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Research paper

Development of orodispersible films with selected Indonesian medicinal plant extracts

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ABSTRACT

This study focused on the incorporation into orodispersible films (ODFs) of the dried extracts of five selected Indonesian medicinal plants: *Lagerstroemia speciosa* (L.) Pers. (LS), *Phyllanthus niruri* L. (PN), *Cinnamomum burmanii* Blume (CB), *Zingiber officinale* Roscoe (ZO) and *Phaleria macrocarpa* (Scheff.) Boerl (PM). Suitable formulae for solvent casting were developed to produce extract containing films with either a combination of hypromellose (HPMC) with carbomer 974P or only hydroxypropyl cellulose (HPC) as film forming agent. Each extract and dose in a formulation rendered different ODF characteristics. Extracts of ZO and CB and a low dose of PM extract (5 mg) could be formulated into an ODF containing HPMC with carbomer 974P. For extracts of LS, PN and high doses of PM extract HPC were the most suitable film forming agents. For each extract a different maximum load in a film was found, up to maximum 30 mg for extracts of LS and PN. Good products were obtained with 5 mg and 10 mg of each extract. The quality of the produced ODFs was tested organoleptically, and characterized by determination of uniformity of weight, thickness, disintegration time, surface pH, crystallinity, mechanical properties, water content, residual ethanol, dynamic vapour sorption, physical stability and control of the qualitative profiling of extract composition in the film. Thin layer chromatography indicated that all five extracts remained chemically unaffected during ODF production. In conclusion, ODFs are a suitable novel dosage form for herbal extracts, provided that tailor-made formulations are developed for each extract and each dose.

1. Introduction

Orodispersible films (ODFs) are a novel advanced pharmaceutical dosage form targeted especially for geriatric and pediatric patients (Slavkova and Breitkreutz, 2015). Various studies have been published on ODFs containing active pharmaceutical ingredients, but literature on the incorporation of dried herbal extracts in ODFs is scarce. Up to now ODFs containing herbal extracts are used limitedly, as over the counter medicine used for the treatment of local diseases such as mouth ulcers (Ambikar et al., 2014; Bhattacharjee et al., 2014; Dixit and Puthli, 2009).

Indonesian traditional herbal medicine, also known as *jamu*, is very popular and broadly used in this country to treat and to prevent diseases. In addition, several Indonesian herbal medicines have been elevated beyond the status of *jamu* and became Standardized Herbal Medicine as well as *fitofarmaka* (phytomedicines, Indonesian for herbal medicinal products), as regulated by the Indonesian FDA. The common dosage forms for oral administration of *jamu* are tablets, pills, powders, pastilles and capsules (Elfahmi et al., 2014; NA-DFC, 2016). ODFs are an interesting alternative dosage form especially for patients who have difficulty in swallowing, and patients who suffer from diseases such as gastrointestinal disorders, migraine, and central nervous system-associated ailments. Furthermore, ODFs have a high dose flexibility and are suitable for intraoral drug delivery.

The aim of this study was the incorporation of dried plant extracts into ODFs. Extracts of five selected Indonesian medicinal plants were used, namely *Lagerstroemia speciosa* (L.) Pers. (LS),

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Phyllanthus niruri L. (PN), *Cinnamomum burmanii* Blume (CB), *Zingiber officinale* Roscoe (ZO) *and Phaleria macrocarpa* (Scheff.) Boerl (PM).

Table 1 lists detailed information about the extracts. In Indonesia LS is commonly used to improve the metabolism of the body and to treat diseases like type 2 diabetes mellitus and obesity (Chan et al., 2014; Kotnala et al., 2013; Rafi et al., 2013). PN has a long tradition in Indonesian *jamu* as an herb against hepatitis infection. It is used for the treatment of kidney stones in the South American countries, and is therefore called 'stone breaker' (Bagalkotkar et al., 2006; Patel et al., 2011). However, in Indonesia PN has been studied clinically as an immunomodulatory agent against mycobacterial infections such as tuberculosis. CB has anti-inflammatory and antibacterial activity. It is traditionally used to treat gastrointestinal tract disorders (Al-Dhubiab, 2012; Veitch et al., 2012). Recently CB has been characterized molecularly as having a mechanism of action similar to that of a proton pump inhibitor to treat hyperacidity (Tjandrawinata et al., 2013). There are several varieties of ZO which are used as spices, as dietary supplements or as herbal medicine to prevent nausea and vomiting in motion sickness (Veitch et al., 2012; Rafi et al., 2013). PM is used to treat premenstrual syndrome and dysmenorrhea (Tjandrawinata et al., 2011). It also has an antihyperglycemic effect and cytotoxic activity (Ali et al., 2012; Hendra et al., 2011; Tjandrawinata et al., 2010).

The five extracts used in the current study were selected based on their popularity in Indonesia and on the availability of extracts of which origin and manufacture are well documented by Dexa Laboratories of Biomolecular Science (DLBS), Indonesia. Furthermore, we strived to include extracts from different plant organs and extracts with different groups of secondary metabolites as major constituents. The extracts have also been chosen due to the existing scientific support for the preclinical and clinical evidences and because of the technologically advanced method of production to provide a reproducible extract. Furthermore, this advanced development is in accordance with Indonesian Government policy to promote *jamu* and to bring the Indonesian herbal medicine into the direction of more evidence-based medicine.

2. Materials and methods

2.1. Materials

2.1.1. Plant extracts

Lagerstroemia speciosa (L.) Pers. (LS), *Phyllanthus niruri* L. (PN), *Cinnamomum burmanii Blume* (CB), *Zingiber officinale* Roscoe (ZO) *and Phaleria macrocarpa* (Scheff.) Boerl (PM) were provided by DLBS, Dexa Medica, Cikarang, West-Java, Indonesia. All proprietary extract materials were produced in a cGMP-certified production plant using SPX e&e Series Extraction Plants (SPX Flow Technology Warendorf GmbH, Warendorf Germany), see also *2.2.1.*

2.1.2. ODFs base materials

Aerosil 200 (silicon dioxide), carbomer 974P, disodium edetate (EDTA), glycerol 85% and trometamol were obtained from Fagron, Capelle aan den IJssel, the Netherlands. Hypromellose 3000 mPa s (HPMC) provided by from Colorcon, Kent, UK. Hydroxypropyl cellulose (HPC) was obtained from Hercules, Wilmington, USA. Benzalkonium chloride was obtained from Bufa, IJsselstein, The Netherlands. Sucralose was obtained from Sigma-Aldrich, St. Louis, USA. Strawberry, lemon and golden flavor were provided by Firmenich, Geneva, Switzerland. All other excipients and chemicals were of analytical grade.

2.2. Methods

2.2.1. Plant material and preparation of the extracts

The dried plant material of all five plants used in the study was macerated in hot water (60 °C–90 °C) for 1–2 h. Plant material and aqueous extract were separated by filtration. The extract was then vacuum evaporated using a rotary evaporator at 60 °C–80 °C. The concentrate was further processed through liquid–liquid extraction using dichloromethane at a ratio of 1:2 to separate from undesired organic components. Subsequently, the water phase was collected and then evaporated using a rotary evaporator at temperatures of 50 °C–120 °C depending on the extract to obtain the final dry extract.

Table 1
Information about the extracts produced by Dexa Laboratories of Biomolecular Science (DLBS), Indonesia.

Plant name, author name and family plus abbreviation used	Indonesian name	Plant part used	Excipients added to extract (filler)	Main functional ingredients	Brand name in Asia, indication, dose and dosage form	References
Lagerstroemia speciosa (L.) Pers. Lythraceae (LS)	Bungur	Leaf	–	Tannins, alkaloids, sterols, triterpenes, ellagic acid	Herbafit (not on the market yet), to improve the metabolism in the body: 100 mg 1–2 times a day (capsule)	Jayakumar et al. (2014),Kotnala et al. (2013) and Rafi et al. (2013).
Phyllanthus niruri L. Euphorbiaceae (PN)	Maniran	Herb	–	Alkaloids, flavonoids, lignans, triterpenes, sterols and volatile oil	Stimuno, to improve the immune system: 50 mg 1–3 times a day (capsule)	Bagalkotkar et al. (2006) and Patel et al. (2011)
Cinnamomum burmannii Blume Lauraceae (CB)	Kayu manis	Stem	–	Cinnamic aldehyde, eugenol, benzaldehyde, coumarin	Redacid, to relieve hyperacidity (peptic ulcer): 250 mg 1–3 times a day (capsule)	Al-Dhubiab (2012) and Veitch et al. (2012)
Zingiber officinale Roscoe Zingiberaceae (ZO)	Jahe	Rhizome	76.5% MCC[a], 8.5% silicon dioxide	Volatile oils, phenols (gingerols, shogaols, zingerone, paradole)	HerbaVomitz, to treat and prevent nausea and vomiting: 150 mg 1–2 times a day (tablet)	DLBS, Rafi et al. (2013) and Veitch et al. (2012).
Phaleria macrocarpa (Scheff.) Boerl Thymelaceae (PM)	Mahkota dewa	Pericarp	5% β-cyclodextrin	Flavonoids (kaempferol, myricetin), naringin, rutin	Dismeno, to relieve pain during menstruation (dysmenorrhoea) and endometriosis: 100 mg 1–3 times a day (capsule)	Ali et al. (2012), Altaf et al. (2013), DLBS, Hendra et al. (2011) and Tjandrawinata et al. (2010, 2011).

[a] MCC = microcrystalline cellulose.