—Regular Articles—

An Investigation into the Mechanisms of Rapid Release of Standard Extract from *Ginkgo biloba* leaf in Polyethylene Glycol 6000 Solid Dispersions

Yuebin GE

School of Pharmacy, Institute of Ethical Medicine, South-Central University for Nationalities, Wuhan 430074, P. R. China

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The rapid-release mechanisms of standard extract from *Ginkgo biloba* leaf (EGb) in the polyethylene glycol (PEG) 6000 dispersions were investigated. The apparent equilibrium solubilities of the total flavone glycosides and the soluble solid materials of EGb increased linearly with the increasing concentrations of PEG 6000 solutions. In DSC curves, the peak, onset and endset temperatures of solid dispersions decreased with the increase of EGb weight percent. At the high drug loading, the initial dissolution rates of the total flavone glycosides of EGb had no significant change while the rates of PEG 6000 reduced with the drug concentration increase. The rates of PEG 6000 had no significant change as well as the rates of drug increased with the drug concentration increase at the low drug loading. The results indicated that there were apparent evidences for eutectic observation and soluble complex formation in the two-component solid dispersion of EGb and PEG 6000. The dispersions may belong to drug–controlled dissolution model at high drug loadings and carrier-controlled dissolution model at low drug loadings.

Key words——standard extract from *Ginkgo biloba* leaf; rapid release; polyethylene glycol; mechanism

INTRODUCTION

The term 'solid dispersion' has been utilized to describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix.[1] The melting, solvent or melting-solvent methods are often used to disperse one or more active ingredients in a water-soluble or water-miscible polymer such as polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP). Through the solid dispersing technique, the *in vitro* dissolution rate of drug is well enhanced compared to conventional dosage forms, with concomitant implications for *in vivo* absorption. For years, solid dispersion has been widely used and led to a broadening of water-insoluble polymer that may yield slow release and absorption.[2] On the rapid release behavior in solid dispersions, there are many reports on the preparation, the solid state structure, the storage stability, the *in vitro*/*in vivo* correlation in literatures.[3,4] In addition, the mechanisms of drug release from solid dispersions are studied using physical chemistry and mathematic models. It provides new views for understanding the rapid dissolution of drug in solid dispersions.[5–8]

Dropping pills are one of the dosage forms using water-soluble carriers to enhance the dissolutions rates of drugs. In the preparation, the melted mixtures of drug and carrier are dropped into the cold liquid medium (immiscible to the carrier) to form spherical pills by the interfacial tension. As a solid dispersion, dropping pills are appropriate for the preparations of active compounds and natural extracts, with the advantages of stable manufacturing process and rapid drug effect.[9,10]

Standard extract from *Ginkgo biloba* leaf (EGb), as the effective part of the herb, is widely used for treatment and prevention of cardiovascular and cerebrovascular diseases. It is reported to have the advantages of good therapy and little side-effect for angina pectoris.[11] In our previous study, in order to obtain rapid effect on angina pectoris, fast-release EGb dropping pills are successfully prepared by the water-soluble carrier PEG 6000. The T_{50} parameter (the time of accumulative dissolution 50% weight percent of drug) *in vitro*, determined by Weibull distribution, is 3.62 min and the time of reaching peak (t_{max}) in drug plasma-concentration profile *in vivo* is 1.08 h after oral administration in dogs, quicker than the t_{max} (3.71 h) of traditional EGb tablets.[12,13] It indicates that EGb dropping pills have rapid dissolution of active constituents and quick effect on angina pectoris by the solid dispersion technique. In this study, the

*e-mail: geyuebin@mail.scuec.edu.cn

purpose was to investigate the mechanisms of rapid release of EGb in PEG dispersions by the solubility, phase diagram analysis, DSC and dissolution experiments. The work will provide the theoretical bases for the improvement on the dissolution rate *in vitro* in terms of physical chemistry and mathematic model.

MATERIALS AND METHODS

Standard Extract from *Ginkgo biloba* leaf (EGb) was purchased from Xianghe Ltd., (Shandong, China), containing 24% flavone glycosides, 6% terpene lactones and <5 ppm ginkgolic acid. Polyethylene glycol 6000 (PEG 6000) was from Shanghai reagent plant. Methanol was chromatographic grade and other reagents were analytical grade.

Solubility Measurement The apparent equilibrium solubilities of the total flavone glycosides and the soluble solid materials of EGb were measured in 0%, 10%, 20% or 30% (w/v) PEG 6000 water solution. Samples were placed in capped tubes and agitated for 48 h in a water bath at 37℃ and then filtered. An aliquot filtrate of 0.1 ml was dried to constantly weigh under 60℃ and weight to determine the soluble solid materials. Another aliquot filtrate of 0.1 ml was added to 20 ml hydrolyzing solution (methanol: 25% hydrochloric acid solution=4 : 1, v/v) and hydrolyzed for 1 h to assay the content of the total flavone glycosides by HPLC (model LC-10AD, Shimadzu, Japan).[14] A Hypersil ODS2 C_{18} column (200×4.6 mm, 5 μm) was selected to separate components with an ultraviolet detector at an operation wavelength of 360 nm. The mobile phase consisted of methanol-0.4% phosphate acid (42 : 58, v/v) and the flow rate was 1.0 ml/min. The column temperature was set 40 ℃. An aliquot of 10 μl from the prepared samples was injected directly onto the HPLC. All studies were repeated thrice.

Melting Temperature Measurement Proper amount of the EGb/PEG 6000 mixtures by 0 : 1, 1 : 5, 1 : 4, 1 : 3, 1 : 2, 1 : 1, 1 : 0.5, 1 : 0.25 or 1 : 0 ratio (w/w) (namely 0, 16.7, 20, 25, 33.3, 50, 66.7, 80, or 100% EGb weight percent) was prepared for physical mixture directly or for solid dispersions by the melting method. Briefly, the mixtures were melt under 80～85℃, then stored in a 4℃ refrigerator for 1 h and at room temperature for a further 24 h in a desiccator. The products were grinded with mortar and pestle, then sieved through 80 sieve mesh. The method of melting temperature measurement in Part I Appendix Ⅶ C Pharmacopoeia of China (2005 edition) was used with a model YRT-2 Mettler (Tianjin, China). The initial and final melting temperature data of the powder samples were recorded, with the stated results being the mean of three determinations.

Differential Scanning Calorimetry Shimadzu DSC-60 was used for the analysis. The DSC was operated under nitrogen purge gas and the heating rate of 10.0℃/min was employed. The physical mixtures or solid dispersions of the EGb/PEG 6000 by 0 : 1, 1 : 5, 1 : 4, 1 : 3, 1 : 2, 1 : 1, 1 : 0.5, 1 : 0.25 or 1 : 0 ratio (w/w) (namely 0, 16.7, 20, 25, 33.3, 50, 66.7, 80, or 100% EGb weight percent) were prepared by the method described in the 'Melting Temperature Measurements.' The DSC curves and data of peak, onset and endset temperatures were recorded.

Dissolution Studies Proper amount of the EGb/PEG 6000 mixtures by 0%, 10%, 15%, 20%, 25%, 30%, 40% or 50% EGb weight percent was melt and directly perfused into the model discs with 10 mm diameter and 5 mm thickness. The prepared solid dispersions were cooled in the same surface area discs.

The dissolution experiments were carried out using the basket method. Firstly, the discs loaded with samples stick under the basket and immersed in the 200 ml dissolution medium of distilled water at 37℃. The rotational speed was set at 100 rpm. Samples (3 ml) were taken through a 0.8 μm membrane filter at designated times. The withdrawn samples were replaced with fresh dissolution medium. The accumulative dissolution amount of the total flavone glycosides of EGb was measured by the complexing-colorimetry method as previously described.[12] PEG 6000 in the samples was determined with the method described by Corrigan.[15] The initial dissolution rate (mg/min) was the slope of linear regression equation to the measured dissolution profiles.

RESULTS

The apparent solubilities of samples were measured after equilibrium for 48 h. The apparent solubilities (S_{app}) of the total flavone glycosides and the soluble solid materials of EGb increased with the increasing concentrations of PEG 6000 solutions, indicating the formation of soluble complexes.[5] The data are shown in Fig 1. In all cases, a linear relationship between the concentrations and solubilities was found and the correlative coefficients were 0.9674 and 0.9358, respectively.

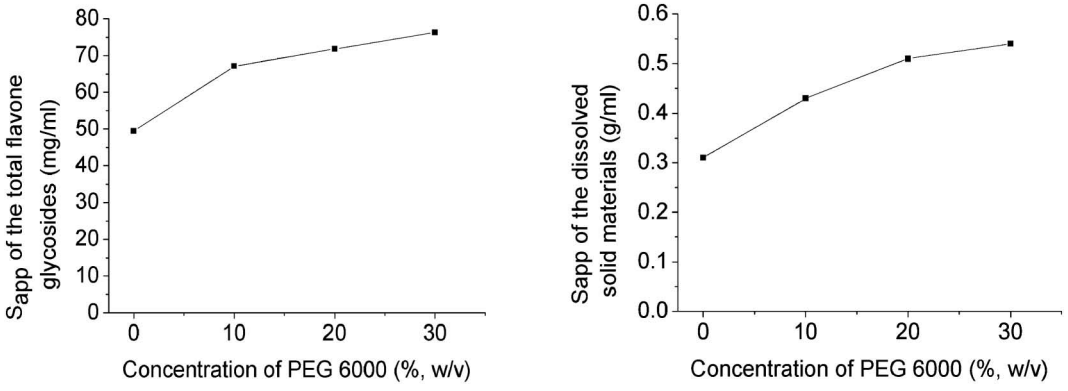

Fig. 1. EGb in Concentrations of PEG 6000 Solutions
Equilibrium solubilities (S_{app}) of the total flavone glycosides (left) and the dissolved solid materials (right). $n=3$.

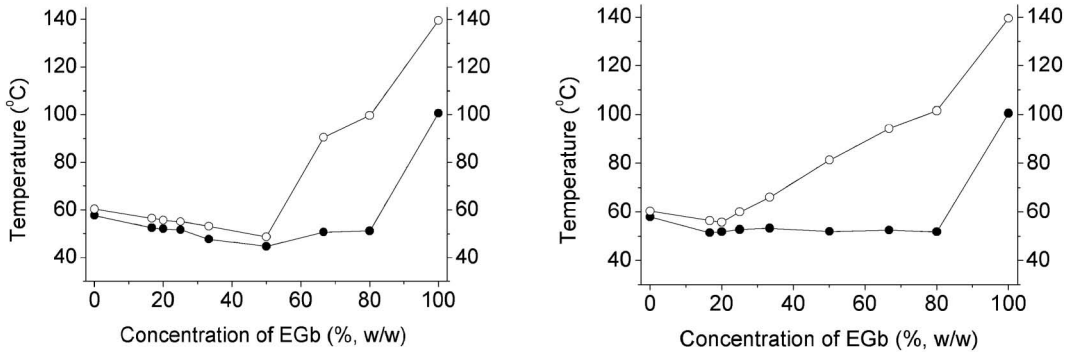

Fig. 2. EGb and PEG6000
Phase diagrams for solid dispersions (left) and physical mixtures (right). (●) initial melting temperature and (○) final melting temperature. $n=3$.

The phase diagrams of the physical mixture and solid dispersion of EGb and PEG 6000 are shown in Fig 2. It was found that the initial and final melting temperatures of solid dispersions decreased with the increasing concentration of EGb in the range from 0 % to 50% weight percent and approached to the lowest points at the 50% w/w. However, the lowering of melting points was not observed in the physical mixture, suggesting that evidence for eutectic formation was apparent in the solid dispersion.

The curves and peak temperature data of DSC are shown in Figs 3 and 4. For the 1 : 5, 1 : 4, 1 : 3, 1 : 2 and 1 : 1 ratios (namely the range from 16.7% to 50 % EGb weight percent), only the peak of PEG 6000 existed and the peak of EGb disappeared in the physical mixtures and solid dispersions. But the temperatures of solid dispersions decreased with the increase of EGb weight percent, to the lowest values for the 1 : 1 ratio while no change was observed in the physical mixtures. For the 1 : 0.5 and 1 : 0.25 ratios (namely 66.7% and 80% EGb weight percents), the

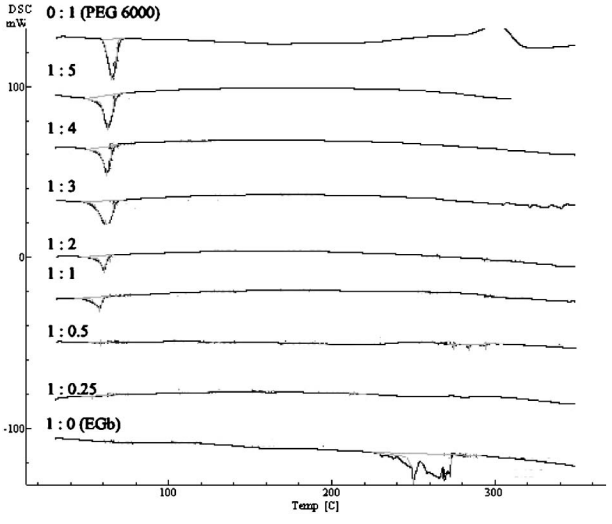

Fig. 3. DSC Curves for Solid Dispersions of EGb and PEG 6000 with Different Weight Ratios of EGb to PEG 6000

peaks of PEG 6000 and EGb both existed in the physical mixtures and solid dispersions. Combining with the results of solubilities and phase diagrams experi-

ments, the observations in the DSC curves were consistant with the melting point changes in the phase diagrams, suggesting that EGb may dissolve in the fused PEG 6000 and form some complex substances.[5,6,8)]

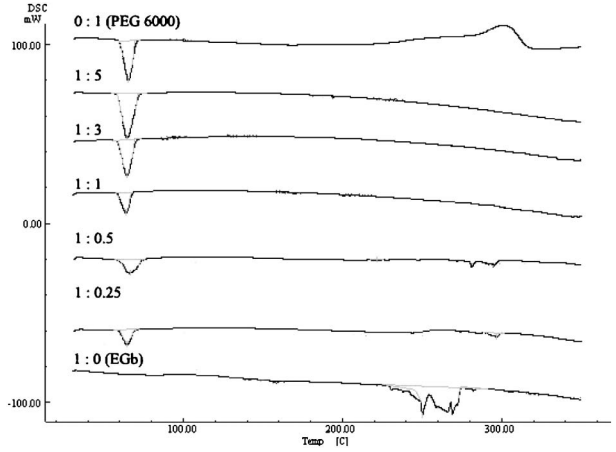

Fig. 4. DSC Curves for Physical Mixtures of EGb and PEG 6000 with Different Weight Ratios of EGb to PEG 6000

The influence of the presence of EGb in the solid dispersions on the dissolution of the total flavone glycosides of EGb and PEG 6000 is illustrated in Fig 5. It was found that the dissolution rate of the total flavone glycosides increased with the concentration of EGb increased in solid dispersions and reached a plateau around 25% w/w. Furthermore, the dissolution rate of PEG 6000 continuously reduced with the concentration of EGb increased from 25% to 50% w/w. The profiles of initial dissolution rates in different concentrations of EGb were presented in Fig 6. The rate of the total flavone glycosides of EGb improved from 0% to 25% w/w dispersions and reached highest in the 25% w/w dispersion as well as small changes in the 25, 30, 40 and 50% w/w dispersions. However, the initial dissolution rate of PEG 6000 had little change from 0% to 20% w/w dispersions and rapidly reduced for the 25, 30, 40 and 50% w/w dispersions.

It was observed that the dissolution rate of total flavone glycosides increased from zero to a plateau while

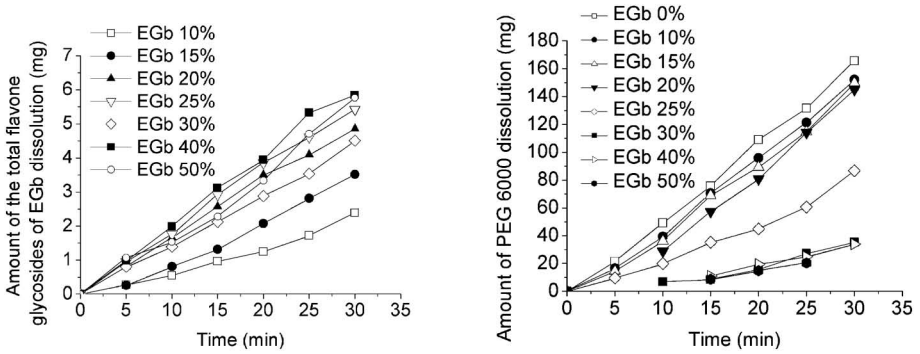

Fig. 5. Solid dispersions of EGb and PEG 6000 with Different Ratios
Dissolution profiles of the total flavone glycosides of EGb (left) and PEG 6000 (right). $n=3$.

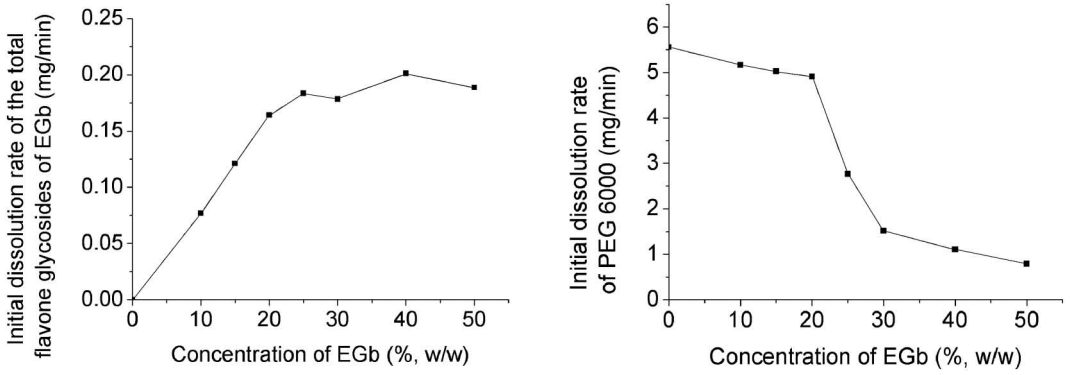

Fig. 6. Relationship between Initial Dissolution Rate and Concentration of EGb in Solid Dispersions
Total flavone glycosides of EGb (left) and PEG 6000 (right). $n=3$.

Table 1. Dissolution Data for Solid Dispersions with Different EGb Weight Percents ($n=3$)

EGb weight percent (%)	Total flavone glycosides weight percent (%)	Dissolution rate (mg/cm²/h)		$\frac{Q_a/A_a}{Q_b/A_b}$
		Total flavone glycosides of EGb	PEG 6000	
10%	2.34	7.22	484.06	0.57
15%	3.51	11.35	470.91	0.58
20%	4.68	15.4	462.91	0.57
25%	5.85	17.2	258.75	0.86
30%	7.02	16.73	142.07	1.17
40%	9.36	18.85	104.01	1.16
50%	11.70	17.67	74.36	1.01

the dissolution rate of PEG 6000 had minor change at high PEG 6000 weight percents in solid dispersions. This result suggested that a pure PEG 6000 surface layer is controlling dissolution in the high concentrations of PEG 6000. The controlling layer at a particular weight fraction is determined by comparing the relative movement of the solid boundary of each component $(Q_a/A_a)/(Q_b/A_b)$, where Q_a and Q_b are the component dissolution rates per area (mg/cm²/h) and A_a and A_b are the amounts per unit volume of the two components a and b respectively.[5] Q_a/A_a presented the dissolution characteristics per unit amount of the total flavone glycosides in EGb and Q_b/A_b presented PEG 6000. The ratio of Q_a/A_a to Q_b/A_b was to compare the relative dissolution characteristics of the two components. The data of the ratio are summarized in Table 1. The three ratios for the 10, 15 and 20% w/w dispersions were approximately one value 0.57, and those for the 30, 40 and 50% w/w dispersions were approximately one value 1.0, and the ratio for the 25% w/w dispersions was a medium value.

DISCUSSION

The mechanisms of drug release from solid dispersions in water-soluble polymers have been previously reported in a number of literatures.[8,16–21] It includes soluble complex formation, solid state changes, coacervate formation, carrier character, dissolution model studies for solid dispersion system, *etc*. Generally, phase diagram and DSC method frequently provide favoured explanations for the the multi-component interacting system in solid dispersions.[22,23] In our study, evidences for eutectic formation in the phase diagram and soluble complex formation in the DSC were apparent in Figs. 2, 3 and 4. The data supplied interpretations for the rapid release of drug in the EGb-PEG 6000 solid dispersion.

Dissolution experiments of drug and carrier are another studying method for the mechanism of drug release. In the dissolution of two-component solid dispersion system, Higuchi *et al*. and Corrigan consider that at high drug loadings, the concentrated drug layer forms at the dissolving surface and drug-controlled dissolution provides a satisfactory explanation. The dissolution rate of drug always keeps constant and is described by the equation $G_A=D_ACs_A/h$ (G is dissolution rate per area, A is the component drug, D is diffusion coefficient, Cs_A is the saturated solubility of drug, h is thickness of diffusion layer). The dissolution rate of carrier will be determined by the rate of the drug and the ratio of two components, desribed by the equation $G_B=N_BG_A/N_A$ (N is the ratio of components, B is the component carrier).[6,16] In our study, the ratios of Q_a/A_a to Q_b/A_b were about 1.0 for the 30, 40 and 50% w/w dispersions (high drug loadings). The initial dissolution rates of the total flavone glycosides of EGb (the component in excess) had no significant change while the rates of PEG 6000 (the minor component) reduced with the ratio increase, suggesting that drug-controlled dissolution model contributed to the 30, 40 and 50% w/w dispersions.

At low drug loadings in solid dispersions, a highly concentrated polymer layer forms at the dissolving surface through which the drug must pass prior to release into the bulk phase (described by Craig Duncan Q. M.). Two models are built to describe the fate of drug during the dissolution process. One model is carrier-controlled dissolution. In this instance drug particles dissolve into the carrier-rich diffusion layer at a sufficiently rapid rate and drug is molecularly dispersed within the concentrated carrier layer. Consequently, the rate-limiting step to dissolution of the drug is the release of the carrier itself. The other

model is drug-controlled dissolution. In this case, dissolution of the drug into the carrier diffusion layer is comparatively slow and the drug is released as solid particles. Thus, the dissolution will not be associated with the carrier but will instead be dominated by the properties (size, physical form, *etc.*) of the drug itself.[8] In our study, the ratios of Q_a/A_a to Q_b/A_b were about 0.57 for the 10, 15 and 20% w/w dispersions (low drug loadings). The initial dissolution rates of PEG 6000 (the carrier-rich diffusion layer) had no significant change while the rates of the total flavone glycosides of EGb (low drug loadings) increased with the ratio increase, which completely accorded with the dissolution characteristics of the two-component solid dispersion system described above. But which model did the EGb-PEG 6000 dispersions belong to at low drug loadings, carrier-controlled or drug-controlled dissolution?

In the two models at low drug loadings, the tendency of the drug to dissolve into the concentrated carrier diffusion layer supplies for predicting the dissolution mechanism.[8] Combining with the result that the solubilities of the total flavone glycosides and the soluble solid materials of EGb increased linearly with the increasing concentrations of PEG 6000 solutions, it suggested that drug-controlled dissolution model contributed to the 10, 15 and 20% w/w dispersions. For the 20% to 30% w/w dispersions (medium range between low and high drug loadings), the initial dissolution rates of PEG 6000 reduced while the rates of the total flavone glycosides of EGb increased with the ratio increase, suggesting the dissolution of the two components were all affected by the ratio in the system.

In conclusion, in the two-component solid dispersions of EGb and PEG 6000, there were apparent evidences for eutectic formation in the phase diagram and soluble complex formation. It suggested that the dispersions belonged to drug-controlled dissolution model at high drug loadings and carrier-controlled dissolution model at low drug loadings, which supplied for understanding the improvements on the dissolution rate *in vitro* and curative effect *in vivo* of EGb dropping pills.

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