



Research Article

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Physicochemical properties of Aspirin in presence of H_3PO_4 as an excipient

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ABSTRACT

Aspirin (acetylsalicylic acid, ASA) is one of the most widely used analgesics. Aspirin is poorly soluble in water and causes gastrointestinal (GI) irritation. The bioavailability of several kinds of drugs solely depends on their dissolution properties in biological systems. In this direction, the physicochemical property of aspirin with phosphoric acid as an excipient has been studied. The kinetic energy obtained from viscosity method indicates that drug-excipient interactions are predominant and kinetic energy decreases with increase in concentration of the excipient. To improve the solubility, hence the bioavailability and minimize the GI irritation, its complexes with H_3PO_4 (in 1:1 ratio) were prepared in 1:1 C_2H_5OH and water. Evaluation of solubility and drug excipient interaction was done using scanning electron microscopy (SEM), FTIR spectra, X-ray diffraction, differential scanning calorimetry (DSC) and in vitro dissolution study. Aspirin- H_3PO_4 complex were found to be having rough surface in SEM. DSC, thermograms, XRD and FTIR confirmed the formation of the complex. Dissolution and pharmacokinetic studies of the designed drug was found to be of subsistence importance of Aspirin- H_3PO_4 as a possible drug to improve bioavailability of the drug. It was concluded that the complex of aspirin in definite proportion by weight may be of potential use for improving the solubility of aspirin and hence its bioavailability.

Key words: Dissolution studies, ASA, SEM, FTIR, XRD, DSC.

INTRODUCTION

Aspirin (acetylsalicylic acid, ASA) is one of the most widely used therapeutic substances due to its analgesic, antipyretic and anti-inflammatory properties. Despite the proliferation in 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 antithrombic properties, ASA is now prescribed at low doses in the prevention and treatment of cardiovascular diseases, strokes and disorders associated with platelet agreeability. [1,2]

ASA use commonly associated with gastrointestinal (GI) side effects ranging from dyspeptic symptoms and ulceration to life-threatening episodes of bleeding.[3] 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 aspirin may prove to be beneficial for improving its absorption.[4]

The rate of release of a drug is a function of its intrinsic solubility and influenced by particle size, crystallinity, drug derivatization and formation of more- soluble complexes.[5,6,7,8,9,10] Various approaches have been investigated to improve the absorption and permeation of biologically active constituents of synthetic and natural origin. These include development of more soluble prodrug, solid dispersions, preparing complexes with complexing agents like metals, cyclodextrin and phospholipids. Apart from other methods used for modifying the solubility, the complexation with phosphoric acid is one of the methods. [11, 12]

Moreover, the formation of complex of NSAIDs with H_3PO_4 may improve GI safety of these drugs. It has been reported that the diffusion of NSAIDs across lipid membranes and into target cells is accelerated when it is present as a complex. [13] Therefore, this study aims to develop the complexes of aspirin to improve solubility and hence its dissolution. The study deals with its characterization for drug content, solubility, crystallinity (XRD), chemical interaction (FTIR), phase transition behavior (DSC) and pharmacokinetic studies by carrying out *in vitro* dissolution study to check role of H_3PO_4 as an excipient and its effect on bioavailability and solubility of aspirin in biological systems.

EXPERIMENTAL SECTION

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

2.2 Preparation of physical mixture and co-ground complex

For viscosity measurement physical mixture of Aspirin and H_3PO_4 prepared by mixing in 1:4 to 1:40 weight proportion in a bottle using a vortex mixture for 5 min. Co-ground complex was prepared by grinding the corresponding physical mixtures in the high energy vibrational mill (CMTTI-200, Tokyo Japan). Ground fine powder is dissolved in 1:1 C_2H_5OH and H_2O :1:1 proportion by weight of the mixture is heated and allowed to crystallize. The crystals are dried, residues were collected and placed in vacuum desiccators overnight and subjected to characterization.

2.3 Physicochemical characterization of drug.

Viscosity measurement.

The rheological study of the solution of this drug was done using Viscometer. In this experiment the time (seconds) of flow was noted, for various drug excipient compositions as shown in table 1. For the time of flow the solution taken was 10 cm^3 . The experiment was carried out at room temperature (25°C) by keeping the viscometer in a water bath in order to minimize the thermal fluctuations. For each composition, the density was calculated with respect to 50% C_2H_5OH .

2.4 Instrumentation

2.4.1 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 $4000\text{--}5000\text{ cm}^{-1}$ and the resolution was 2 cm^{-1} . The infra-red (IR) spectra of the sample Aspirin was compared with the IR spectra of the Aspirin reference provided in Indian Pharmacopoeia.

2.4.2 DSC & Thermograms:

Differential Scanning Calorimetry (DSC) & Thermograms (TG) was 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 behavior was studied by heating $2.0\pm 0.2\text{ mg}$ of each individual sample in a covered sample pan under nitrogen gas flow. The investigations were carried out over the temperature range $25\text{--}250^\circ\text{C}$ with a heating rate of $10^\circ\text{C}/\text{min}$. The instrument was calibrated using indium as reference material. Samples were measured in a 30 RI aluminium pan.

2.4.3 PXRD:

The crystalline state of aspirin 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 $0.4^\circ/\text{min}$). Aspirin- H_3PO_4 complex was analyzed with X-ray diffractions.

2.4.4 SEM:

The surface morphology of the pure drug and drug H_3PO_4 complex 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 ($10\text{--}4\text{ mm}$ of Hg) at $5\text{--}30\text{ KV}$. High resolution imaging was used for measuring particle size. All the images were recorded at typical working distance of 8-10 mm.

2.5. In vitro dissolution studies

In vitro dissolution studies were carried out in 900 ml pH 4 acetate buffer at $37\pm 0.5^\circ\text{C}$ at 100 rpm (Basket method, Electrolab Dissolution Tester TDL-06L). 500 mg of Aspirin or its equivalent formulation was added to the dissolution medium and 3 ml of sample was withdrawn at 5, 10, 15, 30, 60 and 120 minutes 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.

RESULTS AND DISCUSSION

3.1 Viscosity & Kinetic energy results of Aspirin-H₃PO₄ complex.

The study of Aspirin-H₃PO₄ complex which may be formed by H-bonding interaction the processing parameters such as Viscosity, K.E and stability studies were performed with different proportion by weight as discussed and reported below.

K.E of Aspirin with excipient varies linearly as weight of drug –excipient varies from 1:4 to 1:40. K.E linearly decreases with weight proportion of excipient increases (Fig 1).

η vs ρ/t varies linearly As ρ/t increases η decreases (Fig 2).

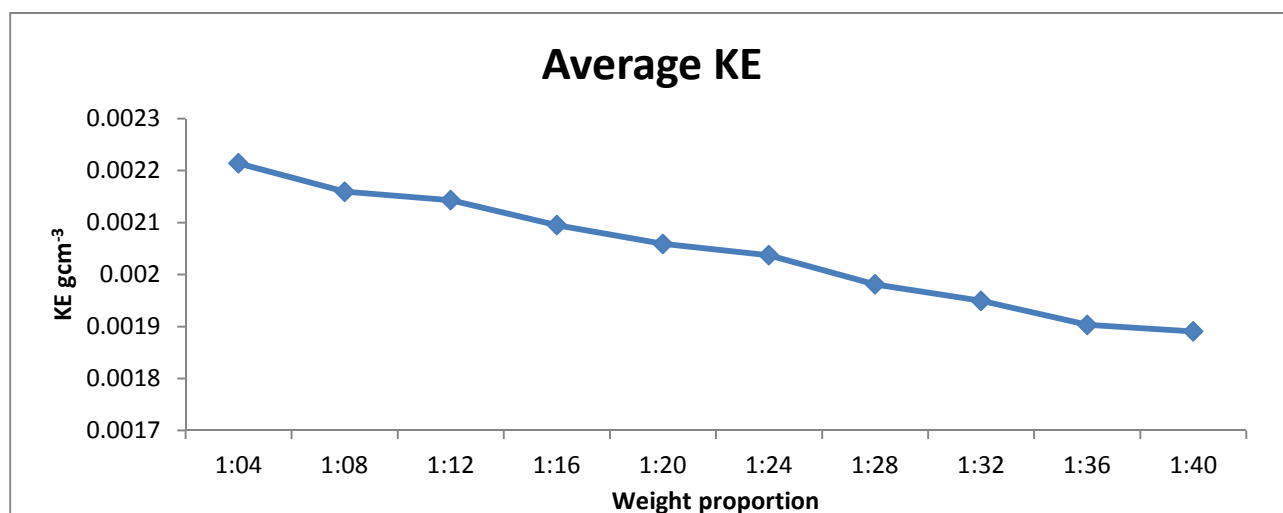


Fig 1: Plot of KE versus weight proportion

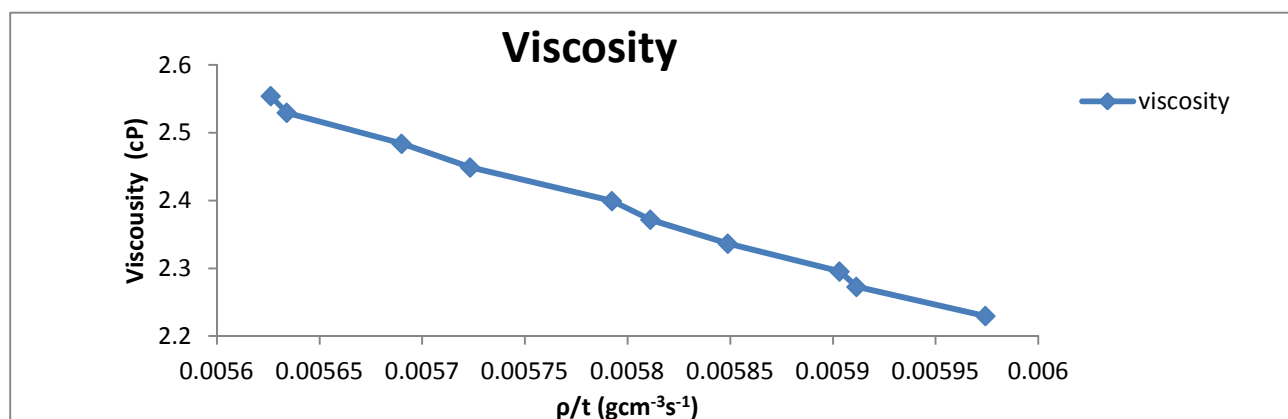


Fig 2: Plot of Viscosity versus ρ/t

3.2 Physico-chemical characterization of Aspirin-H₃PO₄ complex:

The formation of the complex can be confirmed by the IR spectroscopy comparing the spectrum of the complex with the spectra of Aspirin. FTIR spectra for the complex was obtained on a Perkin Elmer FTIR spectrometer in the transmission mode with the wave number region 4,000-500 cm⁻¹. FTIR spectra showed the changes in peaks in complexes and positions from that of aspirin. FTIR spectra of complex were significantly different from that of Aspirin.

Aspirin 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} in aspirin has merged with broadband at 1000cm^{-1} . -OH (in plane) bending at 1377cm^{-1} is missing in the complex. Thus, the FTIR spectra indicate the interaction of H_3PO_4 with the aspirin's -COOH group shown (Fig 3)

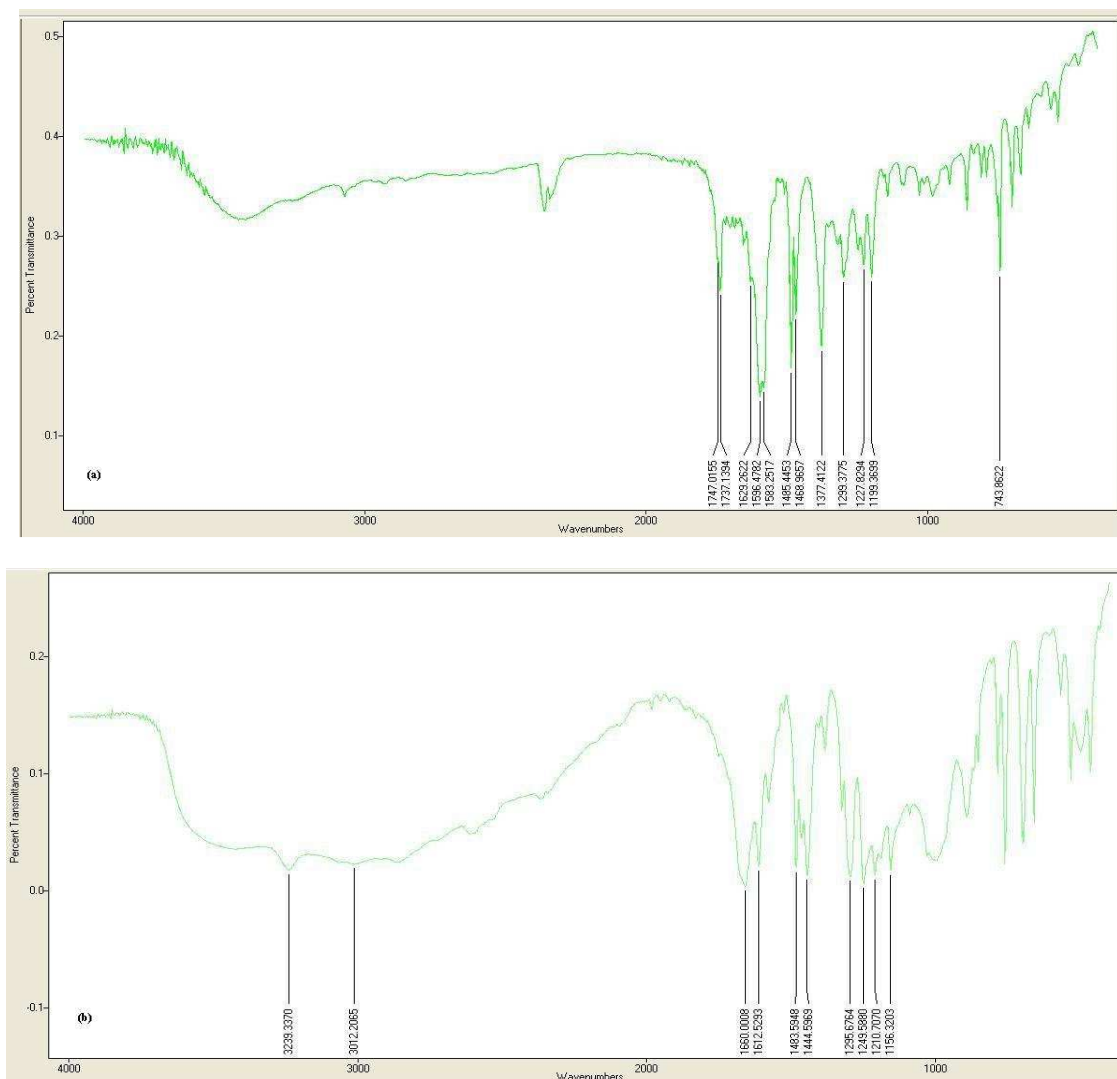


Fig 3: IR for (a) Aspirin and (b) Aspirin with H_3PO_4

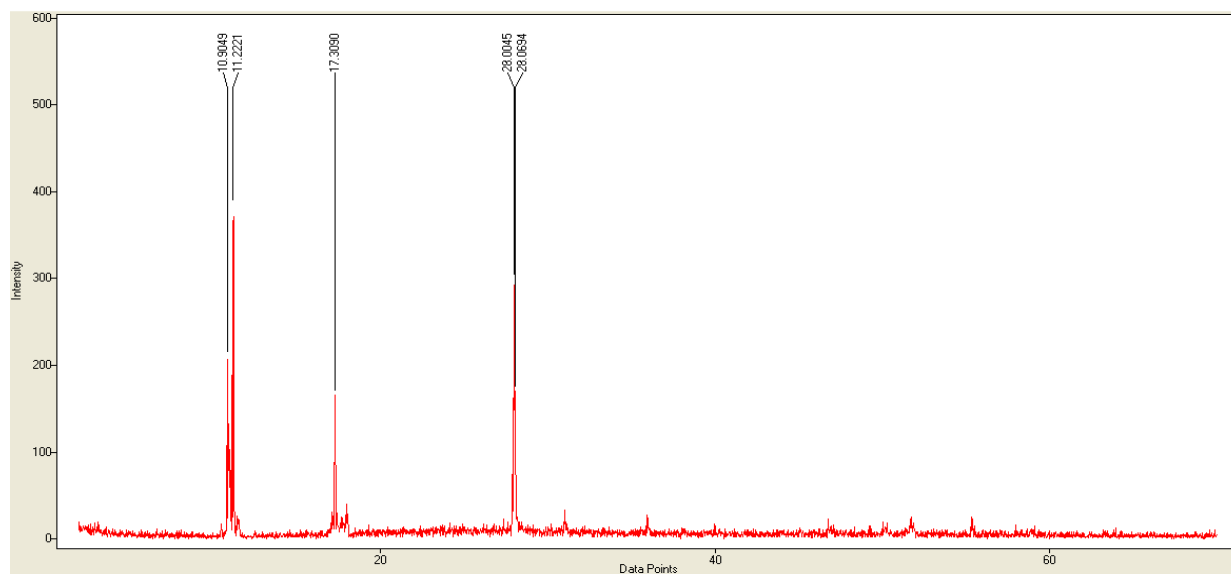


Fig 4: PXRD for Aspirin- H_3PO_4

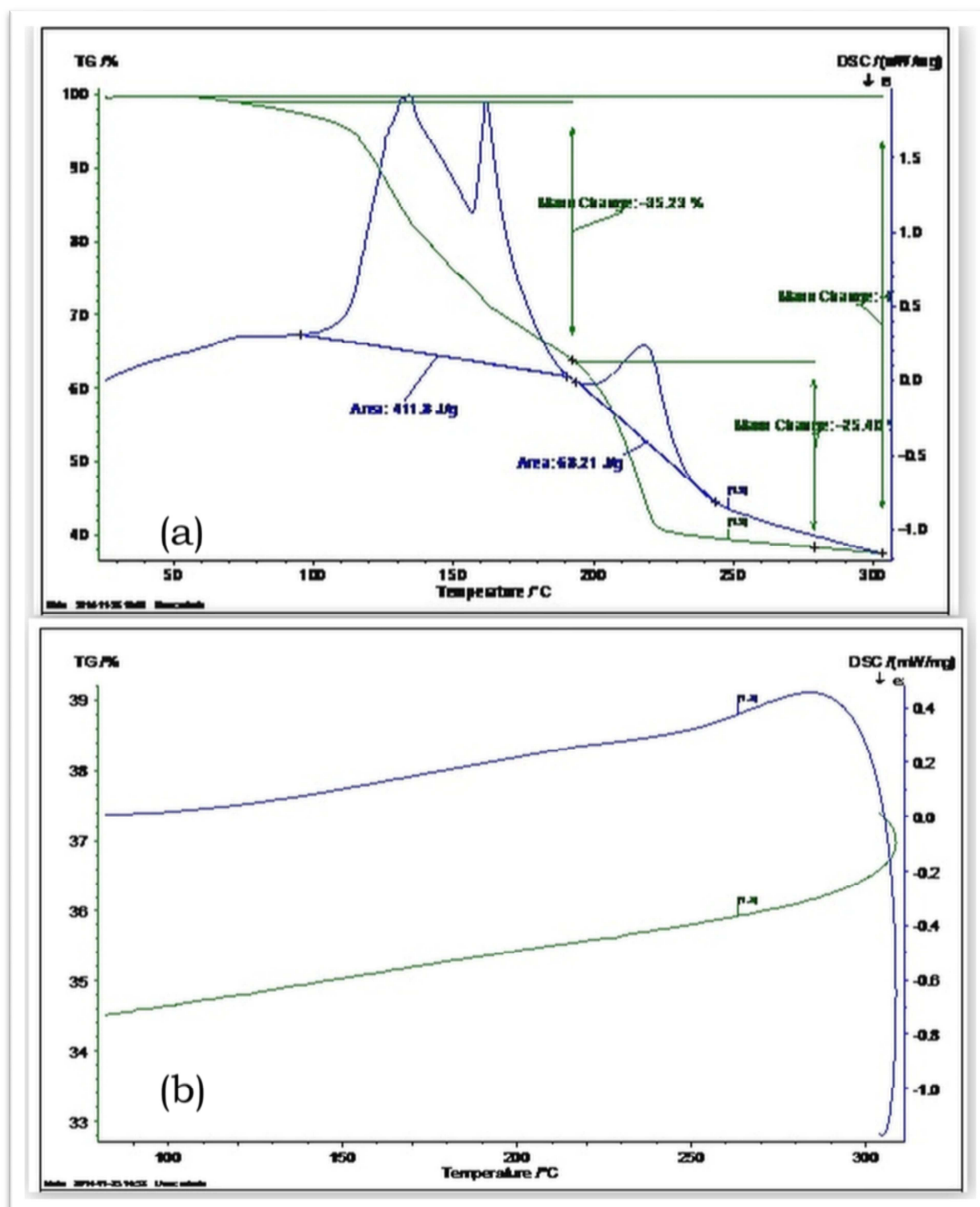


Fig 5: DSC & TG curves for Aspirin- H_3PO_4 (a) heating (b) cooling

To check whether the changes in the aspirin crystal morphology correspond to a polymorphic transition and to study the solid state of aspirin H_3PO_4 complex, 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.4

The disappearance of aspirin crystalline diffraction peaks confirmed the formation of complex with H_3PO_4 . Bonding between drug and H_3PO_4 in the development of the complex might have resulted into the significant change of its X-ray diffraction.(Fig 4)

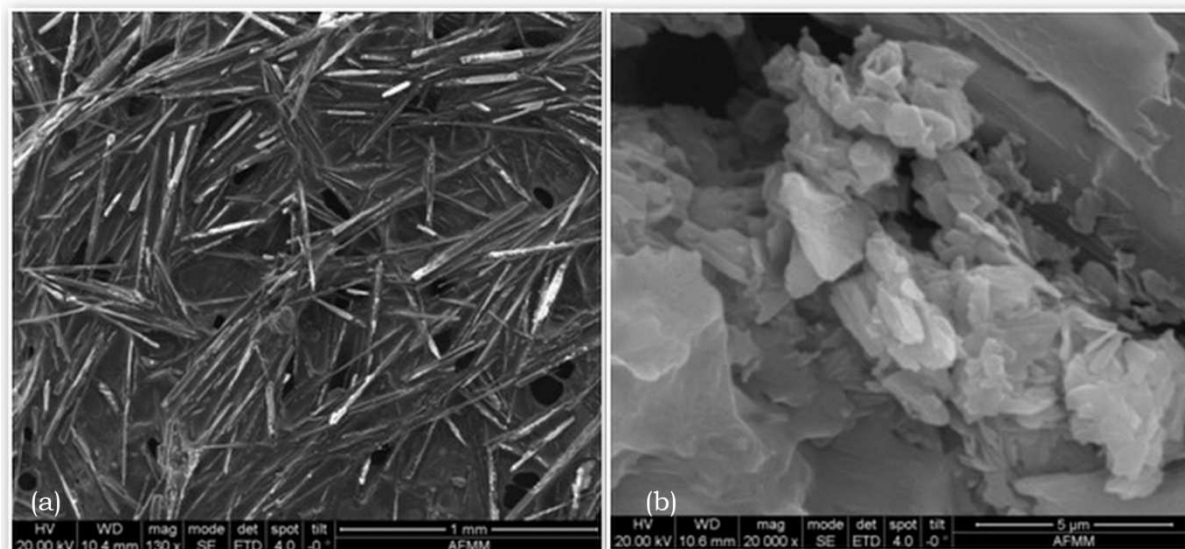


Fig 6: SEM of crystals for Aspirin-H₃PO₄ (a) Magnification 20000x (b) Magnification of 130x

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 [14]. In order to substantiate the association of aspirin with H₃PO₄, DSC analysis was performed on aspirin, and the aspirin-H₃PO₄ complex. DSC of Aspirin-H₃PO₄ complex showed endothermic peaks at 130^oC and 165^oC and total mass change of 60%. The results of the DSC test confirmed the association of aspirin and H₃PO₄ in the complex as both peaks representing aspirin changed position (Fig.5)

Scanning Electron Micrographs of the Aspirin-H₃PO₄ with 1:1 weight proportion are shown in Fig.6. The complex was found to be of disc shaped with rough surface morphology. Variation in weight proportion of excipient may have different effects in shape, form and surface morphology [15].

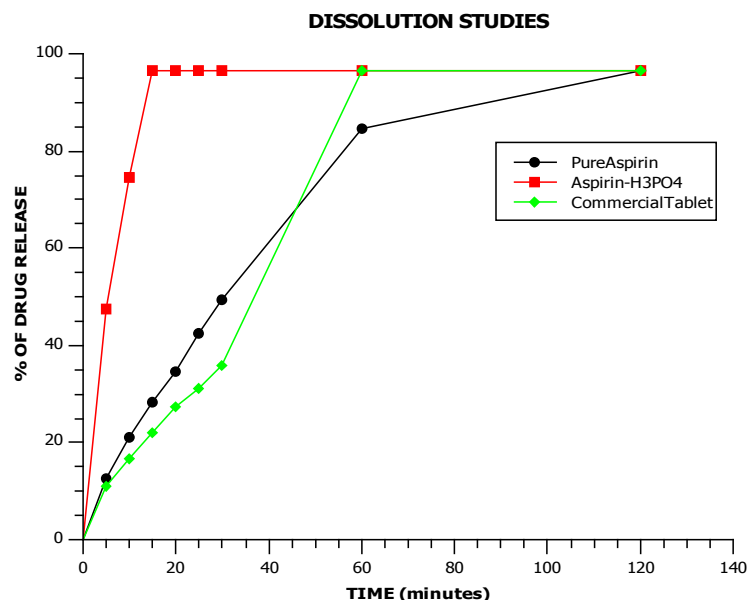


Fig 7: The Aspirin-H₃PO₄ complex showed different dissolution profile than aspirin

3.3 In vitro drug release:

The comparative (Prepared drug v/s pure drug v/s Commercial drug) in vitro release profiles at pH 4 are depicted in Figure 7. The dissolution rates of the Aspirin were greatly influenced by the use of H₃PO₄. The release of Aspirin in the dissolution media was found to be a function of the percent of H₃PO₄ load as well as the pH of the media. At respective pH 4 maximum % release of drug from Aspirin- H₃PO₄ (96.62%) was noticed at 15 minutes and from pure drug (96.62%) was noticed at 120 min and of commercial tablet (96.62%) at 60 minutes. The better release profiles in the Aspirin- H₃PO₄ may be partially ascribed due to reasons such as high surface area of the complex

carrier matrix, enhanced porosity, and the excellent wettability & polarity of H₃PO₄. However, the release profiles may vary with pH of the release medium. By varying the proportion by weight of H₃PO₄ solubility of the drug can be varied and that's why the dissolution profile of the complex can be improved. The maximum drug release at pH 4 is 96.62%.

CONCLUSION

The enhancement of oral bioavailability 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. Amorphisation complex with excipients is one of the processes to improve drug's poor water solubility.

In the present study Aspirin-H₃PO₄ complex was prepared by a simple and reproducible method. The physicochemical investigations showed that Aspirin formed a complex with H₃PO₄ with better solubility and dissolution profile by varying proportion by weight of H₃PO₄. With a particular proportion by weight of H₃PO₄, Aspirin-H₃PO₄ complex may be of potential use for improving bioavailability. These complexes may also be useful or minimize the GI toxicity of Aspirin, which may be validated further through in *vivo* studies. The H₃PO₄ complex may be developed with Aspirin by different proportion by weight, as well as for other NSAIDs with poor bioavailability and GI side effects.

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