ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Dissolution of Curcuminoids from Solid Dispersion Using Different Carriers

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ABSTRACT

The attempt to enhance the curcuminoids dissolution was performed using various kinds of water-soluble carriers. Extract of curcuminoids was prepared from turmeric. It composed of curcumin 39.14%, desmethoxy-curcumin 15.47% and bisdesmethoxy-curcumin 15.90%. The solid dispersion (SD) between the curcuminoids and different carriers (PEG 4000, PEG 6000, PEG 20000, HPMC, xylitol, chitin, ac-di-sol, citric acid, sucrose and β-cyclodextrin) in ratio of 1:10 was prepared by co-grinding. The dissolution of curcuminoids from SD was performed in a dissolution medium containing 0.02%w/v tween 80. The great dissolution rate of curcuminoids was observed in SD using xylitol as carrier. From DSC, IR and powder x-ray diffraction studies, no chemical interaction between curcuminoids and xylitol. The increase of curcuminoids dissolution rate from this co-grinding mixture could be explained by improving wettability of hydrophobic curcuminoids particles. Xylitol effectively increased the dissolution of curcuminoids from solid dispersion.

Keywords: Dissolution, Curcuminoids, Solid dispersion, Carrier

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ISSN: 0975-8585

INTRODUCTION

Turmeric (*Curcuma longa* L.), Family Zingiberaceae, one of the major species, is widely consumed in many countries [1,2]. Turmeric is often quoted in medicinal literature as anti-cancer and anti-inflammatory agent [3].The principally active antioxidant of this herb has been identified as curcuminoids. Main curcuminoids in turmeric powder are curcumin, and two related demethoxy compounds, bisdesmethoxy-curcumin and desmethoxy-curcumin. Curcumin has been used as anti-inflammatory agent associated with its inhibition of cyclooxygenase, lipoxygenase and prostaglandin synthesis [4-6]. Curcuminoids also exhibit other pharmacological activities such as antibacterial, antifungal, cholagogue, antispasmodic, hypocholesterolemic and antiparasitic activities [5-7]. Since curcuminoids contain the aromatic ring in their structure and high molecular weight, their aqueous solubility is very poor. Absorption of curcuminoids from intestinal tract of rat was limited [8,9] Therefore, the improvement of their solubility might be able to enhance the bioavailability after oral administration. The preparation of curcuminoids in soluble form was previously reported. There was the formation of water soluble curcumin-metal complex for use in foodstuffs.[10] The sponification process [11] or solubilization by using surfactant such as polyoxyethylene sorbitan monolaurate were used to increase the curcuminoid solubility [12]. The release of curcumin from gel was increased as the content of Pluronic F-127 was increased [13].

Solid dispersion (SD) technique has been used to increase the dissolution and absorption of poorly soluble drugs by dispersing the drug in a highly water soluble carrier in a solid state [14-19]. This technique has been utilized to improve the solubility of some natural products such as silymarin, quercetin and rutin [20-22]. This study addressed the improvement in the aqueous solubility of curcuminoids by solid dispersion technique using different carriers. The physicochemical alteration of SD was characterized by using DSC, IR and powder x-ray diffraction techniques.

MATERAILS AND METHODS

Materials

Standard curcuminoids (lot 100K3447) was purchased from Sigma Chemical, Louis, USA. Tween 80 (lot (01)09322705024152, APS Finechem, Seven Hills, NSW, Australia) was used as received. The carriers used in this study were hydroxypropyl methylcellulose (HPMC) (Methocel K15M Premium EP, Batch No. KH18012NO2, Colorcon, Singapore), citric acid (lot 333380/1 1194, Fluka Chemika, Buchs, Switzerland), Ac-di-sol (Rama Production Co Ltd., Bangkok, Thailand), β-cyclodextrin (lot 23723, Rama Production Co Ltd., Bangkok, Thailand), polyethylene glycol 4000 (PEG 4000) (Batch No. 2405BS0567, Uniqema, France), polyethylene glycol 6000 (PEG 6000) (lot K23577433 733, E. Merck, Darmstadt, Germany), polyethylene glycol 20,000 (PEG 20,000) (lot 4022536 447834, E. Merck-Schuchardt, Germany), chitin (Kyowa, Technos Co., Japan), xylitol (xylisorb® Roquette, rue Patou-F.59022 Lille Cedex) and sucrose (Mitrpul, Thailand). Acetonitrile (lot 4 022536 154213, Merck, Darmstadt, Germany) and ethyl alcohol (Vallinckrodt Baker, Maxico) were utilized as the solvent. Kieselguhr (Fluka chemika, lot 60779, Switzerland) was used as received.

Preparation of Curcuminoids

Crude ethanolic extract (340.95 g) was prepared from dried turmeric (1.336 kg). After removing as much as oleoresins by washing the extract with petroleum ether, the remained extract (190 g) was exhaustively adsorbed on Kieselghur and eluted with petroleum ether/ethyl acetate gradient from 1:0 to 2:1. The former elution was oleoresins, whereas the later portion (180 g) contained curcuminoids. An orange powder (55.14 g) was obtained by crystallizing the curcuminoids extract with petroleum ether/acetone.

Purity and composition of curcuminoids from this study were comparable with the standard curcuminoids of Sigma grade. Based on the method of spectrophotometry, this curcuminoids extract contained 72.20% curcuminoids calculated as curcumin. The ratio of curcumin : desmethoxy-curcumin : bisdesmethoxy-curcumin was 54.21 : 22.02 : 21.43 determined by TLC-densitometer (TLC Scanner II, (Camag, Switzerland).

Preparation of Solid Dispersion (SD)

Physical mixture was prepared by co-grinding curcuminoids and different carriers (PEG 4000, PEG 6000, PEG 20000, HPMC, xylitol, chitin, ac-di-sol, citric acid, sucrose and β-cyclodextrin) using mortal and pestle for 10 min. at ratio of 1:10 as physical mixture (PM). The xylitol which was a selected carrier was further used to prepare SD with the ratio of curcuminoid:xylitol 1:5, 1:15 and 1:20. Acetonitrile was utilized to dissolve xylitol and curcuminoids to prepare SD by solvent method (SM). After curcuminoid and xylitol were completely dissolved, the acetonitrile was removed and the SD was dried in desiccator. SD between curcuminoids and xylitol was prepared by melt method (MM). Since xylitol was melted at 98°C, curcuminoids were incorporated into the melt and then cooled to room temperature. The resulting SD was kept in desiccator.

The Dissolution of Curcuminoids from SD

Dissolution test of curcuminoids from SD was undertaken using a dissolution apparatus (Prolabo, France) with the paddle method at 100 rpm. A volume of 900-ml 0.02%w/v tween 80 solution equilibrated at 37°C was utilized as dissolution fluid. Samples were collected at specific time intervals and assayed by a UV-Vis spectrophotometer (Perkin-Elmer, Germany) at a wavelength of 430 nm. During dissolution study, the physical change of SD was observed.

Dissolution Profile Fitting

Least square fitting the experimental dissolution data to Hixson and Crowell cube-root equation was carried out using a nonlinear computer programme, Scientist for Windows, version 2.1 (MicroMath Scientific Software, Salt Lake City, UT, USA).

ISSN: 0975-8585

Hixson and Crowell cube-root equation:

$$(100\text{-}W)^{1/3} = 100^{1/3} - Kt$$

Where W is % drug release at time t, and K is release rate constant.

The coefficient of determination (r^2) was used to indicate the degree of curve fitting. Goodness-of-fit was also evaluated using the Model Selection Criterion (MSC), given below.

$$MSC = \ln\left\{\frac{\sum_{i=1}^{n} w_i (Y_{obs_i} - \bar{Y}_{obs})^2}{\sum_{i=1}^{n} w_i (Y_{obs_i} - Y_{cal_i})^2}\right\} - \frac{2p}{n}$$

Where Y_{obsi} and Y_{cali} are observed and calculated values of the i-th point, respectively, and w_i is the weight that applies to the i-th point, n is number of points and p is number of parameters.

Fourier Transform Infrared (FT-IR)

The physicochemical properties of SD prepared by co-grinding, solvent method and melt method were characterized using the FT-IR spectroscopy. The FT-IR spectra were recorded using an IR spectrometer (Magna-IR system 750, Nicolet Biomedical, Madison, WI, USA) by KBr disc method. Spectral scanning was conducted from 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1}.

Differential Scanning Calorimetry (DSC)

The DSC thermograms of specimens were analyzed by a differential thermal analyzer (DSC 7, Perkin Elmer, USA.). The samples of 5-7 mg were accurately weighed into aluminum pans and sealed. The rate of heat was 10 °C/min under nitrogen purge at the temperature of 30-300 °C.

Powder X-ray Diffraction Study

The powder X-ray diffraction pattern were recorded at room temperature using an X-ray diffractometer (Philips diffractometer, model PW 1830, Netherland). The X-ray source was nickel-filtered Cu Kα radiation generated at 30 kV and 30 mA. The target element was Cu-λ = 1.54 A°. The dried film of uniform thickness was carefully placed on glass plate and scanned in the 2θ range of 5 to 50°.

ISSN: 0975-8585

RESULTS AND DISCUSSION

The dissolution profiles of curcuminoids from SD prepared by physical mixing between curcuminoids and different carriers in a ratio of 1:10 are presented in Fig. 1. Since HPMC could generate the viscous gel around the curcuminoids as seen from visual observation, it retarded the dissolution of curcuminoids into dissolution fluid. The viscous environment could decrease the diffusion rate and therefore decrease the dissolution of substances [23]. The dissolution of curcuminoids from SD containing xylitol as carrier was higher than those using the other carriers such as sucrose, cyclodextrin, PEG 20,000, ac-di-sol, PEG 4000, PEG 6000, chitin and citric acid. The rapid dissolution of curcuminoids was observed for SD using ac-di-sol as carrier, however the gel was gradually occurred from this superdisintegrant and thereafter the dissolution of curcuminoids was obviously slower. The enhancement of dissolution of itraconazole by using ac-di-sol was previously reported [24]. Citric acid could not apparently enhance the dissolution. This might be suggested that the acidic environment from citric acid decreased the solubility of curcuminoids which could be ionized and freely soluble in basic medium. Although chitin structure is hydrophilic, it is insoluble in aqueous fluid and therefore it slightly increased the curcuminoids dissolution.

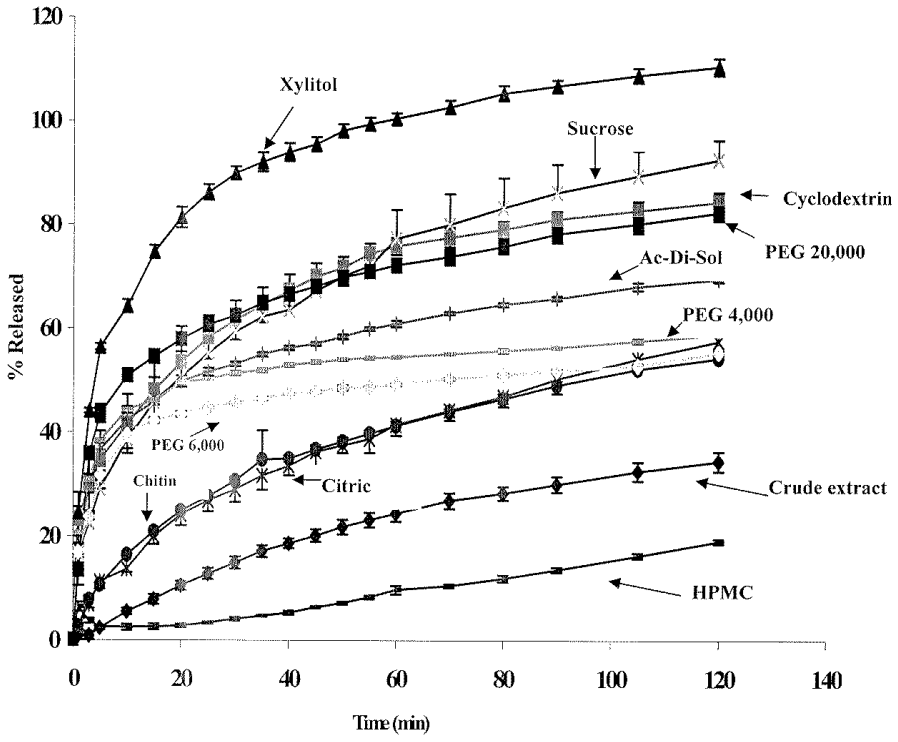

Figure 1. Dissolution of curcuminoids from solid dispersion prepared by physical mixture with co-grinding curcuminoids:carrier in ratio of 1:10 in 0.02%w/v tween 80 solution (n=6).

The dissolution of curcuminoids from SD using xylitol as carrier was compared among preparation methods. The dissolution rate of these compounds from physical mixture was faster than that from solvent method and melt method, respectively, as shown in Fig.2. The fastest release of curcuminoids was observed from SD, containing curcuminoids and xylitol at a ratio of 1:10, prepared by co-grinding as shown in Fig. 3. This advantage of SD prepared

ISSN: 0975-8585

by physical mixing was convenient. Furthermore, excessive heat exposure and utilization of organic solvent during preparation could be avoided [23,25]. For melting method, the melting point of xylitol is 93-94.5°C, which is quite lower than the decomposition temperature (179-186°C). Since its thermal stability is rather high. xylitol is heated in the presence of amino groups, it does not undergo the Maillard (browning) reaction [26]. The dissolution rate of curcuminoids from SD prepared by physical mixture at the ratio of curcuminoids:xylitol (1:10) was faster than that at the ratios of 1:20, 1:15, 1:5, respectively. Therefore, xylitol could increase the dissolution of curcuminoids by physical mixing.

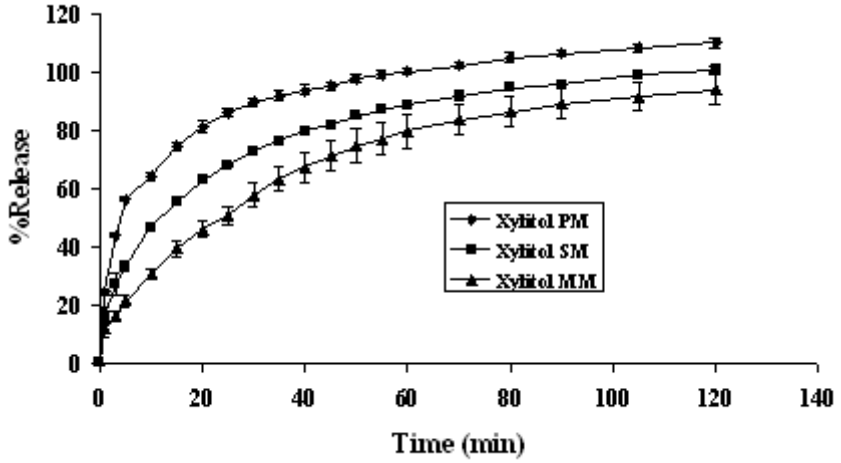

Figure 2. Dissolution of curcuminoids from solid dispersion prepared by physical mixture (PM), solvent method (SM) and melt method (MM) of curcuminoids:xylitol in ratio of 1:10 in 0.02%w/v tween 80 solution (n=6).

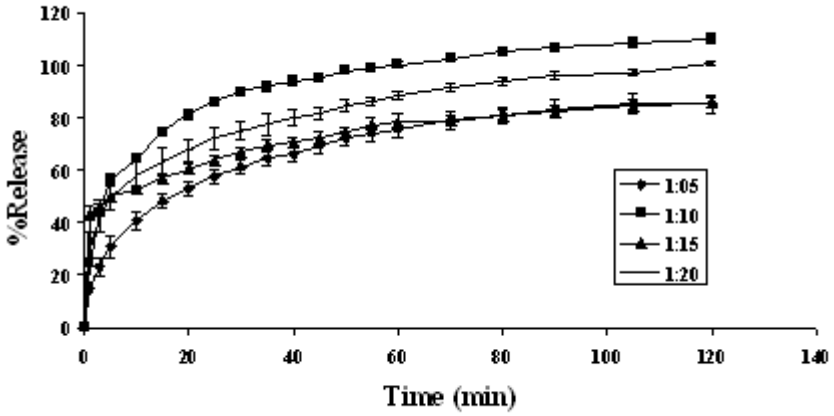

Figure 3. Dissolution of curcuminoids from solid dispersion prepared by physical mixture (PM) of curcuminoids:xylitol at different ratio in 0.02%w/v tween 80 solution (n=6).

For the mathematical evaluation, dissolution data were applied to the Hixson and Crowell cube-root model which has been used to describe the release profile keeping in mind the diminishing surface of the drug particles during the dissolution [27,28]. When this model is applied, it is assumed that the release rate is limited by dissolution rate of drug

ISSN: 0975-8585

particles. Typically, this model has been used for evaluation of the drug release from microsphere or particles. The r^2 from curve fitting to cube root equation was in a range of 0.9198 to 0.9863 and MSC was in range of 2.31 to 4.08 (Table 1). The release rate (K) of substances from different systems was related with the above mentioned.

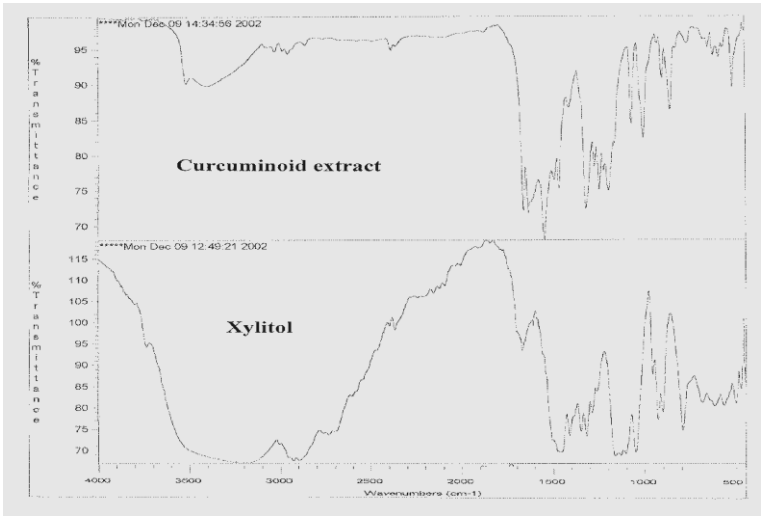

Figure 4. FT-IR spectra of curcuminoid extract and xylitol.

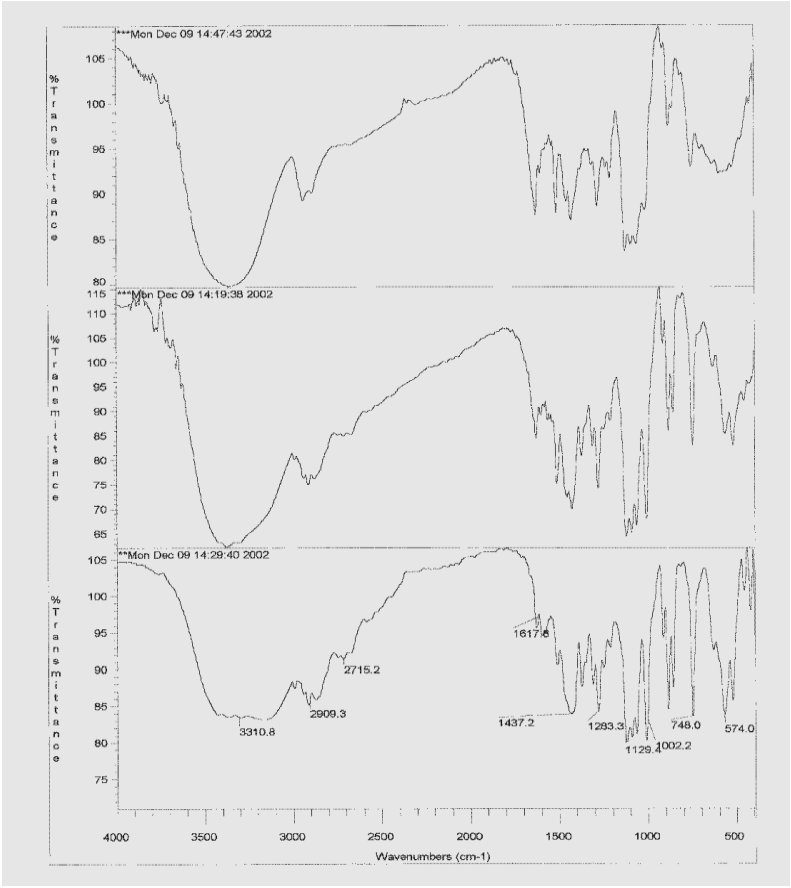

Figure 5. FT-IR spectra of SD prepared by physical mixture, melt method and solvent method of curcuminoids:xylitol at ratio of 1:10.

ISSN: 0975-8585

Table 1 Degree of goodness-of-fit from curve fitting to cube root equation of drug dissolution profiles of solid dispersions.

Formula	Cube root	
	r^2	MSC
PM 1:10	0.9584	2.87
SM 1:10	0.9825	3.80
MM 1:10	0.9863	4.08
PM 1:5	0.9198	2.31
PM 1:15	0.9448	2.69
PM 1:20	0.9604	3.01

Table 2 Estimate parameter from curve fitting to cube root equation of drug dissolution profiles of solid dispersions.

Formula	K ± sd x 10^{-2}	tl ± sd
PM 1:10	1.4601 ± 0.1423	-8.38 ± 1.71
SM 1:10	0.8910 ± 0.0427	-8.81 ± 1.25
MM 1:10	06117 ± 0.0229	-8.29 ± 1.26
PM 1:5	0.4679 ± 0.03975	-21.12 ± 4.18
PM 1:15	0.3043 ± 0.0201	-7.96 ± 1.68
PM 1:20	0.6600 ± 0.0446	-23.78 ± 2.92

From DSC and powder x-ray diffraction studies (data not shown) revealed that there was no chemical interaction between curcuminoids and xylitol. The FT-IR spectrum of curcuminoids extract was similar to that of the standard curcuminoids of Sigma grade. The C=O stretching and O-H stretching were appeared at 1637.9 and 3518.2 cm^{-1}, respectively (Fig.4). The broad O-H stretching was found in FT-IR spectra of xylitol. FT-IR spectrum of SD of curcuminoids-xylitol prepared by co-grinding was similar to that prepared by melt or solvent methods (Fig.5). However, O-H stretching of SD prepared by melt method was broader than that of the others. This indicated that this method might increase the absorption of moisture into the SD. By comparison, the SDs from both melt and solvent method were rather sticky and difficult to reduce the particle size. This could affect to the dissolution of curcuminoids. The improvement in dissolution rate of curcuminoids from this co-grinding mixture could be explained by improving wettability of curcuminoids particles.

CONCLUSION

Curcuminoids extract composed of curcumin 39.14%, desmethoxy-curcumin 15.47% and bisdesmethoxy-curcumin 15.90% was prepared by solvent extraction. To increase the aqueous solubility of curcuminoids, technique of solid dispersion was employed by incorporation of curcuminoids into hydrophilic carrier, i.e., PEG 4000, PEG 6000, PEG 20000, HPMC, xylitol, chitin, ac-di-sol, citric acid, sucrose and β-cyclodextrin. Xylitol could enhance the dissolution rate of curcuminoids greater than the other carriers. From DSC, IR and powder x-ray diffraction studies revealed that there was no chemical interaction between curcuminoids and xylitol. The improvement in dissolution of curcuminoids from SD could be explained by improved wettability of hydrophobic curcuminoids particles.

ACKNOWLEDGEMENTS

This research work was kindly supported by Faculty of Pharmacy, Silpakorn University.

ISSN: 0975-8585

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