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DEVELOPMENT AND CHARACTERIZATION OF ASPIRIN – SUCROSE COMPLEX FOR IMPROVED DRUG DELIVERY

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ABSTRACT

Many drugs fail to reach market due to their poor water solubility. This paper presents an approach to increase solubility of Aspirin in presence of sucrose as an excipient, is suitable for an immediate release formulations. To improve the solubility, hence the bioavailability, its complex with sucrose was prepared in aqueous Ethanol, Kinetic energy calculation, evaluation of dissolution 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-sucrose complex were found to be having rough surface in SEM. DSC, thermograms, XRD and FTIR confirmed the formation of the complex. The 1:1 proportion by weight of aspirin-sucrose resulted in formulation for quick release. It was concluded that the complex of aspirin in definite proportion by weight with sucrose may be of potential use for improving the solubility of aspirin and hence its bioavailability.

KEY WORDS: Dissolution studies, ASA, SEM, FTIR, DSC.

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INTRODUCTION

It is prerequisite for active ingredient in solid dosage form must undergo dissolution to get absorbed from gastrointestinal tract. For most of the pharmaceutical formulations rate limiting step is dissolution. By determining *in vitro* dissolution for a formulation of different batches quality control can be ensured[1]. For water insoluble (lipophilic) drugs, increase in bioavailability can be obtained by enhancement of dissolution rate. Aspirin being an analgesic, antipyretic and anti- inflammatory properties, is one the most effective drugs in rheumatic disease treatment. Even it was prescribed in the prevention and treatment of strokes, cardiovascular diseases and disorder in platelet agreeability [2]. ASA (acetylsalicylic acid) as a medication has been called the twentieth century "Wonder drug". ASA differs from other NSAIDs (non-steroidal anti-inflammatory drugs) in the mechanism of action. Which inhibit the enzyme Cyclooxygenase (COX), in irreversible manner and unlike others affects the COX-1 variant more (which produces Prostaglandins, pro-inflammatory) than the COX-2 varient of the enzyme and also inhibit thromboxanes which promote clotting. In the acidic conditions of stomach ASA is poorly soluble, which delays absorption. Improvement of its absorption can be expected by modifying the solubility[3]. Which depends on crystallinity, particle size, and formation of more soluble complexes[4-9]. To improve the absorption and permeation of biologically active constituents various approaches have been investigated those are development of prodrug which is more soluble, solid dispersions, preparing complexes with complexing agents [10,11]. Sucrose being a good carrier excipient, bulking agent for lyophilisation and is often used in medications to impart a more pleasant taste to often unpalatable chemicals. Hence apart from other methods used for modifying solubility,the complexing with sucrose is one of the methods. Therefore the study aims to develop amorphisation of aspirin in presence of sucrose as carrier 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 *in vitro* dissolution study.

MATERIALS AND METHODS

Materials

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

Preparation of physical mixture and co-ground complex

For viscosity measurement physical mixture of Aspirin and sucrose prepared by mixing in1:4 to1:40 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.

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. The experiment was carried out at room temperature (25^0C) 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 (Whose density was determined with respect to water)

Instrumentation

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) spectra of the sample Aspirin-sucrose was compared with the IR spectra of the Aspirin reference provided in Indian Pharmacoepia.

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 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 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 0.4^0/min).Aspirin-sucrose complex was analyzed with X-ray diffractions.

SEM

The surface morphology of the pure drug and drug - sucrose 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^{-4} mm of Hg) at 5–30 KV. High resolution imagining was used for measuring particle size. All the images were recorded at typical working distance of 8-10 mm.

In vitro dissolution studies

In vitro dissolution studies for aspirin with sucrose, plain aspirin, as well as commercial tablets were performed in triplicate in a USPXXIII six station dissolution test apparatus at 100 rpm and at 37^0C. An accurately weighed amount of the aspirin sucrose complex

equivalent to 500 mg of aspirin 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

The study of Aspirin- sucrose complex which may be formed by H-bonding interaction and resulted in amphiphilic species. The processing parameters such as Viscosity, K.E and stability studies were performed with different proportion by weight as discussed and are reported below.K.E of Aspirin with excipient varies nonlinearly as weight of drug –excipient varies from 1:4 to 1:40.K.E is least when drug sugar weight proportion is 1:12 (Fig 1). Indicates that at low sugar content a preferential drug sugar H-bonding interaction predominates. However at high concentration of carbohydrate preferential sugar-sugar interactions prevailed which leads to increase in K.E.

Kinetic Energy Vs Weight Proportion

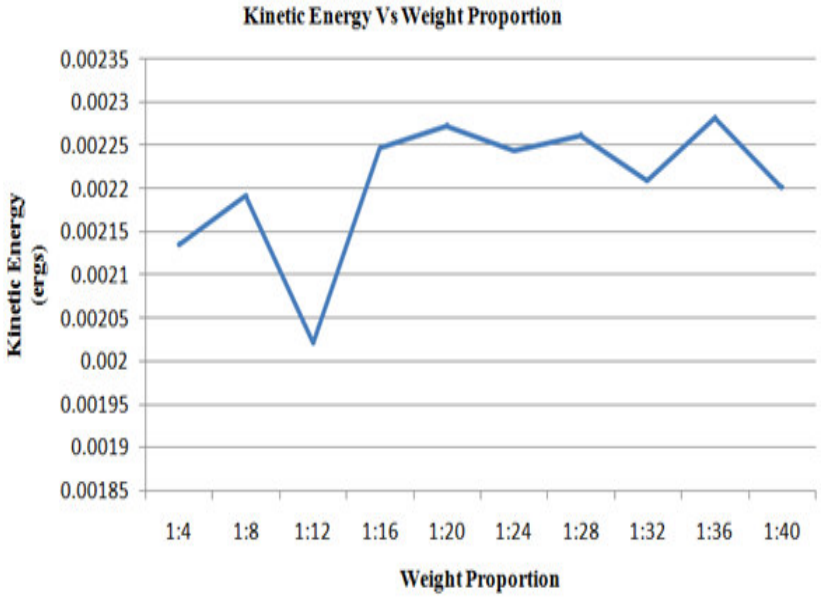
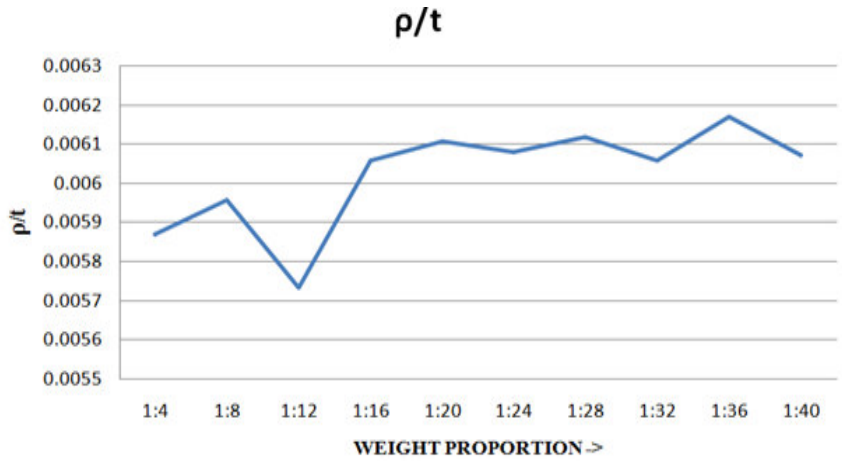


Figure 1

Plot of Kinetic energy versus weight proportion

η vs ρ/t varies nonlinearly. As ρ/t increases η decreases (Figure 2).

ρ/t Vs Weight Proportion graph.



Physico-chemical characterization of Aspirin-sucrose 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 were 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 at1747cm^{-1},C-Ostretching 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. -OH (in plane) bending at 1377cm$^{-1.}$ –OH (acid) in plane stretching vibration --OH (out of plane) at 916 cm^{-1}.are missing in the complex. Thus, the FTIR spectra indicate the interaction of sucrose with the aspirin's -COOH group shown (Fig 3)

FTIR of Aspirin with sucrose

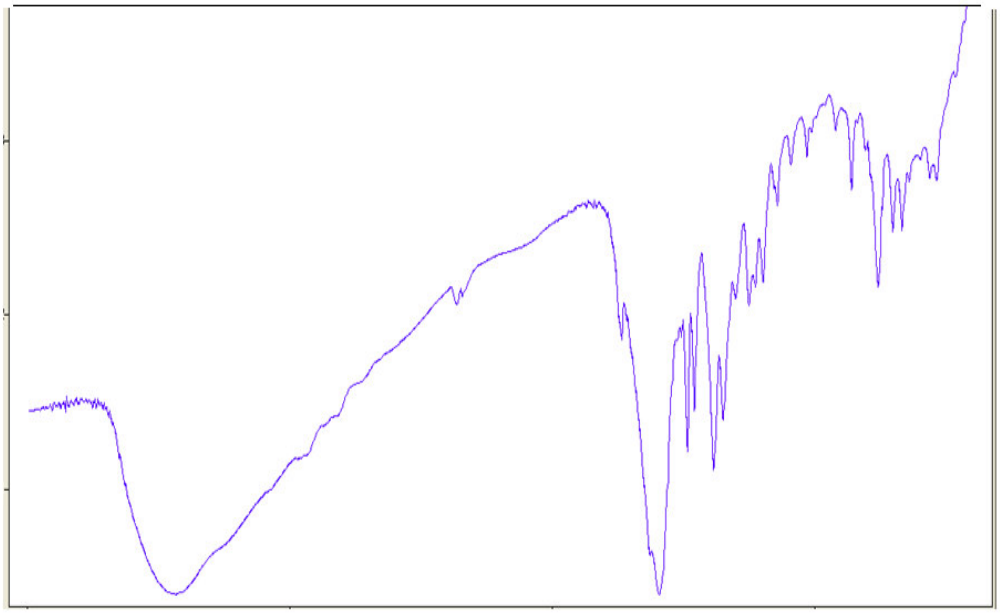


Figure 3
FTIR of Aspirin with sucrose

To check whether the changes in the aspirin crystal morphology correspond to a polymorphic transition and to study the solid state of aspirin –sucrose 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

PXRD of Aspirin with sucrose

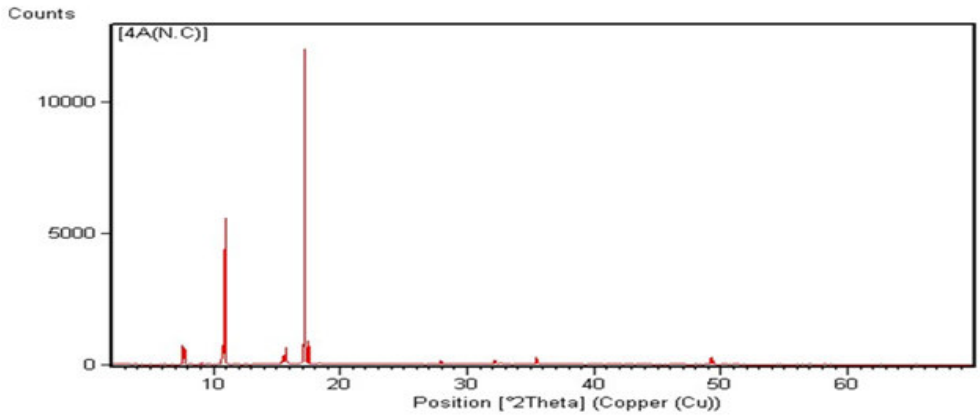


Figure 4
PXRD of Aspirin with sucrose

The disappearance of aspirin crystalline diffraction peaks confirmed the formation of complex with sucrose. Bonding between drug and sucrose in the development of the complex might have resulted into the significant change of its X-ray diffraction. (Fig 4) 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[12]. In order to substantiate the association of aspirin with sucrose DSC analysis was performed on aspirin, and the aspirin-sucrose complex. DSC of Aspirin-sucrose complex showed endothermic peaks at 120^{0}Cand 210^{0}C and total mass change of 67.75%. The results of the DSC test confirmed the association of aspirin and sucrose in the complex as both peaks representing aspirin changed position (Fig.5)

DSC and TGA heating of aspirin and sucrose

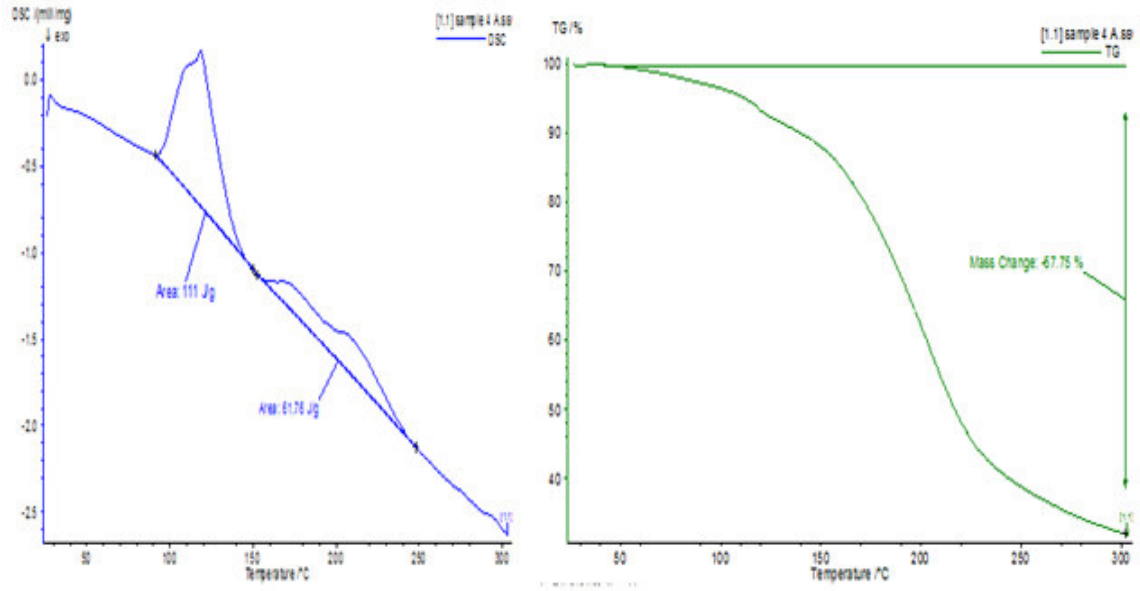


Figure 5
DSC and TGA heating of aspirin and sucrose

Scanning Electron Micrographs of the Aspirin- sucrose 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 [13].

SEM of Aspirin with sucrose

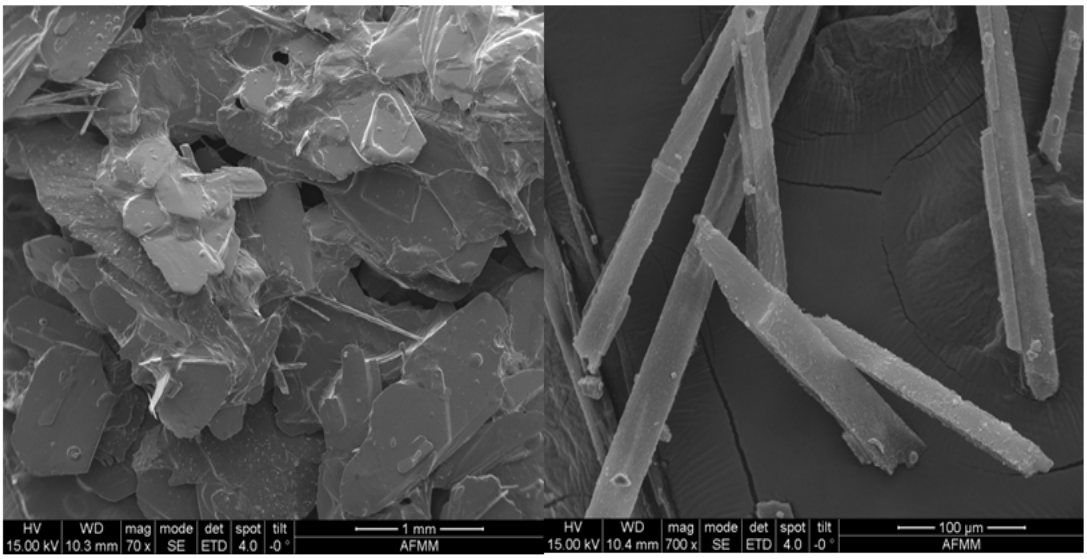


Figure 6
SEM of Aspirin with sucrose

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 in presence of sucrose. The release of Aspirin in the dissolution media was found to be a function of the percent of sucrose load as well as the pH of the media. At respective pH 4 maximum % release of drug from Aspirin-sucrose (1:1pbw)was 80% noticed at the end of 5 minutes and from pure drug (96.62%) was noticed at 120 min and of commercial tablet (96.62%) at 60 minutes. Solid dissolution depends on particle size, crystal habit, wettability, surface area and surface energy [14]. The better release profiles in the Aspirin- sucrose may be due to more number of H-bonding sites in sucrose, 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 sucrose solubility of the drug can be varied and that's why the dissolution profile of

the complex can be improved.

Dissolution Studies

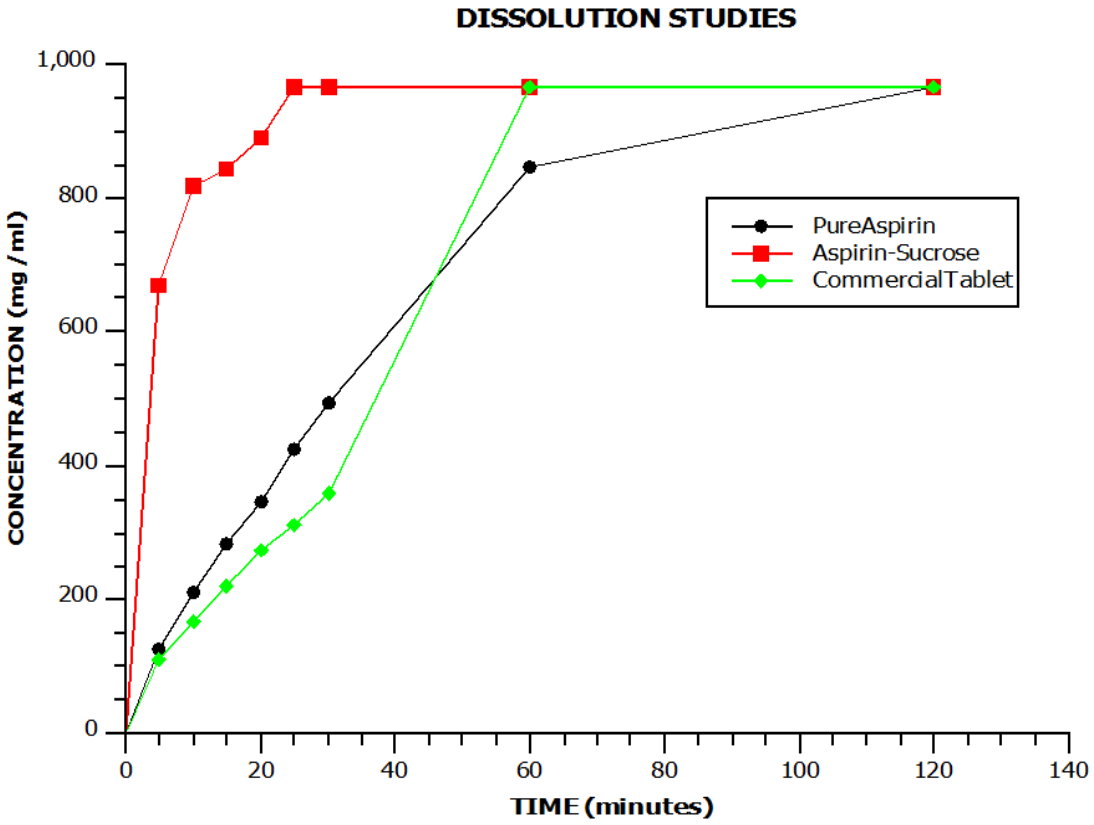


Figure 7
Comparison of pure Aspirin, commercial Aspirin and prepared formulation dissolution

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-sucrose complex was prepared by a simple and reproducible method. The physicochemical investigations showed that Aspirin formed a complex with sucrose showed better solubility and dissolution profile than aspirin as well as commercial drug. sucrose is of low cost, does not leave after taste and may act as preservative ,antioxidant, enhances the viscosity of liquid medicament, Dissolution profile shows sucrose can become good excipient for Oro-dispersible tablets. Hence particular proportion by weight of sucrose, Aspirin - sucrose complex may prove 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 sucrose complex may be developed with Aspirin by different proportion by weight, as well as for other NSAIDs with poor bioavailability and GI side effects.

CONFLICT OF INTEREST

Author declared no conflict of interest.

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