0.263
15	26.95±0.179	74.78±0.274	68.39±0.373	61.17±0.172
30	38.98±0.297	81.38±0.183	75.73±0.233	65.76±0.464
45	42.90±0.157	85.31±0.246	79.04±0.193	68.05±0.257
60	44.45±0.356	91.96±0.169	78.12±0.265	76.15±0.194

Table 6: Raman shift of theophylline, ascorbic acid, and cocrystal in a ratio of 1:1

Functional Group	Raman Shift of THEO	Raman Shift of AA	Raman Shift of TP: AA
>C=O mixed with NH deformation	1689	1662	1667
C-C highly mixed in complex molecule	1251	1258	1250
Ar. ring	919	1321	1318
C-N-CH3	567	628	556

CONCLUSION

The cocrystallization technique of sonocrystallization was found to successfully yield drug–drug cocrystals of theophylline drug with ascorbic acid in stoichiometric ratios of 1:1, 1:2, and 2:1. DSC and XRD examinations were the methods used to observe and validate the crystalline changes in the cocrystal caused by the use of the particular methodology. Modifications to the chemical composition were demonstrated by studies using FTIR spectroscopy. Thus, the physicochemical properties of the theophylline drug were tailormade by the application of the sonocrystallization cocrystallization technique. The aforementioned method can be successfully adopted to administer drug–drug cocrystals in COPD therapy.

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AUTHORS' CONTRIBUTION

The research theme was conceptualized by Harita Desai. The data collection was done by Sakshi Jaiswal. The manuscript writing, editing, and formatting were done by Harita Desai and Ashwini Kondhare. The data interpretation and manuscript draft finalization were done by Harita Desai.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHORS FUNDING

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