

Increased Solubility, Dissolution and Physicochemical Studies of Curcumin-Polyvinylpyrrolidone K-30 Solid Dispersions

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Abstract—Solid dispersions (SD) of curcumin-polyvinylpyrrolidone in the ratio of 1:2, 1:4, 1:5, 1:6, and 1:8 were prepared in an attempt to increase the solubility and dissolution. Solubility, dissolution, powder X-ray diffraction (XRD), differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR) of solid dispersions, physical mixtures (PM) and curcumin were evaluated. Both solubility and dissolution of curcumin solid dispersions were significantly greater than those observed for physical mixtures and intact curcumin. The powder X-ray diffractograms indicated that the amorphous curcumin was obtained from all solid dispersions. It was found that the optimum weight ratio for curcumin:PVP K-30 is 1:6. The 1:6 solid dispersion still in the amorphous form after storage at ambient temperature for 2 years and the dissolution profile did not significantly differ from freshly prepared.

Keywords—Curcumin, polyvinylpyrrolidone K-30, solid dispersion, dissolution, physicochemical.

I. INTRODUCTION

CURCUMIN is the main constituent extracted from the spice turmeric. It has a number of pharmacological effects [1] such as anti-inflammatory, antibacterial, anticancer. Therefore, it is regarded as a high potential to develop into modern drug. Curcumin is practically insoluble in water at acidic or neutral pH. It is incompletely absorbed; its oral bioavailability about 60% [2]. This effect is probably due the poor solubility and slow dissolution. Solid dispersions is one of the successful methods in improving drug dissolution [3],

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[4] and to obtain better bioavailability [5], [6]. Solid dispersion is defined as the dispersion of one or more active ingredients in an inert hydrophilic carrier or matrix at solid state prepared by the fusion, solvent or solvent-fusion method [7]. This system allows a particle size reduction of drug to nearly a molecular level. As this system exposed to aqueous media, the carrier is dissolved and the drug is released as very fine particles for quick dissolution and absorption [8]. Hydrophilic synthetic polymers have been widely investigated as carrier substance for solid dispersions. PVP K-30 is amongst the most frequently used as the carrier. It can improve the solubility and dissolution of many poorly water soluble drugs [9], [10].

The aim of this study was to increase the solubility and dissolution of curcumin by solid dispersion using PVP K-30 as a hydrophilic carrier. The solubility, dissolution and physicochemical characterizations based on X-ray diffractometry, differential scanning calorimetry and FTIR spectroscopy were evaluated. Since the storage time might decrease the dissolution rate, the dissolution property and X-ray diffraction pattern of solid dispersion which exhibited the optimum dissolution were examined.

II. MATERIALS AND METHODS

A. Materials

Pure curcumin was isolated in our laboratory. In brief, dried powder of *Curcuma longa* rhizome was macerated in hexane and ethyl acetate, respectively. The ethyl acetate extract was then dried *in vacuo*, subsequently separated by vacuum silica gel column chromatography using chloroform-methanol system as an eluent and LH-20 gel filtration chromatography using methanol as eluent to produce curcumin (yield; 4.55 %). PVP K-30 (Kollidon 30, average molecular weight of 45,000) was obtained from BASF, Thailand. All other reagents were of analytical-reagent grade.

B. Methods

Solid Dispersion Preparations

Solid dispersions of curcumin:PVP K-30 in the weight ratio of 1:2, 1:4, 1:5, 1:6, and 1:8 were prepared by solvent method.

To the solution of curcumin (1 g) in acetone (50 ml), the amount of PVP K-30 was added. The minimum amount of methanol was added to solubilize the PVP K-30. The solvents were removed under reduced pressure at 40°C and dried under vacuum at room temperature for 5 hours. The samples were pulverized using mortar and pestle and the 0.05-0.25 mm particle size fractions were obtained by sieving.

The physical mixtures were prepared by manually mixing the appropriate amount of the 0.05-0.25 mm particle size fractions of curcumin and PVP K-30.

Solubility Studies

The solubilities of curcumin in various concentrations of PVP K-30 were determined by adding excess amount of curcumin to glass vials containing 20 ml of aqueous solutions of PVP K-30. These vials were shaken in a thermostatically water bath maintained at 37±0.1°C until equilibrium. The supernatants were filtered through a 0.45 µm pore size Millipore membrane filter at the same temperature. The filtrates were suitably diluted with phosphate buffer pH 6.5 and assayed spectrophotometrically at 427 nm for the concentration of curcumin. All experiments were determined in triplicate. The solubilities of curcumin physical mixtures and solid dispersions in simulated gastric fluid without pepsin or simulated intestinal fluid without pancreatin were determined by following the aforementioned.

Powder X-ray Diffraction Studies

X-ray diffraction patterns were obtained using a X-ray diffractometer (Philips PW 3710, Netherland) with CuKα radiation, collimated by a 0.08° divergence slit and a 0.2° receiving slit and scanned at a rate of 2.4°/min over the 2θ range of 2-40°.

Differential Scanning Calorimetry Studies

Differential scanning calorimetry was performed on a differential scanning calorimeter (Perkin-Elmer DSC7, USA). Samples (5-10 mg) were heated in hermetically sealed aluminium pans with a heating rate of 10°C/min under nitrogen atmosphere (flow rate 20 ml/min).

Fourier Transform Infrared Spectroscopy Studies

Fourier transform infrared spectra were obtained on a Perkin-Elmer spectrometer equipped with a deuterated triglycine sulfate detector. Samples were prepared in KBr discs.

Dissolution Studies

The dissolution of curcumin, solid dispersions and physical mixtures was determined using a dissolution apparatus (Hanson Model SR2, USA). The dissolution media consisted of 900 ml of simulated gastric fluid without pepsin and simulated intestinal fluid without pancreatin pH 6.5. The paddles were rotated at 50±1 rpm and the temperature was maintained at 37±0.5°C. The amount of each sample was equivalent to 30 mg of curcumin and sprinkled directly on the surface of the dissolution medium. A 5 ml aliquot was

withdrawn at appropriate time intervals, filtered, diluted with dissolution medium and replaced with a 5 ml of fresh dissolution medium after each sampling to maintain the constant volume. The amount of curcumin was determined spectrophotometrically at 421 nm and 427 nm for simulated gastric fluid without pepsin and simulated intestinal fluid without pancreatin pH 6.5, respectively without the interference of PVP K-30. Curcumin concentration was calculated and expressed as percentage of curcumin dissolved from the mean of six determinations.

Aging Study

Curcumin-PVP K-30 solid dispersion which exhibited the fastest dissolution was selected for stability study. The solid dispersion was stored in screw-capped bottles at ambient temperature (30±2°C) for 2 years. After 1 year and 2 years of the storage, the dissolution and X-ray diffraction pattern were examined.

III. RESULTS AND DISCUSSION

Commercially available curcumin is isolated from the plant *Curcuma Longa* L. The pure curcumin on the market consisted of three naturally occurring curcuminoids: curcumin, demethoxycurcumin and bisdemethoxycurcumin, which curcumin as the main constituent [11]. In this present study, curcumin was isolated from our laboratory by the method described above in order to avoid interference from demethoxycurcumin and bisdemethoxycurcumin.

Solubility Studies

The solubility profile of curcumin in various concentrations of PVP K-30 was shown in Fig. 1. Curcumin was practically insoluble in water. A significant increase in its solubility was observed as the concentration of PVP K-30 increased. Similar result was obtained by Gines, *et al.* [12]. It was suggested that PVP K-30 might form the soluble complex with curcumin.

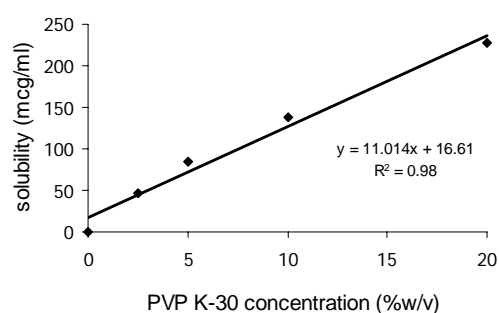


Fig. 1 Solubility profile of curcumin in various concentrations of PVP K-30 at 37±0.1°C

The solubilities of curcumin, physical mixtures, solid dispersions in simulated gastric fluid without pepsin or simulated intestinal fluid without pancreatin, pH 6.5, were

shown in Figs. 2-3. The solubility of curcumin in simulated gastric fluid without pepsin or simulated intestinal fluid without pancreatin pH 6.5 was very low and quantitation of curcumin was not possible because the concentration of curcumin was below the detection limit of the analytical system. For physical mixtures, a slight increase in curcumin solubility compared to the solubility of curcumin in the same medium was found. In all solid dispersion systems, the curcumin solubility was markedly higher than that of pure curcumin and physical mixtures. The increase in curcumin solubility was linear with respect to the weight fraction of PVP K-30. At 1:6 and 1:8 curcumin-PVP K-30 solid dispersions, the increase in curcumin solubility in simulated gastric fluid without pepsin was approximately 16- and 26-fold, respectively compared with 1:2 curcumin-PVP K-30. And at 1:6 and 1:8 curcumin-PVP K-30 solid dispersions, the increase in curcumin solubility in simulated intestinal fluid without pancreatin was approximately 4- and 5-fold, respectively compared with 1:2 curcumin-PVP K-30. The increase in solubility of curcumin by PVP K-30 may probably be due to the formation of soluble complex between PVP K-30 and curcumin.

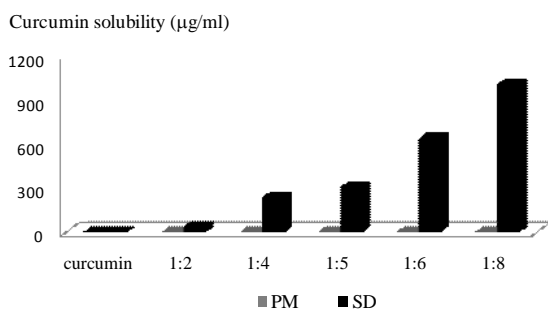


Fig. 2 The solubility of curcumin, physical mixtures and solid dispersions in simulated gastric fluid without pepsin at $37\pm 0.1^\circ\text{C}$

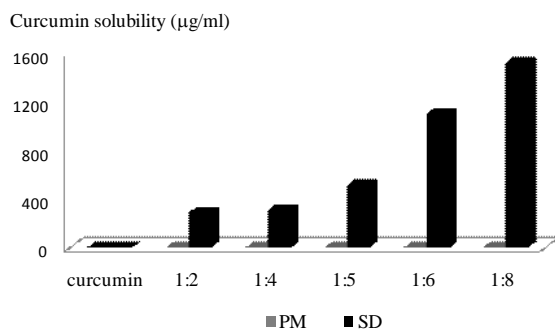


Fig. 3 The solubility of curcumin, physical mixtures and solid dispersions in simulated intestinal fluid without pancreatin at $37\pm 0.1^\circ\text{C}$

Powder X-ray Diffraction

The powder X-ray diffractograms of pure curcumin, physical mixtures and solid dispersions were shown in Fig. 4. The characteristic peaks of curcumin appeared at a diffraction

angle of 2θ at $7.96, 8.90, 12.26, 14.54, 17.24^\circ$, etc indicating that curcumin is present as a crystalline form. PVP K-30 is amorphous powder having no crystalline structure. The diffraction patterns of all physical mixtures showed several peaks which similar to that in pure curcumin, indicating that the crystallinity of curcumin was not changed. The absence of crystalline peaks attributable to curcumin in all solid dispersion systems revealed that curcumin crystals were transformed to an amorphous state. In the crystallization process of curcumin from supersaturated solution, PVP K-30 might inhibit the association of curcumin molecules to form the crystal nucleus and inhibiting the crystal growth [13]. In addition, the hydrogen bonding between curcumin and PVP K-30, verified by FTIR analysis, would inhibit curcumin crystallization and causing curcumin precipitated out in the amorphous form [14]. A similar behavior was previously observed for ketoconazole [15] and flunarizine [9].

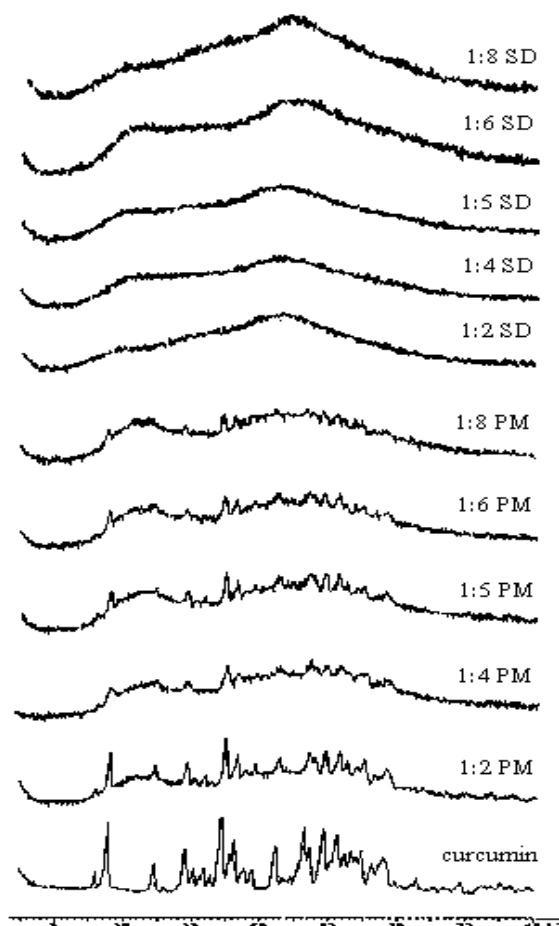


Fig. 4 Powder X-ray diffractograms of curcumin, physical mixtures and solid dispersions

Fourier Transform Infrared Spectroscopy

FTIR spectroscopy was carried out to further elucidate the interaction between curcumin and PVP K-30 in the solid state.

Figs. 5-6 show the FTIR spectra of curcumin, physical mixtures and solid dispersions. The FTIR spectrum of pure curcumin showed an absorption band at 3507 cm^{-1} , assigned to the O-H stretching vibration. FTIR spectrum of PVP K-30 showed broad peaks at about $3050\text{-}3720\text{ cm}^{-1}$. The FTIR spectra of all physical mixtures were similar to the synthetic spectra producing by the addition of curcumin and PVP K-30. This indicates no interaction between curcumin and PVP K-30. This was consistent with the results obtained from X-ray diffraction studies. In particular, the O-H stretching vibration at 3507 cm^{-1} of all solid dispersions was disappeared. Therefore, the solid dispersions show an interaction such as the intermolecular hydrogen bonding between curcumin and PVP K-30. This interaction caused to change curcumin crystalline structure to amorphous form [10].

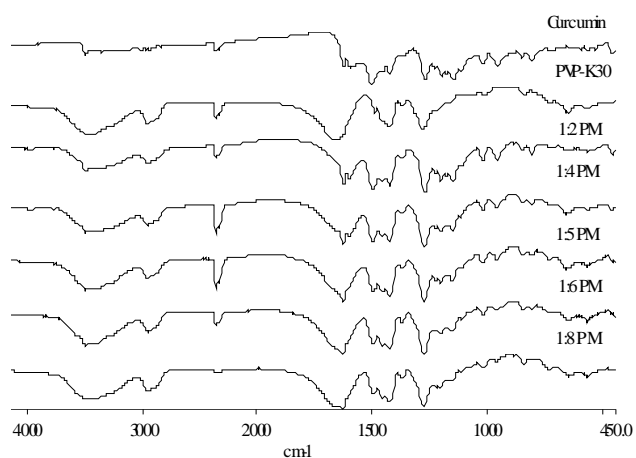


Fig. 5 FTIR spectra of curcumin, PVP K-30 and physical mixtures

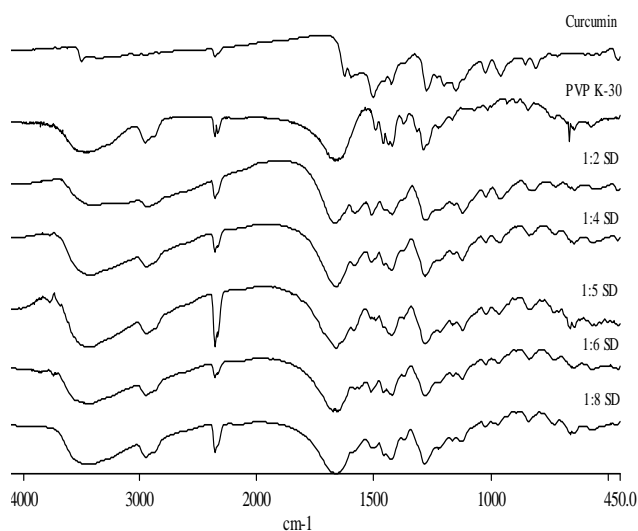


Fig. 6 FTIR spectra of curcumin, PVP K-30 and solid dispersions
Differential Scanning Calorimetry

The DSC thermograms of curcumin, PVP K-30, physical mixtures and solid dispersions were illustrated in Fig. 7. The

DSC curve of pure curcumin showed a single sharp endothermic peak at 181.4°C , with the enthalpy of fusion was 119.8 J/g , corresponding to the melting point of curcumin. In all physical mixtures, the DSC curves showed broad endotherms with peak temperature slightly shifted to lower temperature than pure curcumin and the enthalpy of fusion of curcumin decreased. The decrease of the enthalpy of fusion of curcumin in physical mixtures was the result of the solubilizing effect of PVP K-30 during heating process [16]; only that part of curcumin which is in excess shows a melting endotherm. This indicated that a crystalline form of curcumin still present, confirming the results from X-ray diffraction studies. This type of interaction was previously observed in the physical mixtures of naproxen:PVP [17] and piroxicam-PVP K-30 [14]. On the other hand, all solid dispersion systems showed no endothermic peaks of curcumin. The disappearance of thermal features of curcumin indicates that some interaction between curcumin and PVP K-30 occurred. These findings may be due to the formation of an amorphous solid solution [18] which has been known to cause an increase in drug dissolution [7].

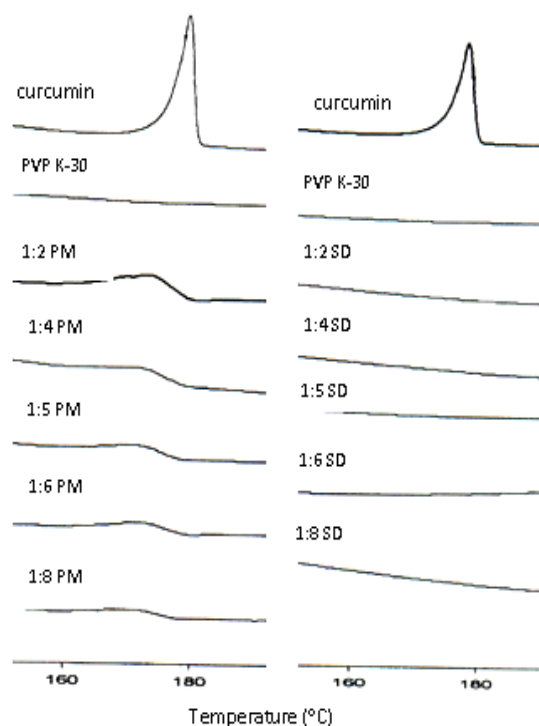


Fig. 7 DSC thermograms of curcumin, PVP K-30, solid dispersions and physical mixtures

Dissolution Studies

The dissolution profiles of pure curcumin, physical mixtures and solid dispersions in simulated gastric fluid without pepsin and simulated intestinal fluid without pancreatin were shown in Figs. 8-9. The dissolution of pure curcumin and physical mixtures was negligible and less than

1% of pure curcumin and physical mixtures being dissolved within 60 minutes. The pure curcumin exhibited the slowest dissolution rate because of its hydrophobicity that caused the powder to float on the surface of the dissolution medium and prevented its surface contacting the medium. In all cases, the dissolution rates of curcumin solid dispersions were remarkably enhanced compared to their corresponding physical mixtures and pure curcumin. Several mechanisms have been proposed to account for the increase in the dissolution kinetic of drug from solid dispersions [19]. These mechanisms include the reduction of drug crystalite size, a solubilization effect of carrier, an absence of drug aggregation and agglomeration, an improvement in drug wettability, the conversion of drug to the amorphous state. The increased in curcumin dissolution from these solid dispersions can thus be contributed by several factors such as an excellent wettability, which could be observed clearly from the solid dispersion since it rapidly left the surface and was dispersed in the bulk of the dissolution medium, a markedly increase in curcumin solubility, the solubilizing effect of the carrier, an absence of aggregation and agglomeration and the formation of high energy amorphous state as confirmed by DSC, FTIR and XRD data. An increase in the curcumin dissolution of solid dispersions was observed until the ratio of 1:6 and then the increase in the weight fraction of PVP K-30 did not marked affect the further release rate of curcumin. This result was similar to that found by Akbuka, *et al.* [20]. No significant difference ($p>0.05$) in curcumin dissolution, in the first 10 minutes, were observed between solid dispersions in ratio of 1:6 and 1:8 which more than 100-fold increase in dissolution as compared with pure drug. It is considered that an optimum weight ratio of curcumin and PVP K-30 is approximately 1:6. This indicated that the amount of PVP K-30 in the system is a determining factor in the diffusion process with in the curcumin-matrix system.

Aging Study

The dissolution profiles of freshly prepared curcumin-PVP K-30 solid dispersions in the ratio of 1:6 and aged samples stored at ambient temperature for 1 year and 2 years were shown in Fig. 10. The dissolution profiles of aged sample showed a slight decrease in drug dissolution. This may be due to the coarsening of the solid dispersion particles. However, the storage for 2 years did not appear to have any marked effect on the dissolution profiles and the 2-way ANOVA yielded no significant difference between the released amount either after 5 min ($p>0.05$) or after 60 min ($p>0.05$). No changes in X-ray diffraction patterns were observed in the aged sample after storage for 1 year and 2 years (the XRD patterns were not shown). This indicative of a stabilization effect of PVP K-30.

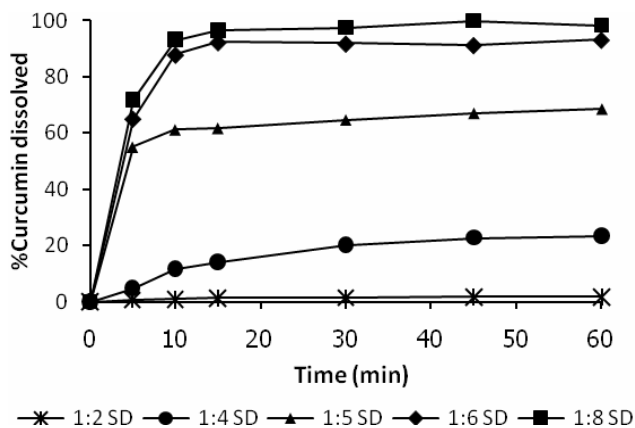


Fig. 8 Dissolution profiles of curcumin, physical mixtures and solid dispersions in simulated gastric fluid without pepsin

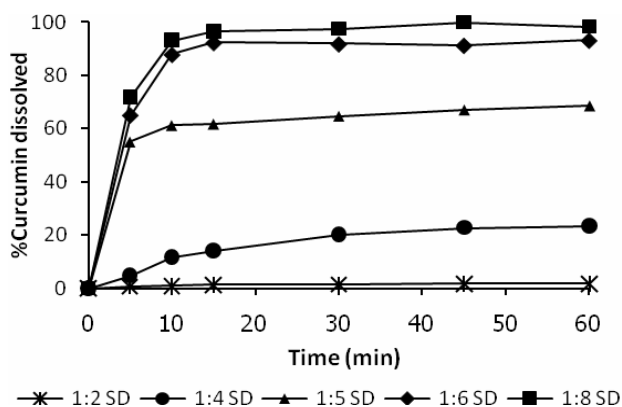


Fig. 9 Dissolution profiles of curcumin, physical mixtures and solid dispersions in simulated intestinal fluid without pancreatin

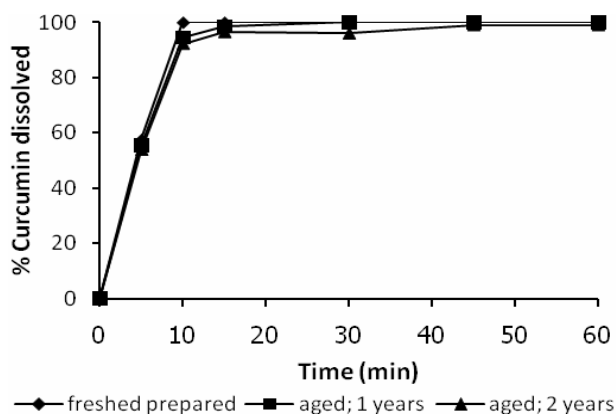


Fig. 10 Dissolution profiles of freshly prepared 1:6 curcumin-PVP K-30 and aged samples in simulated intestinal fluid without pancreatin after storage at ambient temperature for 1 year and 2 years

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