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Original Article

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF ACETYLSALICYLIC ACID VIA CO-CRYSTALLIZATION TECHNIQUE: A NOVEL ASA-VALINE COCRYSTAL

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ABSTRACT

Objective: This study aims to synthesize acetylsalicylic acid (ASA) cocrystals using valine as a coformer via a co-crystallization technique to increase the solubility and dissolution rate of ASA.

Methods: The ASA-valine cocrystal (1:1 molar ratio) was prepared using the solvent evaporation technique with ethanol: water (50:50). The cocrystal was characterized using Fourier transform infrared spectroscopy (FT-IR), Differential scanning calorimetry (DSC), Powder X-ray diffraction (PXRD), Scanning electron microscopy (SEM), melting point to confirm the formation of cocrystal. The evaluation of cocrystal was done by drug content determination, solubility and dissolution studies.

Results: The prepared cocrystal was successfully confirmed for the formation of a hydrogen bond. The melting point of prepared cocrystal was decreased compared to pure ASA and valine, which indicated the formation of a new crystalline form. The FT-IR studies showed the formation of a new hydrogen bond by shifting the-O-H,-C=O and-N-H functional groups. SEM studies ensured that the prepared cocrystals were in needle-like appearance. Finally, DSC and PXRD studies were also indicated the successful formation of ASA-valine cocrystal. The drug release of cocrystal was found to be 100% at 60th min. Where in the case of pure ASA and marketed product of ASA exhibited the dissolution rate of 59% and 69% at 60th min respectively.

Conclusion: The co-crystallization technique can be adopted as the best strategy to increase the solubility and dissolution rate of BCS class 2 drugs. Therefore the prepared ASA-valine cocrystal can be a greater alternative to increase the solubility and dissolution rate compared with pure and marketed ASA.

Keywords: Acetylsalicylic acid, Valine, Co-crystallization, Solvent evaporation technique, Solubility enhancement, Dissolution rate, Cocrystals, Powder x-ray diffraction, Differential scanning calorimetry

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INTRODUCTION

The significant thrust prompted by new technological advancements in pharmaceutical industries is to improve the fundamental properties of an API, such as solubility, flow properties, bioavailability, and physical and chemical stability [1]. As per the reports, nearly 40% of drugs are available in the market, and almost 90% of drugs still in the developmental pipeline are facing solubility issues [2]. The poor aqueous solubility of pure drugs is one of the vital issues encountered while developing the pharmaceutical formulations administered through oral and transdermal routes [3, 4]. The bioavailability of drugs that are administered orally be resultant by aqueous solubility and dissolution rate; thus, poor aqueous solubility can be the stepping stone of inadequate and variable absorption of these drugs making the absorption process solely dependent on aqueous solubility [5, 6]. Thus, to overcome the solubility issue of poorly aqueous soluble drugs, new solid-state forms of old drugs utilizing a variety of solubility enhancement techniques such as salification, cocrystallization, etc. are being looked into, which modifies the physicochemical properties of a drug without changing its pharmacological activity [7-9].

Since the physicochemical properties are often dependent on the crystal structure of drugs, many have reported that the crystal engineering of drugs helps overcome issues related to solubility and thermodynamic stability [10, 11]. The synthesis of cocrystal is one of the significant strategies to improve the physicochemical parameters of pure drug. From the past 15 y, research towards pharmaceutical cocrystals has doubled. They have gained tremendous ability to modify not only ionizable drugs like salts but also non-ionizable drugs or weakly ionizable drugs [12-16]. Cocrystals are solid crystalline materials comprised of two or more distinct molecular components. They cannot be distinguished as either solvates/hydrates or simple salts since they are interconnected via non-ionic interactions such as van der Waals interactions, hydrogen bonding and π-π stacking instead of ionic interactions. Thus, cocrystals are unique, where the proton transfer is unconditionally absent [17-24]. Hence, this area is in enormous expansion and significant over other solid-state modifications. The major dominance of cocrystals is the proficiency of modification of pure drug with refined solubility, dissolution rate, processability, thermal and hydration stability. Along with all the above-mentioned benefits, it is also possible to incorporate extra health benefits through the appropriate coformers. Although several properties of the pure drug are improved, the structure will not *get al.* tered, resulting in unchanged pharmacological activity [25-33].

Aspirin is an acetyl derivative of salicylic acid that belongs to a biopharmaceutical classification system (BCS) class 2 drug with an aqueous solubility less than 1 mg/ml at 73 °F. It possesses a broad count of various bioactivities such as anti-inflammatory, anti-pyretic, it also involved in reducing the risk of heart attack by thinning the blood [34]. Besides, the Carlo patron has reported that aspirin took part in reducing the risk associated with colorectal cancer [35]. Recently, the combinations of aspirin-4,4-bipyridine [36], aspirin-theophylline [37], aspirin-4,4-butane, aspirin-pyridinepoly-2-ene [38] were successfully formed stable cocrystals, but none of them have studied the dissolution behavior of aspirin.

In this present work, we have used valine fig. 1 as a conformer in the synthesis of acetylsalicylic acid (ASA) cocrystals due to their

impeccable potentiality in the formation of a hydrogen bond between the pure ASA fig. 2. Further, crystal structure characterizations, intermolecular interactions, thermal behaviors and dissolution behaviors of cocrystals were investigated using FT-IR, DSC, SEM, PXRD, solubility studies and *in vitro* dissolution studies. The main goal of this study is to not only synthesize cocrystals of ASA with improved solubility and dissolution rate but also to furnish new insight into the design of cocrystals using valine as conformers, which is believed to construct potential cocrystals by forming non-ionic interactions between pure drugs.

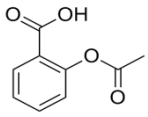

Fig. 1: Structural formula of acetylsalicylic acid (ASA)

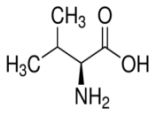

Fig. 2: Structural formula of valine

MATERIALS AND METHODS

Materials

Acetylsalicylic acid (Aspirin) was purchased from Vasa Scientific Company (Bangalore, India). Valine of analytical grade was purchased from Central Drug House Pvt. Ltd (Karnataka, India). Absolute ethanol was purchased from Vasa Scientific Company (Bangalore, India). All chemicals were used as received without any further purification.

Preparation of cocrystals

Acetylsalicylic acid (540 mg) and valine (351 mg) (1:1 molar ratio) were ground by using the high energy vibrational mill into a finely grounded state (CMTTI-200, Japan) for about 3-5 min, further transferred into a 25 ml glass beaker and added 20 ml of 50% ethanol-water mixture. The mixture was stirred until a clear solution was obtained. Thereafter, allowed to crystallize at room temperature by slow evaporation for 10 d. White coloured crystals were obtained at the end of the 10^{th} d.

Drug content determination

ASA-valine cocrystal equivalent to 10 mg of pure ASA was taken separately into a 100 ml volumetric flask. The contents in the flask were dissolved in absolute ethanol. From the resultant solution 1 ml of solution taken and diluted to 10 ml of absolute ethanol. The absorbance of the resultant solution was recorded at 268 nm using UV-1700 double beam spectrophotometer (Shimadzu, Japan). The average of three readings was taken [39].

Melting point study

Melting points of the pure ASA, valine and ASA-valine cocrystal were measured using a Digital Melting temperature apparatus (Secor, India).

Fourier transform infrared spectroscopy

The Fourier Transform Infrared Spectroscopy (FT-IR) spectral analysis was identified as an additional channel to manifest the development of cocrystals. The distinct and novel peaks in the FT-IR spectra of cocrystals were indicative of the formation of new intermolecular hydrogen bonding. FT-IR spectrums of cocrystals were recorded on a Perkin Elmer FT-IR spectrophotometer (USA) using the KBr pellet method in the spectral range 4000-500 cm^{-1} with a resolution of 2 cm^{-1} [40].

Scanning electron microscopy

The surface characteristics and shape of the ASA-valine co-crystals were analyzed by Scanning Electron Microscopy (SEM) (Joel Jsm-5600, Japan). The samples for scanning electron microscopy were prepared by gently spreading the co-crystals on a double adhesive tape, which is stuck to an aluminum stub. The samples were then imaged using a 20 kV electron beam [41].

Differential scanning calorimetry

The Differential Scanning Calorimetry (DSC) analysis was conducted on a 2910 Modulated DSC V4.4E instrument (USA). The samples were weighed accurately (2 to 3 mg) and placed in hermetically sealed 40 ml aluminium crucibles, scanned from 25-300 °C at a heating rate of 10 °C/min under a dry nitrogen atmosphere [42].

Powder x-ray diffraction

The Powder X-Ray Diffraction **(**PXRD) patterns were collected on a Shimadzu XRD-7000 X-ray diffractometer (Japan) maxima with Cu-Kα radiation (1.540Å). The tube voltage and amperage were set at 20 kV and 35 mA, respectively. Each sample was scanned between 5 and 60° 2θ with a step size of 0.02°. Before performing the experiments, the instrument was calibrated using a silicon standard [43].

Solubility study

The solubility of ASA-valine cocrystal was determined by adding excess amounts of cocrystals in a Schott Duran bottle containing 5 ml of pH 4.5 acetate buffer solutions. The mixture was stirred continuously at 25±0.5 °C for 48 h to achieve equilibrium. The resultant solution was filtered using a whatman filter paper. The supernatant was then diluted to make sure that the solution concentration point falls on the standard curve. The filtrate was analyzed by UV-1700 double beam spectrophotometer (Shimadzu, Japan) at 268 nm after suitable dilution. The absorbance of the solution was taken as the solubility of the ASA in terms of concentration.

In vitro dissolution study

The dissolution test was carried out in a USP type 1 apparatus (Basket method). The samples were placed in size 00 hard gelatin capsules. 900 ml of pH 4.5 acetate buffer was used as dissolution media at 37±0.5 °C temperature and maintaining the stirring speed at 50 rpm. The samples were drawn at the interval of 5, 10, 15, 20, 25, 30, 45, 60, 90, and 120 min. Further fresh volume of the dissolution medium was replaced with the withdrawn volume to maintain the sink conditions. Samples withdrawn were analyzed at wavelength 268 nm using UV-1700 double beam spectrophotometer (Shimadzu, Japan) for determining the percentage of cumulative drug release [44].

RESULTS AND DISCUSSION

Drug content determination

The drug content in the prepared ASA-Valine cocrystal was found to be 95.3%. Since some of the product was retained in the beaker and could not able to remove completely, the percentage of drug content was not able to achieve 100%. This estimate of drug content will help in determining the concentration of cocrystals to be taken for dissolution studies to compare with pure ASA and marketed ASA.

Melting point study

The melting point is determined to study the thermal behaviour of the prepared cocrystals. The melting point of the prepared cocrystal was found to be 126 °C shown in table 1, which is in between the melting point of pure ASA and valine. Thus this confirms the formation of a new crystalline form other than ASA and valine.

Fourier transform infrared spectroscopy

Cocrystal formation in the present study was initially confirmed by comparing the IR stretching frequencies of various functional groups present in cocrystal with pure ASA [45]. Technically no shift in the

carbonyl stretching frequency was observed for ASA-valine cocrystal. This indicated the carbonyl groups in both ASA and valine remain untouched. A considerable shift in amine/hydroxyl stretching frequency was observed for ASA-valine cocrystal, which confirms the formation of a hydrogen bond between ASA and valine. The detailed stretching frequency of ASA and the prepared cocrystals are shown in table 2. The FT-IR spectra of pure ASA and ASA-valine cocrystal are shown in fig. 3, 4.

Table 1: Melting point of pure ASA, valine and ASA-valine cocrystal

S. No.	Sample	Mean melting point (°C)±SD
1	ASA	133±04
2	Valine	294±02
3	ASA-valine cocrystal	127±04

*All values are expressed as mean±SD, (n=3).

Table 2: FT-IR stretching frequencies of ASA and ASA-valine cocrystals

S. No.	Type of band	ASA (cm^{-1})	ASA-valine cocrystal (cm^{-1})
1	-O-H (st)	3430 (s)	3466 (vs)
2	-C=O (st)	1594 (vs)	1594 (vs)
3	-N-H (st)	-	3255 (m)

*(vs):-very strong; (s):-strong; (m):-medium; (st):-stretching.

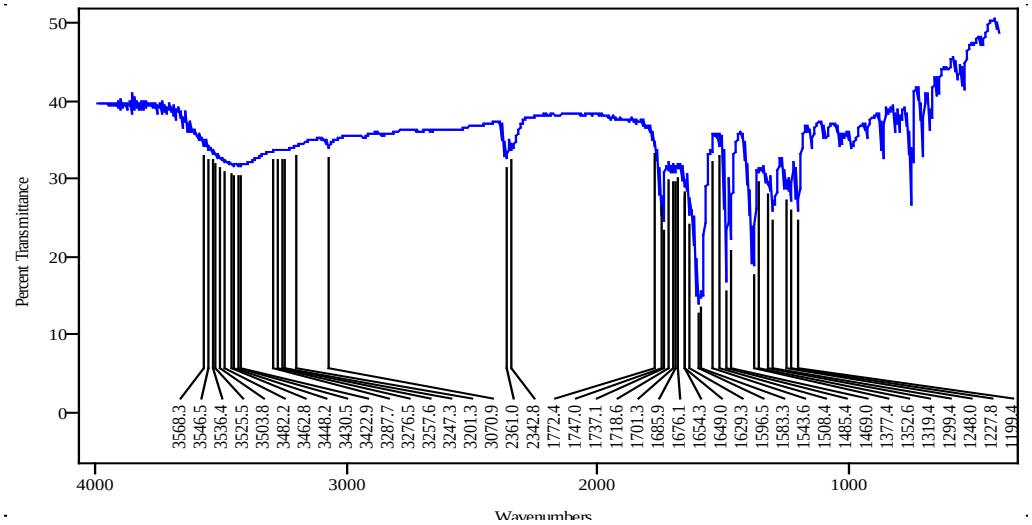

Fig. 3: FT-IR spectra of pure ASA

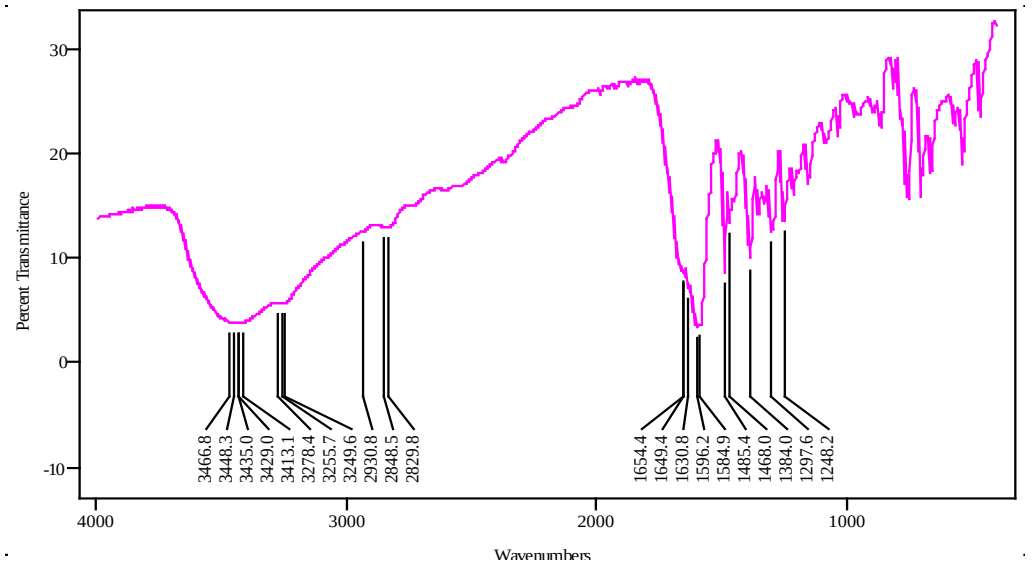

Fig. 4: FT-IR spectra of ASA-valine cocrystal

Scanning electron microscopy

The surface morphology and appearance of the ASA-valine cocrystal was examined by SEM. As observed from the SEM images, the crystals were in needle-like appearance. The image of ASA-valine was shown in fig. 5.

Differential scanning calorimetry

DSC analysis of the synthesized cocrystals was performed to determine the exact melting temperature and to correlate the melting temperature with crystal density and intermolecular interactions. It is known that the melting temperature of the cocrystal often falls between the melting temperature of starting materials or below the starting material melting point [46]. In the present work, the ASA-valine cocrystal was found to melt exactly in between the melting temperature of pure ASA and valine as shown in fig. 6. At the temperature range of 120 °C, the decomposition of ASA-valine was observed, which corresponds to the mass change of 57% that assigned the separation of valine from ASA due to the breakage of a hydrogen bond between ASA-valine cocrystal.

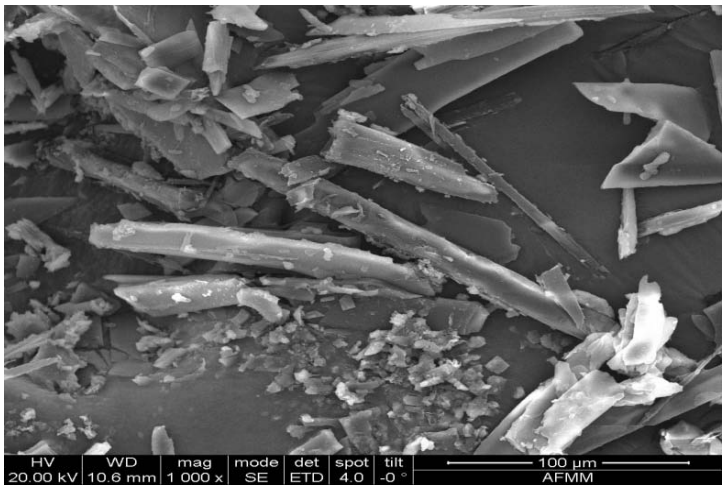

Fig. 5: SEM observation of ASA-valine cocrystal

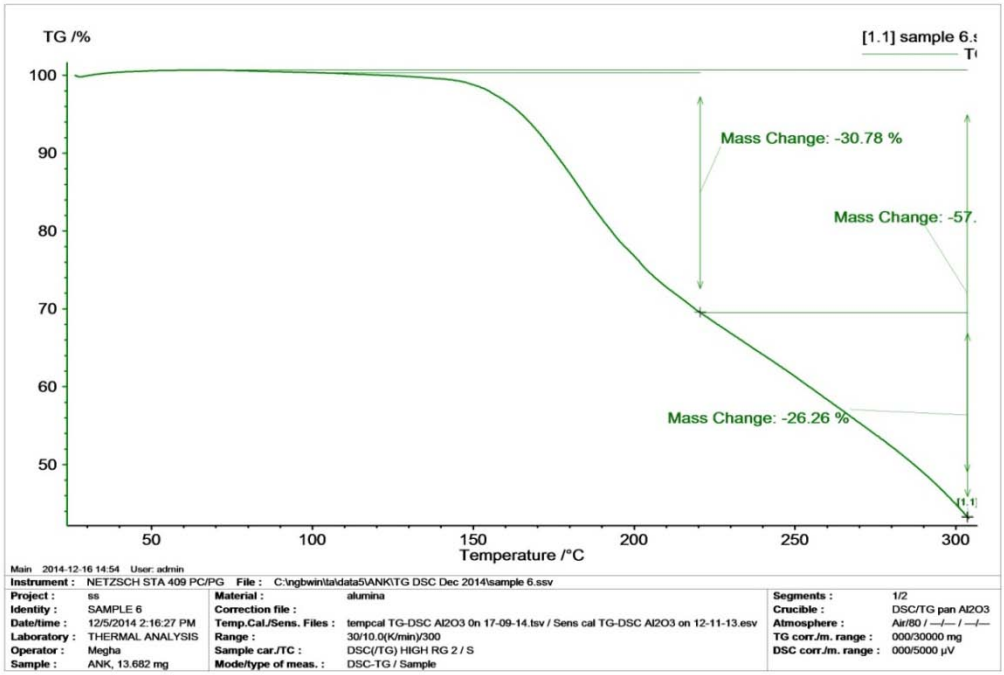

Fig. 6: DSC thermogram of ASA-valine cocrystal

Powder x-ray diffraction

PXRD is a reliable technique to characterize the formation of a new crystalline phase in solid-state. A different PXRD pattern of the product after cocrystallization experiments from the individual components confirms the formation of a new crystalline phase [47]. The PXRD patterns for ASA and ASA-valine cocrystal are shown in fig. 7, 8. ASA exhibited characteristic crystalline peaks at 2θ values of 11°, 16°, 18°, 23.5°, 29.5°, 31.5°, 32.5° and 40°, whereas ASA-valine cocrystal exhibited characteristic crystalline peaks at 2θ values of 10.5°, 17.5°, 28°, 32° and 36°. The different peaks in the cocrystal's PXRD pattern could imply the existence of interactions between ASA and valine to form a new cocrystalline phase.

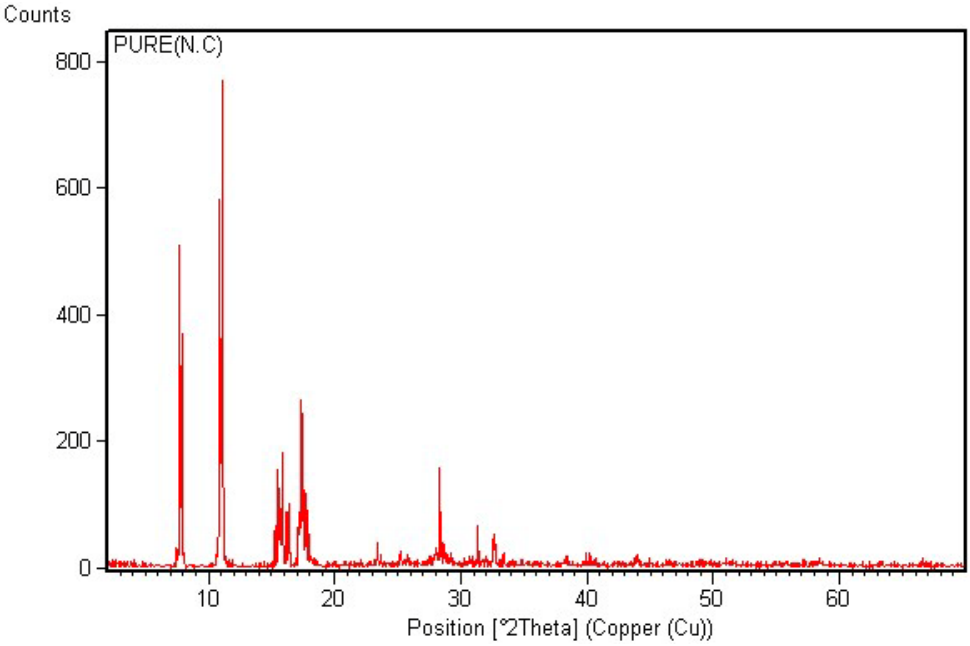

Fig. 7: PXRD pattern of pure ASA

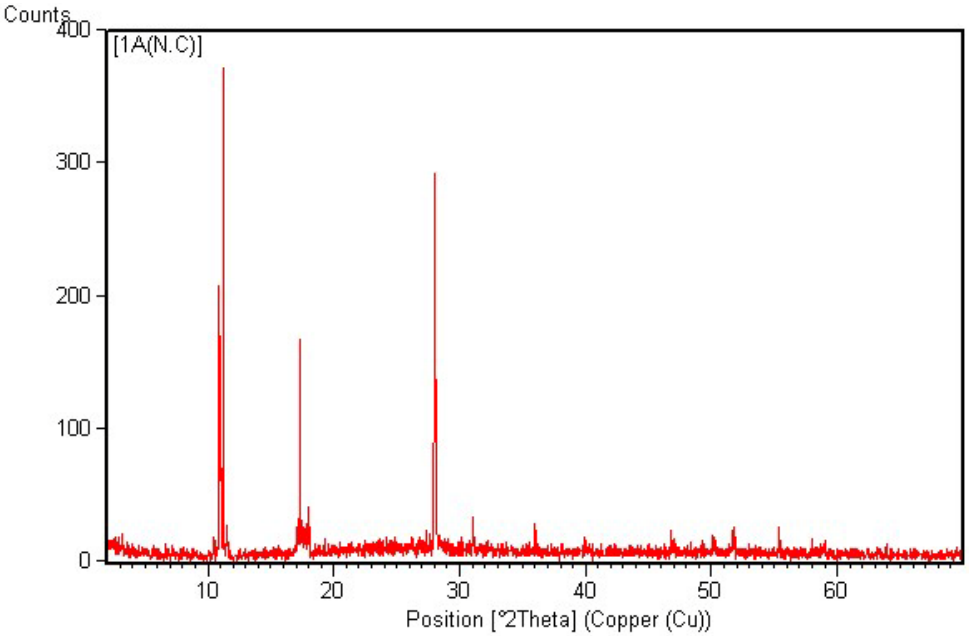

Fig. 8: PXRD pattern of ASA-valine cocrystal

Solubility study

The solubility of ASA-valine cocrystal was performed in a pH 4.5 acetate buffer solution. The pure ASA exhibited a solubility of 3 mg/ml. The ASA-valine cocrystal was showed an increased solubility of 17 mg/ml compared to pure ASA. This is due to the formation of a hydrogen bond between ASA and valine. Due to the presence of a hydrophilic chain in the cocrystal, solubility has increased to a greater extent.

***In vitro* dissolution study**

The *in vitro* drug release study of ASA-valine by USP type 1 apparatus (Basket method). The cocrystal was placed in a size 00 hard gelatin capsule. The dissolution media was filled with 900 ml of pH 4.5 acetate buffer solution maintained at temperature 37±0.5 °C with a stirring speed of 50 rpm. The samples were drawn at the interval of 5, 10, 15, 20, 25, 30, 45, 60, 90, and 120 min. The drug release of ASA-valine cocrystal was found to be 100% at 60th min. Where in the case of pure ASA and marketed product of ASA exhibited the dissolution rate of 59% and 69% at 60th min, respectively. The increase in dissolution rate of ASA-valine co-crystal may be due to strong intermolecular hydrogen bonding between ASA and valine. This is due to the presence of free carboxylic acid and amine functional groups in the valine. Nevertheless, the hydrophilic group present in the valine is responsible for the formation of hydrophilic ends in the ASA-valine co-crystals. Thus, the ASA-valine cocrystal showed a 1.7 and 1.44 folds increase in dissolution rate compared to pure ASA and marketed product of ASA, respectively as shown in fig. 9.

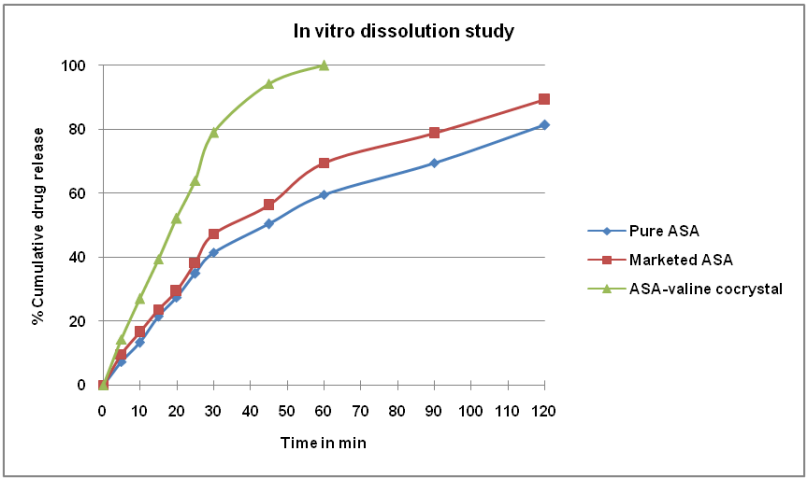

Fig. 9: Dissolution graph of pure ASA, marketed ASA and ASA-valine cocrystal, *All values are expressed as mean±SD, (n=3)

CONCLUSION

Co-crystallization technique can be an efficient technique for enhancement of the solubility and dissolution rate of BCS class 2 drugs. In this study, a novel cocrystal of ASA-valine was synthesized using the solvent evaporation technique and characterized. The melting of the prepared cocrystal remained lesser than the pure ASA, thus confirming the formation of a new crystalline form. The FT-IR, DSC and PXRD studies revealed the successful formation of cocrystals. The surface morphology by using SEM revealed the formation of needle-like crystals. The dissolution studies exhibited an increased dissolution rate compared to pure ASA and marketed ASA. Thus the ASA-valine cocrystal can be a greater alternative for increased solubility and dissolution rate compared to pure ASA.

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Nil

AUTHORS CONTRIBUTIONS

All the author has contributed equally.

CONFLICTS OF INTERESTS

The authors declare no conflict of interest.

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