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STUDY OF INTERACTION (COMPATIBILITY) AND EVALUATION OF SOLUBILITY OF ACETYL SALICYLIC ACID IN PRESENCE OF EXCIPIENT LYSINE

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ABSTRACT

Studies of pharmaceutical drug/active pharmaceutical ingredient (API) compatibility represent an important phase in the design or development of new formulation stage and drug delivery systems. Excipients in the formulations influence the chemical nature, stability, manufacturability, drug bioavailability or delivery of the drug to the patient. Acetyl Salicylic Acid (ASA) is one of the most widely used analgesic, which is poorly soluble in water and causes gastrointestinal irritation. Its cocrystal with Lysine (1:1 part by weight) were prepared in 50% aqueous ethanol and evaluated for Scanning Electron Microscopy, FT-IR spectra, X-ray diffraction, Differential Scanning Calorimetry and *in vitro* dissolution study. Acetyl Salicylic Acid-Lysine cocrystal were found to be disc shaped with rough surface in SEM, drug content in the complex was found to be 60% DSC thermograms PXRD and FT-IR confirmed the formation of the cocrystal. Solubility of the prepared cocrystal was found to be improved, ASA-Lysine cocrystal showed 96.62% release at 5 minutes and pure ASA showed 96.62% release at 120 minutes and commercial aspirin showed 96.62% release at 60 minutes at PH 4 acid buffer. It was concluded that ASA-Lysine in definite proportion by weight may be of potential use for improving the solubility of ASA and hence its bioavailability..

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INTRODUCTION

Studies of actual pharmaceutical drug and active excipient suitability represent a major stage in the design or development of the improvement of all dosage forms or drug delivery systems, one of which is the actual pharmaceutical drug or active pharmaceutical ingredient (API). The possible physical and chemical interactions between drugs and active excipients can affect the chemical structure, stability, manufacturability, bioavailability of drugs or delivery of the drug to the patient and their therapeutic effect and safety [1]. Pharmaceutical drugs and active excipient compatibility studies aids in efficacious dosage form [1-11].

It is prerequisite for active ingredient in solid dosage form must undergo dissolution to get absorb from gastrointestinal tract. The rate of release of a drug is a function of its intrinsic solubility which is the rate limiting step and influenced by particle size, crystallinity, drug derivitazation and formation of more soluble complexes [12] they can also be converted to solid forms such as polymorphs, salts, solvates, hydrates, amorphous and cocrystals. Each of them imparts a different physiochemical property and affects other performance characteristics stability, bioavailability, purification, and manufacturability of the drug in their own better way. Taking this into consideration, it is critical to understand the relationship between the particular solid form of a compound and its functional properties. By determining *in vitro* dissolution for a formulation of different batches quality control can be ensured [13]. For water insoluble (lipophilic) drugs increase in bioavailability can be obtained by enhancement of dissolution rate.

Acetyl Salicylic Acid is one of the most widely used therapeutic substances due to its analgesic, antipyretic and anti-inflammatory properties. Despite the proliferation in the development of new non-steroidal anti-inflammatory drugs (NSAIDs), ASA remains one of the most effective 'over the counter' drugs in the treatment of rheumatic diseases. Furthermore, due to its anti-thrombic properties, ASA is now prescribed at low doses in the prevention and treatment of cardiovascular diseases, strokes and disorders associated with platelet agreeability [14].

ASA is poorly soluble in the acidic conditions of the stomach, which can delay absorption of high doses for 8 to 24 hours. Modifying the water solubility of ASA may prove to be beneficial for improving its absorption.

The maximum development and interest area are being diverted to co-crystallisation. Co-crystallisation can be achieved only when the physicochemical properties (hygroscopicity, solubility, and compaction behaviour) of the formulation as a whole is involved. Co crystals consists of two components that are the API and the former, the former can be any other excipient or food additive, preservatives, vitamins ,minerals, aminoacids, and other biomolecules or another API, which, when given in combination, reduces the dose and also the side effects. Hence, even if the API is the same changing the former will change the pharmaceutical properties (chemical stability, bioavailability, solubility, melting point, moisture uptake, dissolution, etc). Totally, co-crystallisation is the most dynamically developing group of solid pharmaceutical substances.

According to the BCS classification, the API belonging to class II and IV have always posed a challenge in case of enhancing the solubility. Hence, one such option is co-crystallisation. The most appropriate co-crystal can be selected using various analytical techniques and rational physicochemical studies that include investigations of solubility and stability. If the difference between P^{Ka} of the API and the excipient is greater than 1 then it leads to the formation of the co-crystals of salt [15].

In the acidic conditions of stomach ASA, which is class II group of drugs, is poorly soluble which delays absorption. Improvement of its absorption can be expected by modifying the solubility [16].

Therefore the study aims to develop the co-crystal of ASA in presence of Lysine excipient, to evaluate its compatibility, by Physico-chemical characterization of drug in presence of excipient Lysine for crystallinity(XRD), chemical interaction (FTIR), phase transition behaviour (DSC) as well as to know the improvement in solubility hence its dissolution rate *in vitro* dissolution study was conducted.

MATERIALS AND METHODS

Materials:

All the chemicals were of analytical grade and purchased from Sigma Aldrich.

Preparation of physical mixture and cocrystallisation

ASA and Lysine in 1;1 proportion by weight was ground finely by using the high energy vibrational mill (CMTTI-200, Tokyo Japan), was dissolved in 50% aqueous ethanol and crystallised by solvent evaporation method. The crystals were dried, residues were collected and placed in vacuum desiccators overnight and subjected to characterization.

Physicochemical characterization of drug by analytical techniques

FTIR:

Fourier-transform infrared (FTIR) spectroscopy was conducted on Perkin Elmer Life and Analytical Sciences, MA, USA, using KBr disk method (1 mg sample in 100 mg KBr). The scanning range was 4000– 500 cm^{-1} and the resolution was 2 cm^{-1}.The infra-red (IR) spectrum of the sample ASA-Lysine was compared with the IR spectrum of ASA reference provided in Indian Pharmacoepia.

DSC & Thermograms:

Differential Scanning Calorimetry (DSC) & Thermograms (TG) were performed using a 2910 Modulated differential scanning calorimeter V4.4E instrument. DSC curves were evaluated with Modulated differential scanning calorimeter V4.4E software. The thermal behaviour was studied by heating 2.0+0.2mg of each individual sample in a covered sample pan under nitrogen gas flow. The investigations were carried out over the temperature range 25^0C-250^0C with a heating rate of 10^0C/min. The instrument was calibrated using Indium as reference material. Samples were measured in a 30 Rl Aluminium pan.

PXRD:

The crystalline state of ASA in the different samples was evaluated with X-ray powder diffraction. Diffraction pattern were obtained on a Bruker Axs-D8 Discover Powder X-ray generator was operated at 40 KV tube voltages and 40mA of 20 in step scan mode (step width 0.4^0/min).ASA-Lysine cocrystal was analyzed by X-ray diffractions.

SEM:

The surface morphology of pure ASA and ASA -Lysine cocrystal were characterized at IISc, Bengaluru by Scanning Electron Microscope (JEOL JSM 5600). They were mounted directly on to the SEM sample stub using double-sided sticking tape and coated with gold (thickness 200 nm) under reduced pressure (10−4 mm of Hg) at 5–30 KV. All the images were recorded at typical working distance of 8-10 mm.

***In vitro* dissolution studies**

In vitro dissolution studies for ASA with Lysine,plain ASA, as well as commercial tablet were performed in triplicate in a USPXXIII six station dissolution test apparatus at 100rpm and at 37^0C.An accurately weighed amount of the ASA-Lysine cocrystal equivalent to 500mg of ASA was put into 500ml pH 4 acetate buffer.3 ml of sample was withdrawn at different interval of time and replaced with fresh media. The solutions were filtered (240 nm) and concentration of the drug in release media was estimated using a double beam UV-visible spectrophotometer (Shimadzu 1700), at 240 nm by the regression equation of standard curve developed in the same media.

RESULT AND DISCUSSIONS:

Physico-chemical characterization of ASA-Lysine co-crystal:

The formation of the co-crystal can be confirmed by the IR spectroscopy comparing the spectrum of the co-crystal with the spectrum of pure ASA. FTIR spectrum for the co-crystal was obtained on a Perkin Elmer FTIR spectrometer in the transmission mode with the wave number region 4,000-500 cm^{-1} FTIR spectrum showed the changes in peaks in the co-crystal in comparison to that of ASA. FTIR spectrum of the co-crystal was significantly different from that of ASA.

As per the reference provided in Indian Pharmacoepia ASA showed the characteristic IR (KBr) peaks of O-CO- stretching at 1747cm^{-1},C-O stretching at 1199.3cm^{-1}, -OH bending at 1495.44cm^{-1} aromatic ring C=C at 1596 cm^{-1} C-H stretch at 3000cm^{-1}, -OH (out of plane) bending at 916cm^{-1} and -OH (in plane) bending at 1377$cm^{-1.}$

The peak around at 3400 cm^{-1} shows -N-H stretching and the peak at 1390 cm^{-1} is due to the symmetric carboxylate, -OH both in plane, out of plane and –OCO stretching vibrations were missing in the co-crystal. Thus, the FTIR spectrum indicates the interaction of Lysine with the Acetyl Salicylic Acid -COOH group (Fig.1).

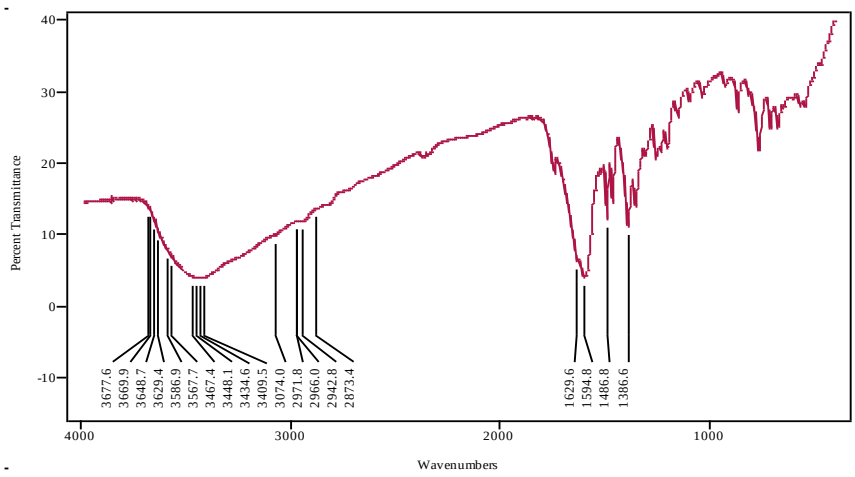

Fig 1. FTIR of ASA with Lysine.

To check whether the changes in the ASA- lysine co-crystal morphology corresponds to a polymorphic transition and to study the solid state of ASA – Lysine co-crystal, PXRD analysis was conducted. From these patterns, the degree of crystallinity could be evaluated using the relative integrated intensity of reflection peaks in the given range of reflecting angle, 2θ .The value of 2θ means the diffraction angle of ray beams, which is shown in the abscissa of Fig.2.

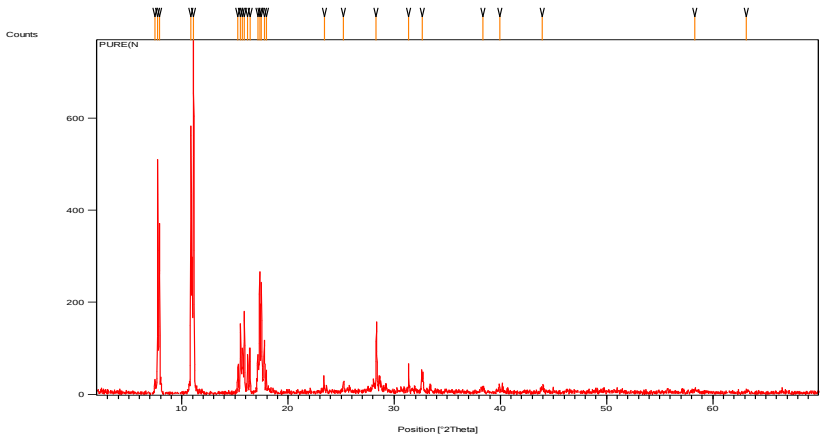

Fig 2. PXRD of ASA with lysine.

On comparison with the standard PXRD of ASA, with PXRD of ASA-Lysine co-crystal, the disappearance of ASA crystalline diffraction peaks confirmed the formation of co-crystal with Lysine. Bonding between ASA and Lysine in the development of the co-crystal might have resulted into the significant change of its X-ray diffraction.(Fig.2)

The Differential Scanning Calorimetry and Thermo Gravimetric Analysis are the tools used to measure the temperature and energy variation involved in the phase transitions, which reflects the degree of crystallinity and stability of the solid state of pharmaceutical compounds [16]. In order to substantiate the association of ASA with Lysine, DSC analysis was performed on ASA, and the ASA-Lysine co-crystal. DSC of ASA-Lysine co-crystal showed endothermic peaks at 130^0C and 165^0C and total mass change of 60%. The results of the DSC test confirmed the association of ASA and Lysine in the co-crystal as both the peaks representing ASA changed the position (Fig.3)

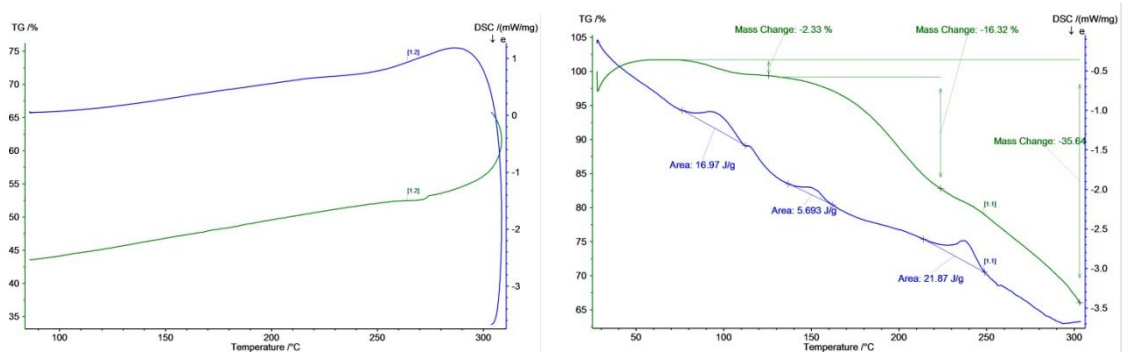

Fig 3. DSC and TGA heating of ASA with Lysine.

Scanning Electron Micrographs of the ASA- Lysine with 1:1 weight proportion are shown in Fig 4. The co-crystal is found to be of disc shaped with roug1h surface morphology. Variations in weight proportion of excipient may have different effects in shape, form and surface morphology [17].

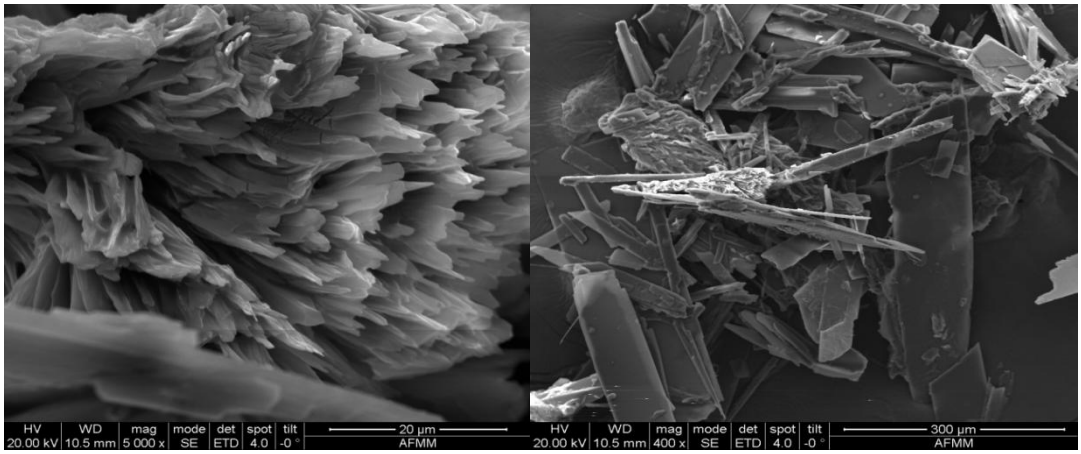

Fig 4. SEM of ASA with Lysine at magnification 5000X and 400X.

In vitro drug release:

The comparative (ASA with Lysine, v/s pure ASA, v/s Commercial Aspirin tablet *in vitro* release profiles at pH 4 is depicted in Figure 5.

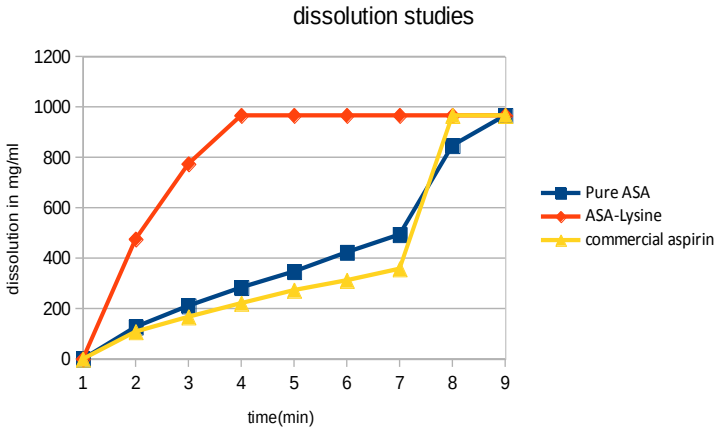

Fig 5. Comparative dissolution of ASA in presence of Lysine v/s pure ASA v/s commercial Aspirin.

The dissolution rates of the ASA are greatly influenced in presence of Lysine. The release of ASA in the dissolution media is found to be a function of the percent of Lysine load as well as the pH of the media. At respective pH 4 maximum % release of drug from ASA-Lysine(1:1pbw) is 96.62% noticed at 5 minutes and from pure ASA (96.62%) is noticed at 120 min and of commercial Aspirin tablet (96.62%) at 60 minutes. Solid dissolution depends on particle size, crystal habit, wettability, surface area and surface energy [18]. The better release profiles in the ASA- Lysine may be due to amphiphilic nature of Lysine which leads to wetting and dispersion. However, the release profiles may vary with pH of the release medium. By varying the proportion by weight of Lysine, solubility of the drug may be varied and that's why the dissolution profile of the co-crystal can be improved.

CONCLUSION

The enhancement of oral bio availability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Poorly water soluble drugs may present a lack of therapeutic effect, because of their low bioavailability. Co-crystal formation with excipients is one of the processes to improve drug's poor water solubility.

In the present study ASA-Lysine co-crystal is prepared by a simple and reproducible method. The physicochemical properties of ASA-Lysine co-crystals showed difference to those of ASA shows that ASA formed a co-crystal with Lysine which resulted in a better solubility and dissolution profile than ASA as well as the commercial Aspirin drug. In addition the *in vitro* dissolution test showed that the dissolution of the co-crystal is significantly higher than ASA and the commercial Aspirin drug. With a particular proportion by weight of Lysine, ASA - Lysine co-crystal may be of potential use for improving bioavailability. These co-crystals may also be useful or minimize the GI toxicity of Aspirin, which may be validated further through *in vivo* studies. The Lysine co-crystal may be developed with ASA by different proportion by weight, as well as for other NSAIDs with poor bioavailability and GI side effects.

Recommended future research

The co-crystal development and evaluation of compatibility and solubility can be done for other NSAIDs as well as with different excipients in varying proportion with poor bioavailabilty and GI side effects.

LIST OF ABBREVIATIONS

ASA -Acetyl Salicylic Acid
SEM -Scanning Electron Microscopy
FTIR -Fourier Transform Infra-Red
PXRD -Powder X-Ray diffraction
DSC -Differential Scanning Calorimetry
TG -Thermo Gravimetric
NSAIDs-Non Steroidal Anti Inflammatory Drug
GI - Gastro Intestinal Tract

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Competing Interests:
Authors have no conflict of interest

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