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Original Research Paper

# Improved dissolution of *Kaempferia parviflora* extract for oral administration by preparing solid dispersion via solvent evaporation

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ARTICLE INFO

*Article history:*
Received 19 August 2016
Received in revised form 13 September 2016
Accepted 20 September 2016
Available online 4 November 2016

*Keywords:*
Poorly water-soluble drug
*Kaempferia parviflora*
Solid dispersion
Solvent evaporation

ABSTRACT

*Kaempferia parviflora*, a plant in the family Zingiberaceae, has been used in Thai traditional medicines for treating hypertension and promoting longevity with good health and well-being. However, its limited aqueous solubility and low dissolution restrict its bioavailability. The aim of the study was therefore to improve the dissolution rate of *K. parviflora* extracted with dichloromethane (KPD) by solid dispersions. Different water-soluble polymers were applied to improve dissolution of KPD. The solid dispersions in different ratios were prepared by solvent evaporation method. Only hydroxypropyl methylcellulose (HPMC) and polyvinyl alcohol-polyethylene glycol grafted copolymer (PVA-co-PEG) could be used to produce homogeneous, powdered solid dispersions. Physical characterization by scanning electron microscopy, hot stage microscopy, differential scanning calorimetry and powder X-ray diffractometry, in comparison with corresponding physical mixtures, showed the changes in solid state during the formation of solid dispersions. Dissolution of a selected marker, 5,7,4′-trimethoxyflavone (TMF), from KPD/HPMC and KPD/PVA-co-PEG solid dispersions was significantly improved, compared with pure KPD. The dissolution enhancement by solid dispersion was influenced by both type and content of polymers. The stability of KPD/HPMC and KPD/PVA-co-PEG solid dispersions was also good after 6-month storage in both long-term and accelerated conditions. These results identified that the KPD/HPMC and KPD/PVA-co-PEG solid dispersions were an effective new approach for pharmaceutical application of *K. parviflora*.



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Peer review under responsibility of Shenyang Pharmaceutical University.
http://dx.doi.org/10.1016/j.ajps.2016.09.005

## 1. Introduction

*Kaempferia parviflora* Wall. Ex Baker is a member of the family Zingiberaceae and found in the northern part of Thailand. In Thai traditional medicine, rhizome of the plant has been used for treating hypertension, erectile dysfunction, inflammation and abdominal pain, as well as for the promotion of longevity with good health and well-being [1]. In Laos folk medicine, the rhizome has been used for treating high blood glucose level, increasing blood flow and improving vitality [2]. In Japan, *K. parviflora* extract is marketed as a nutrition supplement for the treatment of metabolic syndrome [3]. Several researchers have revealed the pharmacological activities of ethanol extract form *K. parviflora* such as aphrodisiac activity in male rats and prevention of myocardial ischemic-reperfusion injury in isolated rat heart [4]. Ethyl acetate extracted *K. parviflora* was investigated in an *in vivo* study, by Akase et al. [2] and Shimada et al [5]. The dichloromethane extracted *K. parviflora* (KPD) demonstrates the pharmacological activities such as decreasing vascular responsiveness to phenylephrine, decreasing visceral and subcutaneous fat and decreasing fasting serum glucose and triglyceride levels in middle-aged male rats [6].

The methoxyflavones, i.e., 5,7-dimethoxyflavone (DMF), 5,7,4′-trimethoxyflovone (TMF), and 3,5,7,3′,4-pentamethoxyflavone (PMF), were used as standard markers of *K. parviflora*. The major problem associated with methoxyflavones is inadequate solubility in biological fluids and their high lipophilicity with log P values ranging from 2.0 to 3.5 that finally limit their bioavailability and clinical utility after oral administration [7,8]. Therefore, it is important to develop a suitable formulation to increase its solubility and bioavailability. A number of methods have been developed to improve the oral absorption of poorly water-soluble compounds such as milling [9], salt formation [10], micronization [11], solubilization using co-solvents, use of lipid-based formulations and solid dispersions [12,13], etc. Solid dispersions are generally accepted as a method to enhance dissolution of poorly water-soluble drugs. The term solid dispersion refers to a group of solid substance consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The drug can be homogeneously dispersed, in the form of amorphous particles or crystalline particles [14,15]. Several methods have been used to produce the solid dispersions, i.e., melting, solvent evaporation and melting-solvent methods. Melting method is a process to prepare solid dispersions by mixing drug and carrier together, and heating them directly until they melted. The molten mixture is then solidified to get the solid mass. In solvent evaporation method, drug and carrier are dissolved in a common solvent and then the solvent is removed to form the solid mass. Nevertheless, the solvent evaporation method is a popular method because it uses low temperature to remove the solvent and requires simple equipment [16–19]. Various carriers can be used to prepare solid dispersions [20–23], i.e., polyethylene glycols, polyvinylpyrrolidone, polyols, polysaccharides, polyacids, etc. However, the study on development of herbal products using solid dispersion technique is still limited. To the best of our knowledge, solid dispersion containing *K. parviflora* extract is not available to date. Therefore, in this study, the solid dispersions of KPD were developed in order to improve the dissolution of KPD by solid dispersion using solvent evaporation method. The solid state characteristics and dissolution behavior of solid dispersions were investigated. The stability of KPD solid dispersions, after storage in long-term and accelerated conditions was also tested.

## 2. Materials and methods

### 2.1. Materials

KPD was extracted by maceration method as described previously [6]. Briefly, fresh rhizomes of *K. parviflora* were blended and extracted successively by macerating with 95% ethanol for 48 h, followed by extracting with dichloromethane. The dichloromethane-soluble part was filtered and then evaporated. The dried residue from the dichloromethane extract was further treated by vacuum condition in order to remove residual dichloromethane and then a yellowish gummy of KPD was obtained.

Polyvinyl alcohol polyethylene glycol graft copolymer (Kollicoat® IR, referred to as PVA-co-PEG) and polyethyleneglycol-polyvinyl acetate-polyvinylcaprolactame grafted copolymer (Soluplus®, referred to as PCL-PVAc-PEG) were a gift form BASF (Thai) Co., Ltd. (Bangkok, Thailand). Polyvinylpyrrolidone K30 (referred to as PVP), hydroxypropyl methylcellulose K4M (referred to as HPMC) and polyethylene glycol 4000 (referred to as PEG) were purchased form P.C. Drug Center (Bangkok, Thailand). Other chemicals were of pharmaceutical grade or analytical grade and used without further purification.

### 2.2. Preparation of solid dispersions

Solid dispersions of KPD and polymer were prepared by solvent evaporation method. The ratios of KPD to polymer are shown in Table 1. The KPD and polymer were separately dissolved in 5-ml dichloromethane. The clear solutions of KPD and polymer were mixed and the solvent was then evaporated in water bath at 50 °C for 24 h. The dried samples were kept in desiccator until further investigation.

### 2.3. Analysis of the content

The samples were dissolved in methanol and filtered with 0.45-μm nylon membrane filter. The filtered solution was analyzed by high performance liquid chromatography (HPLC) equipped with a photodiode array detector (model Agilent 1100 Series HPLC System, Agilent Technologies, USA) using Luna 5 μ C18 (5 μm, 4.6 nm × 25 cm, Phenomenex®, USA). The analysis as

**Table 1 – Formulation of KPD solid dispersions.**

| Ratio | KPD (mg) | Polymer (mg) |
|---|---|---|
| 1:0.5 | 90 | 45 |
| 1:1 | 90 | 90 |
| 1:2 | 90 | 180 |
| 1:4 | 90 | 360 |