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Solubility Enhancement of Gliclazide via Co-crystallization with Malonic Acid

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In recent years, a number of studies have focused on the preparation of molecular co-crystals. Within crystal engineering of molecular solids assembly may principally be through hydrogen–bonding interactions, as documented by numerous papers on hydrogen bonded crystal engineering strategies. Our recent study has focused on the synthesis, the solid-state characterization and the solubility study of gliclazide/ malonic acid co-crystal. The co-crystallization has been performed using co-precipitation techniques. The solid-state characterization of the co-crystals has been carried out using XRPD, DSC, FTIR, NMR and SEM. The XPRD results of the co-precipitated mixture of gliclazide with malonic acid at ratio (1:1) showed that new peaks at 2θ = 28.6, 29.0, 38.63 and 48.11 were observed. The DSC results showed that the co-precipitated mixture shows an endothermic peak at 164.5 °C, different to those of starting materials. The SEM micrograph of the co-precipitated mixture was also different from that of the physical mixture. These results indicated that gliclazide might have formed a co-crystal with malonic acid. The solubility data clearly show that the solubility profile of the co-crystals was higher than that of the pure compound or the physical mixture.
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The poor aqueous solubility of drug molecules is becoming increasingly prevalent in the research and development for most of the pharmaceutical companies. There are a number of challenges in the pharmaceutical development provided by this type of molecules, including slow dissolution in biological fluids, insufficient systemic coverage and sub-optimal efficacy in patients, principally when given by the oral route of administration. Efforts have already been done in the pharmaceutical sciences to establish a number of approaches for enhancing low aqueous solubility. These strategies embrace salt forms engineering to enhance dissolution rate profiles[1], increased surface area for dissolution via micronization[2], the use of co-solvents to solubilize drugs[3], and micellar solutions[4], improving the delivery of lipophilic drugs by using the lipidic system[5], and drug complexation with cyclodextrins[6]. Despite the effectiveness of these techniques in enhancing the bioavailability, their success is dependent on the specific physicochemical nature of the molecules being studied. The ability to engineer materials with suitable dissolution characteristics, whilst maintaining suitable physical and chemical stability provide strong driver in the drug delivery system design for the utilization of new and existing crystal engineering approaches. In recent years, a number of studies have focused on the preparation of molecular co-crystals[7-9]. Within crystal engineering of molecular solids assembly may principally be through hydrogen–bonding interactions, as reported in literature[10,11].

Gliclazide of pharmaceutical grade, was a kind gift provided by AMRIYA Pharmaceutical Company, Egypt, malonic acid, methanol and chloroform were purchased from Sigma-Aldrich, Germany. All other materials were analytical grades and were used without further treatment.

Preparation of (1:1) gliclazide/malonic acid co-crystal via co-precipitation: Gliclazide (2 g) was added to malonic acid (0.64g) were dissolved in 50 ml acetone and 50 ml methanol (60°). The solution was removed from heat, and allowed to cool at ambient temperature. Solids then precipitated, filtered, collected on a filter paper and dried at room temperature for 24 h.

Preparation of physical mixture of gliclazide/malonic acid: Gliclazide was physically mixed with malonic acid at molar ratio of 1:1 in a glass

vial and shaken by hand for 10 min, the chemical structures for gliclazide and malonic acid are shown in fig. 1.

The Unisantis X-ray diffractometer, type XMD-300, was used to obtain XRPD spectra for samples at room temperature. Powder samples were placed into a sample holder and leveled using a glass cover slide. Samples were scanned over 5-50° 2θ at a rate of 1° 2θ/ min by a copper Ka radiation source of wavelength 1.542Å with 1mm slits. The simulated patterns of the co-crystal have been calculated from CSD using CanQuest 1.10 software.

DSC profiles were obtained using a calorimeter (SHIMADZU DSC-60, Japan) with a refrigerated cooling accessory. The instrument was calibrated with pure indium and zinc standards at the heating rates of interest. Samples weighing between 1-10 mg were accurately weighed into an aluminum pan and an aluminum lid crimped onto the pan (closed system with a pin-hole). The samples were heated in an atmosphere of dry nitrogen at a heating rate of 10°/min. over a predetermined temperature range. The energy (heat flow) required maintaining the contents of the sample pan (accuracy 0.1mW) at the same temperature as an identically prepared empty reference pan was measured.

Scanning electron microscopy of all samples was carried out using FEI INSPECT S50.

Infrared spectra (IR) were done using BRUKER TENSOR 37 spectrophotometer and absorption was expressed in wave number (cm^{-1}) using KBr disc.

The proton magnetic resonance 1H-NMR spectra were recorded on a BRUKER AVANCE II spectrometer-Germany at 500 MHz in the specified solvent (dimethyl sulfoxide, DMSO-6d), chemical shifts were reported on the δ scale and were related to that of the solvent and J values are given in Hz.

A weighed amount of theophylline equals 25 mg was dissolved in 100 ml distilled water (pH 6.2) and the final solution was scanned between 200 nm to 400 nm using UV-Vis 8600 JENWAY, UK.

Construction of calibration curve of gliclazide in distilled water (pH 6.2): Stock solution of gliclazide (250 µg/ml) was prepared by dissolving an accurately weighed amount of gliclazide in distilled water (stock I). In a 100 ml volumetric flask, 10 ml from stock I was transferred and diluted with distilled water to prepare 25 µg/ml (stock II). Appropriate volumes of stock II solution were transferred to 10 ml volumetric flask and diluted to 10 ml with distilled water to obtain a concentration range of 2.5-25 µg/ml. The absorbance of the prepared solutions of gliclazide was measured spectrophotometrically at λ_{max} = 271 nm, using distilled water as a blank. Each reading was the average of three determinations. Standard calibration curve was constructed, by plotting the obtained absorbance versus its corresponding concentration.

The data presented in fig. 2 clearly show that the co-precipitated mixture possessed XRPD patterns different from those of the physical mixture. However, the new PXRD peaks observed at 2Θ = 28.6, 29.0, 38.63 and 48.11 is indicative of the formation of gliclazide/ malonic acid co-crystal.

The DSC traces of the gliclazide/ malonic acid system are presented in fig. 3. As shown in Figure 3, the melting points of gliclazide and malonic acid are 173° and 133° respectively. The co-precipitated mixture shows a melting point at 164°. These results indicated that gliclazide might have formed a co-crystal with malonic acid.

From fig. 4 it can be seen that physical mixture possesses SEM micrograph, very different from co-precipitated mixture. The SEM micrograph of the co-precipitated mixture possesses clear Rod shaped-like crystals with flat surfaces, while SEM micrograph of the physical mixture exhibits nearly aggregated particles with rough surfaces. These results are consistent with XRPD, DSC, and confirm a phase transformation via co-precipitation.

FRIR is a unique analytical technique to trace the changes in the vibrational modes of the functional groups that contribute to the co-crystal formation. As shown in fig. 5, the co-precipitated mixture shows spectra different from that of the physical mixture or starting materials in the wave number regions 3500-500 cm^{-1}. A major shift was observed in the –SO2 stretch of gliclazide, from 1163 and 1349 cm^{-1} to 1165 and 1350 cm^{-1}, respectively, while –CO of the carboxylic group of malonic acid shifted from 1702 cm^{-1} to 1708 cm^{-1}, assuming an interaction between gliclazide and malonic acid in this region. These results suggest that gliclazide formed a co-crystal with malonic acid.

As shown in fig. 6, H-NMR spectrum of malonic acid revealed a sharp singlet signal at 3.18 ppm due to the methylene group and a broad singlet signal at 11.93 attributed to the protons of the carboxylic acid group.

The H-NMR spectrum of gliclazide revealed the signals of the aliphatic protons of the hexahydrocyclopenta[c]pyrrol and the methyl group appeared in the range of 1.40 to 2.90 ppm. Two doublets appeared at 7.39 and 7.85 ppm due to the para-substituted phenyl ring, in addition to two singlet signals at 8.09 and 9.90 ppm attributed to the two NH groups of the urea moiety.

The H-NMR spectrum of co-precipitated and the physical mixture of gliclazide and malonic acid (in equimolar ratio) revealed the signals of both gliclazide and malonic acid. The stacked spectra showed the carboxylic proton as a broad singlet in the range of 9 to 11 ppm. Moreover, the signals of gliclazide appeared at nearly the same chemical shift of the pure drug. These results indicate that no chemical interaction has taken

place and confirm that a co-crystal between gliclazide and malonic acid may have formed.

To evaluate the enhancement in solubility of Gliclazide in different formulation, saturation solubility measurements were carried out and compared these data with that of pure Gliclazide. Solubility analysis was performed by adding known excess amount of pure Gliclazide and equivalent weight of Gliclazide from different formulation (100 mg) to a capped glass test tube containing 5 ml of distilled water. the test tube were then placed in a shaking water bath adjusted at 100 rpm and temperature was maintained at 37±0.5° for 72 h, which had been previously determined to be an adequate time for equilibration . the sample were then filtered, suitably diluted, and analyzed by UV-VIS spectrophotometer (JENWAY, UK) at λ_{max} 228 nm and the concentration of the drug was determined from the established calibration curve. The obtained results are illustrated in Table 1 and fig. 7. It is clearly show that the co-precipitated mixture exhibited higher solubility profiles compared with either physical mixture or pure compound. These results indicated that the co-crystallization of gliclazide with malonic acid via co-precipitation has obviously enhanced the solubility of gliclazide.

Pharmaceutical co-crystallization is emerging as an attractive alternative to polymorphs, salts and solvates in the modification of an active pharmaceutical ingredient (API) during dosage form design. The physicochemical properties of the API and the bulk material properties can be modified, whilst maintaining the intrinsic activity of the drug molecule. The aim of this study was to investigate in depth, the impact of the co-processing of drugs and co-crystal formers on the phase transformation, the potential solid-state characterization, and the solubility profile of the synthesized co-crystals. Pharmaceutical co-crystals have been studied by other researchers in the perspective of crystal engineering but have not been widely investigated in detail for drug formulation. In the first stage, the model drug and the co-crystal former were chosen, and the preparation of co-crystals was carried out using co-precipitation technique. After the preparation of the co-crystals, intensive investigations had been carried out to characterize the new compounds using different techniques such as X-ray powder diffraction, DSC and SEM.

In the co-crystallization of gliclazide/ malonic acid system, the XRPD, DSC, SEM confirmed the formation of the co-crystal by co-precipitation method. Formation of a new phase was also supported by FTIR and NMR. The XPRD results of the co-precipitated mixture of gliclazide with malonic acid at ratio (1:1) showed that new peaks at 2θ = 28.6, 29.0, 38.63 and 48.11 were observed.

In conclusion, within this study, XRPD, DSC, and SEM revealed excellent means of solid-state characterization of gliclazide/ malonic acid. In addition, the co-crystallization can be considered as a reliable and potential toolbox technology for the enhancement of oral drug solubility.

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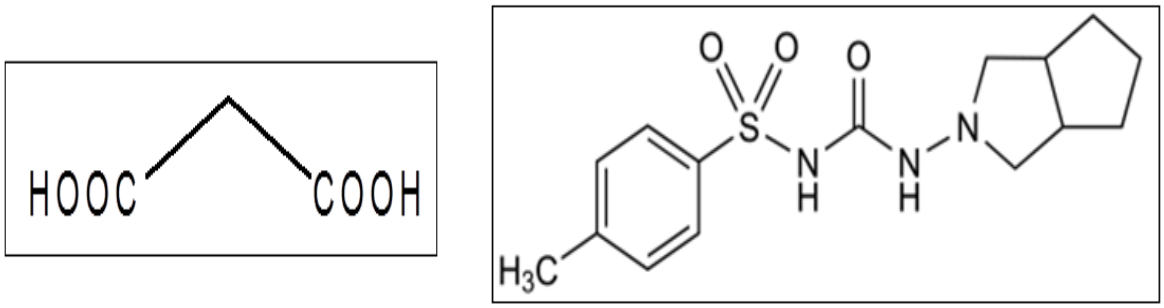
Running title: Solubility Enhancement of Gliclazide

TABLE 1: SATURATION SOLUBILITY DATA OF GLICLAZIDE/ MALONIC ACID SYSTEM

Sample	**Saturation Solubility (mg/ml) ± SE**
Glz ph	0.217 ± 0.0687
Glz Ma ph	0.698 ± 0.0588
Glz Ma cp	6.33± 0.0588



A B

Fig. 1: Chemical structures of gliclazide and malonic acid
A: Malonic acid; B: Gliclazide

Fig. 2: X

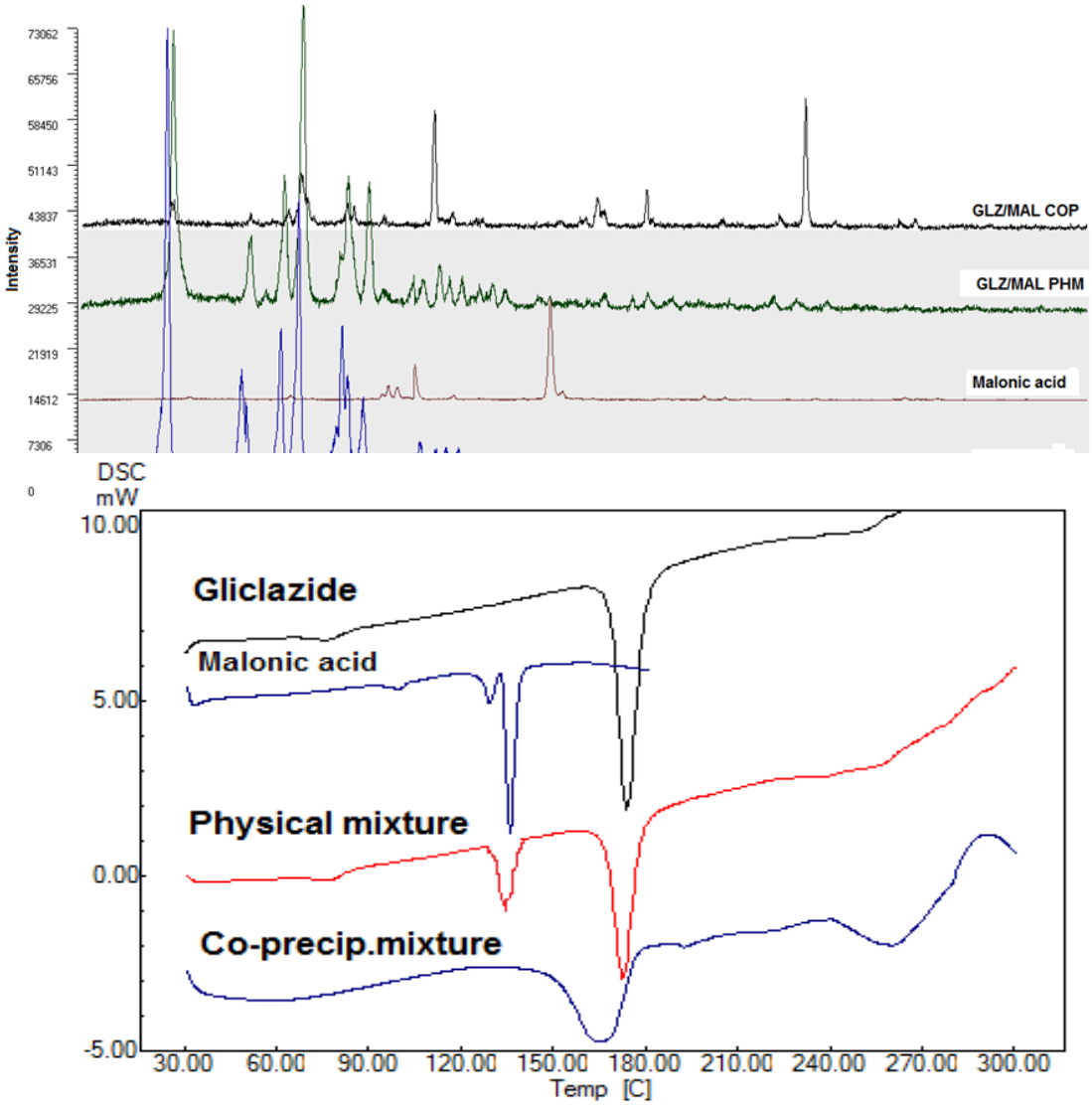
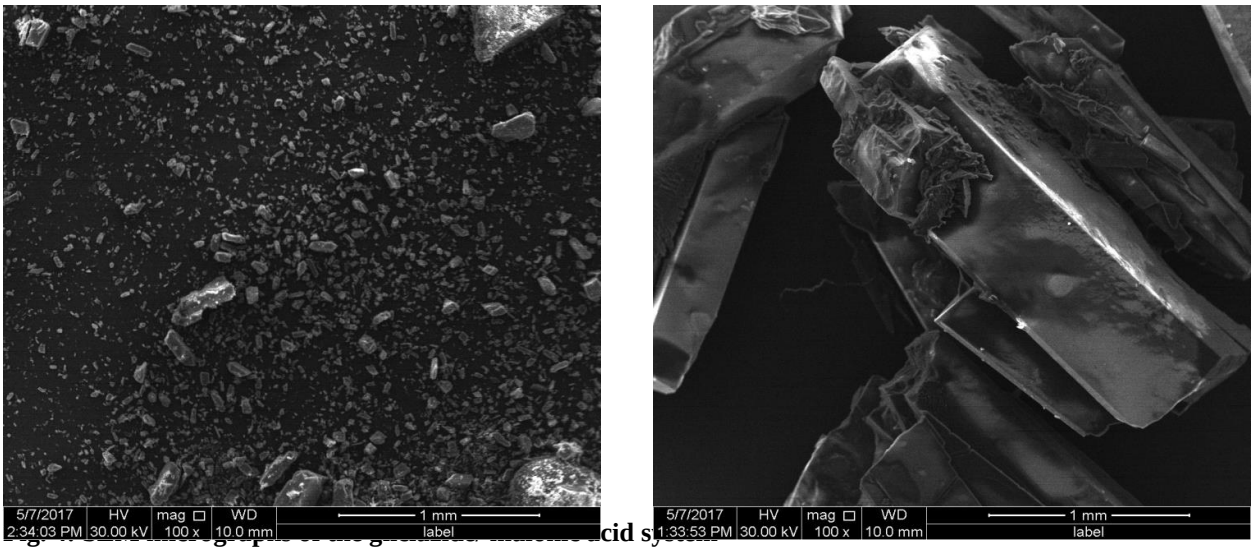


Fig. 3: DSC traces of the gliclazide/ malonic acid system (sample weight 4-6mg, scan rate 10°/min)



A = Physical mixture and B = co-precipitated mixture

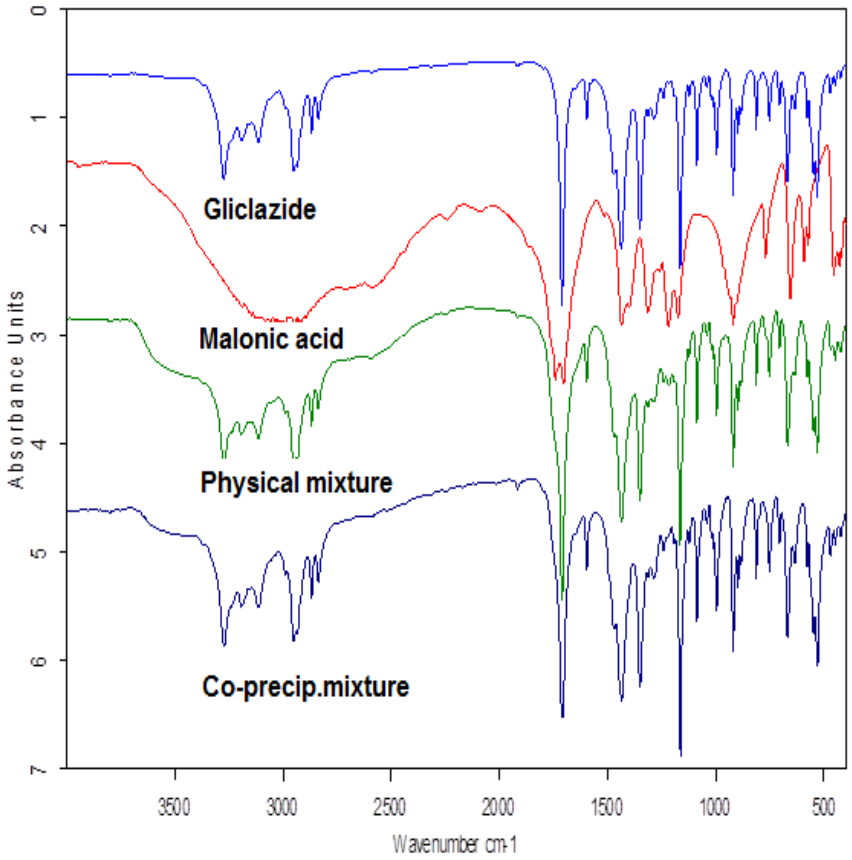


Fig. 5: I

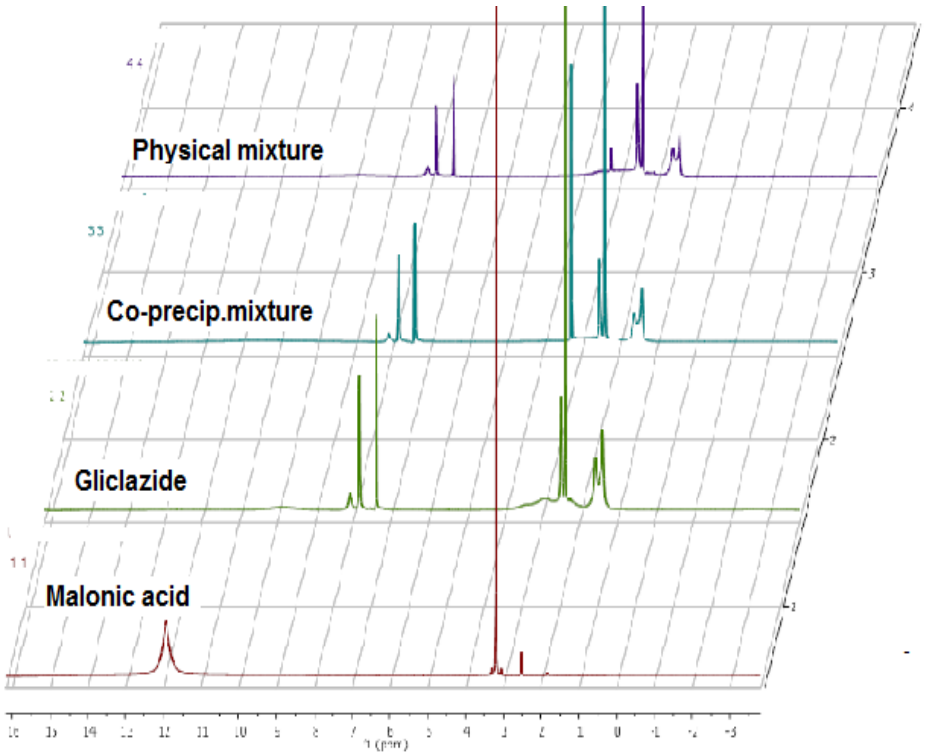


Fig. 6: NMR spectra of gliclazide/malonic acid system

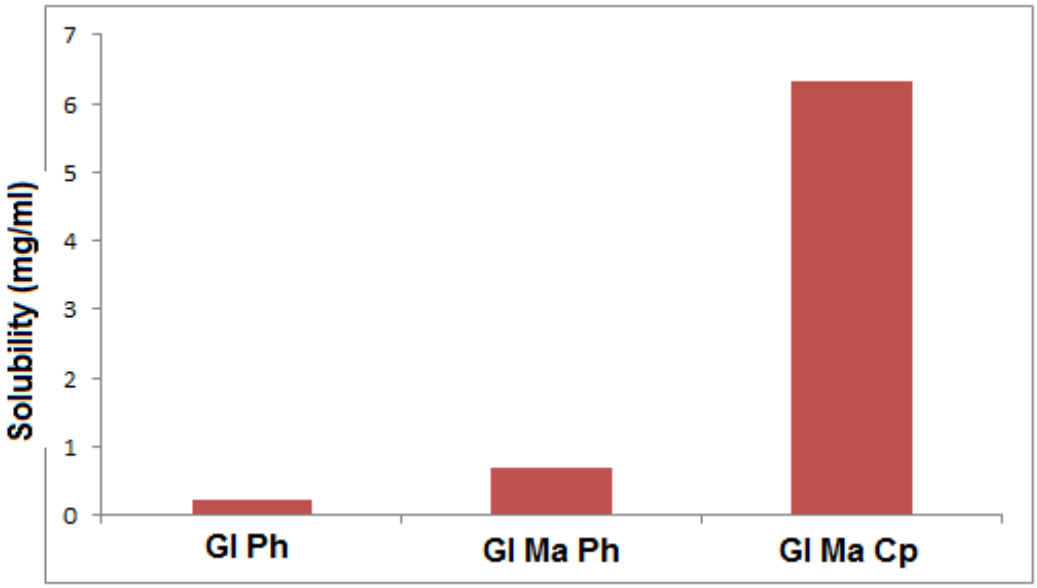


Fig. 7: Saturation solubility of gliclazide/ malonic acid co-crystals

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