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Enhanced dissolution rate and oral bioavailability of *Ginkgo biloba* extract by preparing solid dispersion via hot-melt extrusion ☆

Wenping Wang [a], Qian Kang [a], Na Liu [a], Qing Zhang [a], Yewen Zhang [a], Hui Li [a], Bochen Zhao [a], Yanyan Chen [a], Yi Lan [a], Qiang Ma [b], Qing Wu [a,*]

[a] Department of Pharmaceutical Sciences, Beijing University of Chinese Medicine, Beijing 100102, China
[b] Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100005, China

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ABSTRACT

The aim of this study was to improve the dissolution rate and oral bioavailability of *Ginkgo biloba* extract (GBE) through the preparation of *G. biloba* extract solid dispersions (GBE-SD) via hot-melt extrusion (HME). First, we prepared the GBE-SD based on a Kollidon® VA64/Kolliphor® RH40 (85:15) spray dried powder. Then physicochemical properties were investigated by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and Fourier transform infrared spectroscopy (FT-IR). The results indicated that GBE dispersed well in a carrier matrix. Subsequently, we studied the dissolution profile of total flavonoids (TFs) by HPLC-UV and total terpene lactones (TTLs) by HPLC-ELSD. The dissolution percentage of TFs and TTLs was improved within 120 min. Finally, we studied the pharmacokinetic characteristics and bioavailability in rats by UPLC-MS/MS. The results showed that the C_{max} and AUC_{0-t} of bilobalide (BB), ginkgolide A (GA), ginkgolide B (GB), ginkgolide C (GC), quercetin (QCT), kaempferol (KMF) and isorhamnetin (ISR) in rats were significantly increased after the oral administration of GBE-SD compared with results after the oral administration of GBE. These results suggest that the solid dispersion preparation by HME could serve as a promising formulation approach to enhancing the dissolution rate and oral bioavailability of GBE.

1. Introduction

Ginkgo biloba is a medicinal plant that is widely used to treat various diseases, especially cardiovascular and neurodegenerative diseases [1]. Commercial *G. biloba* extract (GBE), such as EGb761, a standardized *G. biloba* leaf extract, is currently sold worldwide as a phytomedicine and a dietary supplement and has become one of the best-selling herbal products [2–5]. Standardized *ginkgo* extract is a complex mixture containing 24% flavonoids and 6% terpene lactones. Bilobalide, ginkgolide A, ginkgolide B, ginkgolide C, quercetin, kaempferol and isorhamnetin are the primary active ingredients of *ginkgo* products [6]. Several studies have shown that these active ingredients are responsible for a range of pharmacological effects, including scavenging free radicals [7], improving hemorheological properties [8] and anti-platelet aggregation [9]. There are various pharmaceutical products of GBE on the market as granules, tablets, capsules, dripping pills, etc. [10]. *Ginkgo* products have also been routinely prescribed in many countries and as dietary supplements in the US.

However, the low oral bioavailability of GBE is due to its poor water solubility and limits the desired effect of marketed

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* Corresponding author at: Department of Chinese Pharmaceutics, School of Chinese Materia Medica, Beijing University of Chinese Medicine, No. 6, Zhong Huan Nan Lu, Wangjing, Chaoyang District, Beijing 100102, PR China.
E-mail address: qwu@sina.vip.com (Q. Wu).

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products [11]. There are a number of formulation strategies for poorly soluble drugs. The commonly employed strategies are crystal modifications, particle size reductions, amorphizations, self-emulsifications and pH modifications [12,13]. In recent years, several approaches were reported for enhancing the dissolution rate and the oral bioavailability of GBE, such as solid dispersions [14], self-emulsifications [15–18] and phospholipid complexations [19–21].

In recent years, hot-melt extrusion (HME) has been shown to be a promising pharmaceutical technology to produce solid dispersions with enhanced oral bioavailabilities of poorly soluble drugs [22–24]. HME is an efficient technology for producing solid molecular dispersions, and there are various solid dispersion systems as pharmaceutical products on the market [22]. In the HME process, active pharmaceutical ingredients are embedded in a molten polymer matrix in an amorphous state by both distributive and dispersive mixing [25]. In addition, HME offers several advantages over traditional pharmaceutical processing techniques. The HME process is a continuous operation that reduces the number of processing steps to shorten production times to final products. Solvents and water are not necessary in the HME process; this eliminates time-consuming drying steps and reduces environment pollution [26,27]. Studies have been reported that have applied HME to produce solid dispersions of botanical medicines [28–31].

In the present study, HME was used to prepare a solid dispersion of GBE based on a polymeric matrix to enhance the dissolution properties and bioavailability of GBE. Then a characterization of the solid dispersion was carried out by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and Fourier transform infrared spectroscopy (FT-IR). In addition, we studied the dissolution properties of total flavonoids (TFs) and total terpene lactones (TTLs) by HPLC-UV and HPLC-ELSD, respectively. Moreover, a UPLC-MS/MS method was used for the comparative study of the *in vivo* bioavailability of GBE and GBE-SD by simultaneous quantification of concentrations of BB, GA, GB, GC, QCT, KMF and ISR in rat plasma.

2. Materials and methods

2.1. Materials and reagents

GBE was provided by Kanion Pharmaceutical (Lianyungang, China), with BB, GA, GB, GC, QCT, KMF and ISR contents of 2.78%, 1.99%, 0.51%, 0.78%, 3.64%, 4.60% and 1.76%, respectively [32]. Kollidon® VA64/Kolliphor® RH40 (85:15, w/w) spray dried powder was kindly donated by BASF Company (Germany) and was used as a carrier matrix (CM). Reference standards of bilobalide (PubChem CID: 12308750, BB), ginkgolide A (PubChem CID: 9909368, GA), ginkgolide B (PubChem CID: 6324617, GB), ginkgolide C (PubChem CID: 161120, GC), quercetin (PubChem CID: 5280343, QCT), kaempferol (PubChem CID: 5280863, KMF) and isorhamnetin (PubChem CID: 5281654, ISR) and the internal standard of domperidone (IS) were all purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). The chemical structures of BB, GA, GB, GC, QCT, KMF and ISR were shown in Fig. 1. Acetonitrile (HPLC grade) was supplied by Fisher Scientific Company, Inc. Formic acid (HPLC grade) was supplied by Sigma-Aldrich. Deionized water was further purified by the Millipore ultrapure water system. All other reagents were of analytical grade.

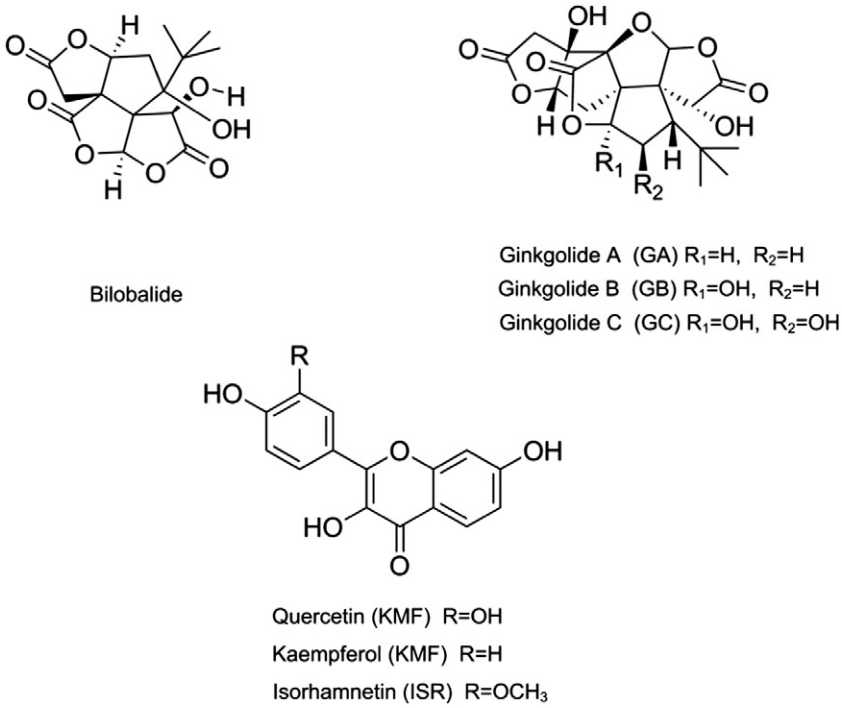

Fig. 1. Chemical structures of BB, GA, GB, GC, QCT, KMF and ISR.