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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.

2.2.2. Preparation of the casting solution and ODFs

As a starting point the casting solution recently developed (Visser et al., 2015b) was used, further referred to as 'the standard casting solution'.

The solution consisted of the film forming agents HPMC (9.81 g) and carbomer 974P (0.45 g), the plasticizer glycerol (1.2 g), the excipients disodium EDTA (0.045 g) and trometamol (0.45 g) and water up to 100 g as the solvent. Disodium EDTA was used to bind calcium and magnesium ions that interfere with the cross-linking in carbomer 974P gels, thereby improving the viscosity enhancement. Trometamol was used to neutralize the carboxylic acid groups of carbomer 974P resulting in gel formation.

Based on the results with the standard casting solution adaptions in the formulation were made to improve the casting solution and the ODFs prepared thereof (see Paragraph 2.2.3). The film forming agents, extract and relevant excipients were dissolved in water or in a water-glycerol mixture under constant stirring at 1000 rpm using a magnetic bar. If necessary, the extract was first dissolved in ethanol 96% (see results, Table 4). After a clear solution had been obtained, stirring was continued at 50 rpm overnight to remove entrapped air bubbles. The solution was then casted onto a release liner (Primeliner® 410/36, Loparex, Apeldoorn, the Netherlands) with a quadruple film applicator using a casting height of 1000 μm and a casting speed of 10 mm/s. The release liner was fixed to the film applicator (Erichsen, Hemer, Germany) by vacuum suction. Subsequently, the film layer was dried at 30 °C during 1.5–9 h depending on the formulation used and ambient relative humidity. After drying, the films were punched using an Artemio perforator (Artemio, Wavre, Belgium) in squares of 1.8 × 1.8 cm, yielding stamp-shaped ODFs.

2.2.3. Evaluation of the casting solution and the ODFs

An amount of extract was added to the standard casting solution to yield ODFs containing 5 mg extract per ODF. Various tests were performed on the casting solution and on the ODFs prepared thereof. The casting solutions containing the various extracts were judged on their suitability to form ODFs. The appearance, flexibility, handling properties, disintegration time after application on the tongue, mouth feel and taste of all prepared ODFs were evaluated by a test panel as described recently (Visser et al., 2015a). Five volunteers between 20 and 60 years of age evaluated the ODFs on mouth feel and taste. Taste masking of the herbal ODFs was carried out by applying a combination of sucralose with tastes of strawberry, lemon or golden flavour (see results, Table 4). The same test panel judged whether the taste was sufficiently masked. The requirements mentioned in Table 2 were used for the different parameters.

In case the casting solution was considered suitable, the amount of extract was increased in steps of 5 to 10 mg per ODF until the maximum achievable extract load was achieved. In case the casting solution or the ODFs prepared thereof were considered unsuitable, the formulation was adjusted by using a different film forming agent, i.e. HPC, by adding a co-solvent, by adjusting the amount of glycerol or by adding benzalkonium chloride or silicon dioxide. All ODFs were sealed in plastic and stored in the dark before further testing as described in Paragraphs 2.2.4.–2.2.13. All tests were performed ultimately within two days after preparation of the ODFs.

2.2.4. Surface pH

The surface pH was measured using a pH meter (Consort R735, Turnhout, Belgium) with a universal pH electrode (type 662-1772, VWR Pennsylvania, USA).

The ODFs (n = 3) were allowed to swell in 1 mL of distilled water (±20 °C) for 2 h. Subsequently, the electrode was brought in contact with the surface of the ODF and allowed to equilibrate for 1 min before the surface pH was measured.

A pH range between 4 and 8 is considered to be acceptable (Gittings et al., 2015; Hoffmann et al., 2011; Preis et al., 2013).

2.2.5. Thickness

A micro-screw meter (Mitutoyo, Neuss, Germany) was used to measure the thickness of the ODFs (n = 20) at five different points: in the corners and in the middle of the prepared film.

2.2.6. Disintegration

The disintegration time was measured using the method as described recently (Visser et al., 2015a). The ODFs (n = 5) were clamped in an arm which moved up and down at a frequency of 30 ± 1 cycles per minute, over a distance of 55 ± 2 mm in 700 mL purified water of 37 °C ± 2 °C. The time at which complete dissolution had occurred was considered as the disintegration time. The disintegration time was measured immediately after preparation of the ODFs and after 18 months of storage in sealed plastic bags under dry, dark conditions at ambient temperature. Analogously to tablet or capsule disintegration, this was judged by visual inspection. Since there are no limits concerning disintegration time of ODFs the commonly used requirements for orodispersible tablets (ODTs) were used in our study. The disintegration time should be less than 30 s according to the guidance for industry for orally disintegration tablets as set by the Food and Drug Administration (FDA) or less than 180 s according to the Ph. Eur. 8th edition, monograph 0478, dispersible tablets (FDA, 2008 and European Pharmacopoeia, 2015).

2.2.7. Loss on drying

The water content was measured using an infrared moisture analyser (Moisture analyzer MA40, Sartorius Göttingen, Germany). Per extract load approximately 1.5 g of ODFs were weighted and subsequently heated at 105 °C for at least 90 min until equilibrium in mass was reached. Loss on drying was the difference (in%) in mass between the initial weight and the final weight at equilibrium. There are no requirements concerning residual moisture in the Ph. Eur. 8th edition for ODFs.

2.2.8. Uniformity of mass

Uniformity of mass was determined according to the Ph. Eur. 8th edition: uniformity of mass for single-dose preparations (Method 2.9.5) on which also the requirements were based (Ph. Eur.). Twenty randomly chosen ODFs were weighted individually

Table 2
Quality requirements applied to the casting solution with herbal extract and to ODFs prepared thereof.

Parameter	Requirement
Casting solution	No formation of lumps or precipitates and suitable viscosity
Appearance ODF	Smooth non gritty, uniform colour
Flexibility ODF	Easy to bend, no breaking
Disintegration in mouth ODF	<180 s
Mouth feel ODF	Immediate stick to the tongue or palatal
Handling properties ODF	Removal from release liner without breaking

on an analytical balance. Subsequently the average mass and weight variation were calculated.

2.2.9. Mechanical properties

An Instron series 5500 load frame with a load cell of 100 N (Instron, Norwood, USA) was used to analyse the mechanical properties of the ODFs. Samples were cut using a stamp into a bone shape according to ISO-527 (plastics – determination of tensile properties) (NEN-EN-ISO, 2012). A minimum of 6 samples per ODF formulation were tested. The ODFs were fixed between two clamps which were subsequently moved away from each other with a crosshead speed of 50 mm/min until tearing or breakage of the ODFs. The tensile strength (N/mm^2) is the maximum force applied to the ODF until tearing or breakage and was calculated using Eq. (1) (Dixit and Puthli, 2009; Sudhakar et al., 2006).

$$\text{Tensile strength} = \frac{\text{load at autobreak} \times 100}{\text{cross} - \text{sectional area of the film}} \quad (1)$$

Young's modulus, also known as elastic modulus (N/mm^2), defines the stiffness of the ODF and was calculated using Eq. (2) (Dixit and Puthli, 2009; Morales and McConville, 2011).

$$\text{Young's } \textit{mod}\text{ulus} = \frac{\text{slope of stress} - \text{strain curve}}{\text{film thickness} \times \text{cross} - \text{head speed}} \quad (2)$$

Elongation at break (%) is defined as the elongation of the ODF when force is applied and was calculated using Eq. (3) (Dixit and Puthli, 2009; Morales and McConville, 2011).

$$\text{Elongation at break} = \frac{\text{increase in length at break}}{\text{initial film length}} \times 100 \quad (3)$$

2.2.10. Dynamic vapor sorption

A Dynamic Vapor Sorption analyzer (DVS-1000 water sorption instrument, UK) was used to measure the water sorption isotherms for ODFs containing 5 and 10 mg of extract per ODF. Measurements were performed at ambient pressure and a temperature of 25 °C. For each experiment 20–40 mg ODFs were used. The ODFs were dried at 0% relative humidity (RH) until constant weight was achieved (change in weight less than 0.0005 mg during 10 min). Subsequently, the RH was raised with increments of 10%, from 0 to 90%, each step until constant weight was achieved.

2.2.11. Measurement of residual ethanol

A headspace gas phase chromatography (Agilent Technologies 7890 GC system, Amstelveen, The Netherlands) was used to measure the ethanol content of ODFs containing 10 mg of extract under the following conditions: column, J&W scientific DB-wax (30 m × 0.53 mm: film thickness 1 μm). Oven and detector (FID) temperature were set at 80 and 300 °C, respectively; and the carrier gas was N_2. Ethanol content was measured of freshly prepared ODFs. The ODFs were dissolved in 500 μL water in a 10 mL caped sample vial. The solution was warmed to 65 °C and samples of 500 μL were injected directly into the injection port with a syringe (injection temperature: 80 °C). The ethanol content of the ODFs was measured in duplicate and measurements were corrected for blank measurements. Results were calculated from a calibration line with reference aqueous ethanol solutions. The casting solution for ODFs containing 10 mg extract contained 10 to 30% ethanol as co-solvent (as% of the total water amount, approximately 10–30 mg ethanol per ODF) before drying.

2.2.12. X-ray powder diffraction

X-Ray Powder Diffraction (XRPD, Bruker, Delft, The Netherlands) was used to visualize crystallinity of the extracts as well as the ODFs prepared thereof (n = 1 per extract). The ODF samples were cut into small pieces and placed into the sample holder. The samples were scanned at a diffraction angles range from 5° tot 60° 2^{θ}, with an angular step width of 0.004 2^{θ} and a scanning rate of 1 s.

2.2.13. Thin layer chromatography

Thin layer chromatography (TLC) was used to evaluate and to compare qualitative profiling of the extracts and the ODFs prepared thereof. The profiling of the extract ZO was determined according Ph. Eur. 8th edition, method 2.2.27 (Ph. Eur.). The extracts LS, PN, CB and PM were determined according to procedures developed by DLBS. 100 to 200 mg of herbal extract (as provided by DLBS) were extracted with 5–10 mL methanol or ethanol (70% v/v), depending on the herbal extract (see Table 3), in an ultrasonic bath for 10 min. The extract was subsequently filtered over filter paper, the residue was flushed with 2–4 mL of extraction fluid and combined with the filtrate. This solution was evaporated to dryness at room temperature and 1 mL of ethanol or methanol added to the residue. This sample was used for TLC.

A quantity of ODFs corresponding to the amount of pure herbal extract used for the TLC analysis above was extracted with the same fluid as the herbal extract. Solid phase extraction (normal phase) combined with vacuum suction was used to clean the herbal extracts from constituents of the ODFs. The solid phase column was flushed with 10 mL of extraction fluid and combined with the extract. The solution was evaporated to dryness at room temperature and the residue taken in 1 mL of methanol or ethanol. This sample was used for TLC.

TLC was performed on silica gel 60 F_{254} plates (size 20 × 20 cm) in a chamber with saturated eluent atmosphere. The elution range was 8 cm. The experimental setup and the mobile phase used are shown in Table 3. The chromatograms were evaluated under ultraviolet light at 254 nm, 366 nm and under visible light after spraying with 10% sulfuric acid. The profiles of the TLC chromatograms of the ODFs containing herbal extracts were compared to those of the herbal extracts as such.

3. Results and discussion

3.1. Evaluation of the casting solution and ODFs prepared thereof

The standard casting solution appeared to be unsuitable for any of the five extracts and its composition needed to be adjusted.

ODFs prepared with the extract LS were too brittle. Both LS and PN formulated into ODFs elicited spots indicating inhomogeneous

Table 3
Experimental setup for TLC of herbal extracts and the ODFs prepared thereof.

Extract	Mobile phase
LS (10% w/v in methanol)	Toluene: ethyl acetate: formic acid: methanol (30:30:8:4 v/v/v/v)
PN (10% w/v in methanol)	Toluene: ethyl acetate: formic acid: methanol (30:30:8:4 v/v/v/v)
CB (25% w/v in ethanol 70% v/v)	1-Butanol: acetic acid: water (5:2:2 v/v/v)
ZO (20% w/v in ethanol 70% v/v)	Hexane: ether (40:60 v/v)
PM (40% w/v in ethanol 70% v/v)	Chloroform: methanol (9:1 v/v)

distribution of the extract in the ODF. Therefore, an alternative casting solution was developed containing a different film forming agent: HPC.

With the extracts CB and PM the standard casting solution became highly viscous and could not be casted properly. Therefore the co-solvent ethanol was added.

ODFs prepared with the extract ZO elicited white spots at the edges of the ODFs which were caused by the fillers in the extract (microcrystalline cellulose and silicon dioxide). For that reason the fillers were removed from the extract. This was achieved by dissolving the ZO extract in ethanol and separating the solution from the remaining filler by filtration.

After the first evaluation and adjustment of the casting solution to produce ODFs with 5 mg of extract, the amount of extract was increased step by step with increments of 5 mg to determine the maximum possible extract load. After each increment the casting solution and the ODFs prepared thereof were evaluated. For all extracts the casting solutions needed to be adjusted when the extract load was increased. In Table 4 the adjusted composition of the respective casting solutions are listed.

In case of LS, PN and CB the ODFs became too brittle with increasing extract load. Therefore an increasing amount of glycerol was added. However, ODFs with an extract load of 30 mg LS were sticky enough by themselves to adhere to the oral mucosa. They could be prepared without glycerol. To dissolve larger quantities of extract of LS, PN and CB and to reduce the viscosity of the casting solution some ethanol was added. In all cases the ethanol evaporated during the drying process.

In case of ZO the casting solution displayed an unequal spread over the release liner with increasing extract load. Benzalkonium chloride was added to lower the surface tension and to obtain a better spread over the release liner.

In case of PM the standard casting solution was not suitable with increasing extract load. For that reason HPC was used as film forming agent. Ethanol was added to lower the viscosity of the casting solution. To obtain a better distribution of the extract in the final ODF some silicon dioxide was added. Visual inspection of the ODFs indicated that the extracts were homogeneously distributed. Fig. 1 shows an example of ODFs containing 5 mg CB and 5 mg ZO.

The maximum amount of extract that could be incorporated into an ODF varied for each type of extract. In the case of LS and PN the maximum extract load was 30 mg per ODF. Increasing extract loads resulted in ODFs that did not stick to the tongue or palate immediately (LS) or in ODFs that broke on removal from the release liner (PN). In case of CB the maximum extract load was only 15 mg per ODF. Increasing extract loads could not be dissolved which resulted in a casting solution with too high viscosity unsuitable for casting.

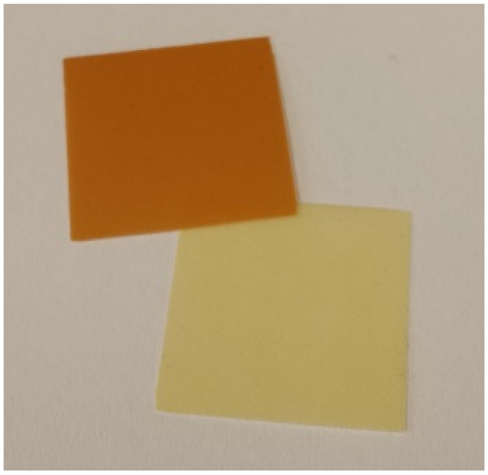

Fig. 1. ODFs containing 5 mg CB (left) and 5 mg ZO (right).

Table 4
Optimized composition of the casting solutions for the extracts.

Extract	HPMC	Carb. 974P[a]	HPC	Disodium EDTA	Trometamol	Glycerol	Benz. Cl.[a]	SiO_2[a]	S[a]	F[a]	Ethanol (wt% of water)
LS										Golden	
5			10			2.4			0.04	0.05	
10			10			2.4			0.08	0.1	10
20			10			4.8			0.16	0.2	30
30			10			–			0.18	0.25	40
PN										Golden	
5			10			2.4			0.04	0.05	
10			10			2.4			0.08	0.1	10
20			10			2.4			0.16	0.2	30
30			10			4.8			0.2	0.3	30
CB										Strawberry	
5	9.81	0.45		0.045	0.45	1.2			0.04	0.05	10
10	9.81	0.45		0.045	0.45	1.2			0.04	0.05	10
15	9.81	0.45		0.045	0.45	4			0.1	0.13	15
ZO										Lemon	
5	9.81	0.45		0.045	0.45	1.2	0.1		0.04	0.05	30
10	9.81	0.45		0.045	0.45	2.4	0.2		0.08	0.1	30
20	9.81	0.45		0.045	0.45	4.8	0.4		0.16	0.2	30
25	9.81	0.45		0.045	0.45	4.8	0.5		0.20	0.25	30
PM										Golden	
5	9.81	0.45		0.045	0.45	1.2			0.04	0.05	30
10			10			2.4		0.5	0.08	0.1	30
20			10			4		0.5	0.16	0.2	30
SC[a]	9.81	0.45		0.045	0.45	1.2					

[a] Carb. 974P = carbomer 974P, Benz.Cl = benzalkonium chloride, SiO_2 = silicon dioxide, S = sucralose, F = flavour, SC = standard casting solution. Water up to 100 g for all formulations presented.

In case of ZO the maximum extract load was 25 mg per ODF. Increasing extract loads resulted in ODFs that were brittle and broke during handling. In case of PM the maximum extract load was 20 mg per ODF. Increasing extract loads resulted in sticky films that could not be punched into the required size.

To increase the extract load per ODF the thickness or the surface area can be increased. However, this might negatively influence acceptance by the user.

All extracts had a characteristic taste that was not always judged as pleasant. Therefore taste masking was considered. An increasing amount of sucralose was added with increasing extract load. The choice of the flavour (see Table 4) was based on the taste of the respective extracts. LS, PN, CB and PM tasted bitter and ZO tasted spicy. The tastes 'golden' and 'strawberry' were used to mask a bitter sensation, while 'lemon' was used to mitigate a spicy note. The addition of sucralose in combination with a flavour sufficiently masked the (slightly) bitter taste of LS, PN, CB and PM. The volunteers in the test panel concluded that the taste of ZO was adequately masked, however, a slight tingling sensation was still felt. Although the perception of taste varies from person to person, the test panel concluded that the taste of ODFs containing herbal extracts was acceptable to good.

3.2. Characterization of the ODFs with varying extract loads

The characteristics of the ODFs with varying extract loads are listed in Table 5.

3.2.1. Surface pH evaluation

ODFs should not provoke mucosal irritation in the mouth especially when they are used on a daily basis.

The surface pH of the ODFs containing CB or ZO decreased with increasing extract load. ODFs containing the extracts PN, LS and PM displayed an influence on the surface pH which was unpredictable in terms of extract load applied. It was probably due to different compositions of the casting solutions. However, all ODFs containing extracts were within the pH range between 4 and 8 as found acceptable in literature.

3.2.2. Thickness and disintegration

The thickness of the ODFs influences the disintegration time. The thicker the ODFs the longer the disintegration time will be. Furthermore, thicker films will lead to an unpleasant feeling in the mouth.

In general an increased extract load led to an increased thickness of the ODFs and an increased disintegration time. However, the relationship between load thickness and disintegration time was not always predictable.

For the ODFs containing the extract ZO the disintegration time and thickness increased with increased extract load. This dose dependent increase was not seen in ODFs containing the extracts CB and PM (Note that the ODFs containing 5 mg PM per ODF contained the film forming agents HPMC and carbomer 974P while the ODFs containing 10 and 20 mg PM per ODF contained the film forming agent HPC). Although a dose-dependent increase in thickness was observed, the disintegration time decreased. This can be explained by an increased brittleness of the ODFs with increasing extract load.

For the ODFs containing the extract PN and LS an increase of the disintegration time and thickness was observed with increasing extract load, except for the ODFs containing 10 mg PN and LS per ODF. This may be caused by the addition of ethanol which was completely evaporated, leading to thinner films and hence a faster disintegration time. This only seems to apply for the lower extract loads. In ODFs containing a higher extract load the increase of thickness can be mainly ascribed to the enhanced extract load while the influence of fast evaporating ethanol comes in second place.

For all ODFs, containing one of the herbal extracts in different extract loads, the disintegration time immediately after preparation was well below the upper limit of 180 s as given as the criterion in the Ph. Eur 8th edition. The disintegration time of the ODFs was

Table 5
Characterization of ODFs containing extracts with different loads (mean ± SD).

Extract	Surface pH (n = 3)	Thickness μm (n = 20)	Disintegration time s, (n = 5) shortly after preparation	Disintegration time s, (n = 5) after 18 months	UoM mg (n = 20)	Loss on drying% (n = 1)
LS						
5	5.1 ± 0.02	102 ± 5	32 ± 4	30 ± 2	30.8 ± 1.9	16.1
10	5.1 ± 0.04	93 ± 6	59 ± 1	57 ± 5	32.3 ± 2.0	20.7
20	5.0 ± 0.08	113 ± 4	42 ± 5	45 ± 2	47.0 ± 1.9	19.1
30	4.9 ± 0.01	138 ± 3	121 ± 11	118 ± 4	53.5 ± 0.9	12.7
PN						
5	5.2 ± 0.01	84 ± 11	23 ± 1	21 ± 2	30.6 ± 1.2	16.8
10	5.2 ± 0.04	82 ± 5	33 ± 5	28 ± 3	31.5 ± 2.5	14.7
20	5.3 ± 0.01	118 ± 8	31 ± 1	29 ± 4	46.1 ± 3.3	15.6
30	5.2 ± 0.01	190 ± 11	16 ± 2	15 ± 2	68.1 ± 4.6	18.3
CB						
5	6.5 ± 0.03	89 ± 5	34 ± 4	32 ± 3	31.7 ± 2.1	12.9
10	6.3 ± 0.13	123 ± 9	26 ± 2	27 ± 2	39.9 ± 2.8	14.1
15	6.0 ± 0.09	192 ± 7	26 ± 1	24 ± 4	55.6 ± 3.1	22.6
ZO						
5	6.9 ± 0.01	113 ± 2	42 ± 2	39 ± 1	31.6 ± 1.5	12.9
10	6.7 ± 0.07	152 ± 5	46 ± 1	44 ± 2	38.1 ± 2.1	16.2
20	6.4 ± 0.11	186 ± 3	52 ± 2	51 ± 1	56.7 ± 1.4	19.2
25	6.3 ± 0.04	187 ± 2	67 ± 4	60 ± 1	60.7 ± 1.1	20.3
PM						
5	5.8 ± 0.01	69 ± 5	46 ± 8	46 ± 5	27.7 ± 1.4	12.3
10	5.3 ± 0.05	87 ± 5	30 ± 5	28 ± 3	30.5 ± 1.8	18.0
20	5.5 ± 0.35	127 ± 7	19 ± 5	17 ± 2	49.4 ± 3.3	18.8

also measured after 18 months of storage and compared to the disintegration time measured immediately after preparation. Although slight differences were seen, none was statistically different. This indicates that the ODFs were physically stable. Based on these results a preliminary shelf life of the ODFs of 18 months seems justified although further analysis of the stability of the herbal extract in the film should be advised.

3.2.3. Loss on drying and uniformity of mass

Loss on drying tests showed that the ODFs contained between 12 and 22% residual water. An increase in water content will result in an increased stickiness of the ODFs. This is unfavourable in terms of handling properties. Besides, a high water content will elicit the growth of micro-organisms (Visser et al., 2015a). The amount of residual water was dose-dependent in case of CB and ZO. For these extracts the film forming agents HPMC and carbomer 974P were used. This dose-dependency of residual water was not observed in ODFs prepared with the film forming agent HPC. This apparent unpredictability can be due to the different casting solutions used containing different film forming agents for each extract and for each extract load. In ODFs prepared with ZO benzalkonium chloride was used to lower the surface tension. Besides, as a surfactant benzalkonium chloride can be used as a preservative. The use of a preservative in ODFs is rarely mentioned in literature (Krampe et al., 2016) but should be considered in case of a high water content or in case microbiological sensitive excipients are used, on the condition that the added amount is safe for oral intake.

All ODFs met the uniformity of mass (UoM) requirements according to the Ph. Eur. 8th edition. Not more than two of the individual masses of the ODFs deviated from the average mass by more than 10% and none deviated by more than 20%.

3.2.4. Mechanical properties

The results of mechanical property measurements are listed in Table 6.

For mechanical properties no requirements are described in the Ph. Eur. 8th edition. There is however a guideline included in monograph 1807 (oromucosal preparations) describing [that] "measures are taken to ensure that [ODFs] possess suitable mechanical strength to resist handling without being damaged". This guideline is translated in the literature on ODFs as follows: an ideal ODFs should have moderately high tensile strength, high elongation at break and a low elastic modulus (Young's modulus) (Hoffmann et al., 2011; Preis et al., 2014).

Table 6
Mechanical tests on ODFs containing extracts with different loads (mean ± SD, n = 6).

Extract	Tensile strength N/mm²	Young's modulus N/mm²	Elongation at break %
LS			
5	0.8 ± 0.2	56.0 ± 9.9	55.6 ± 17.0
10	1.2 ± 0.1	100.5 ± 7.1	32.6 ± 4.1
20	0.7 ± 0.1	64.9 ± 10.0	26.7 ± 2.8
30	0.4 ± 0.1	188.2 ± 45.1	7.2 ± 12.8
PN			
5	0.9 ± 0.1	60.7 ± 13.4	49.0 ± 9.4
10	0.7 ± 0.2	56.8 ± 11.1	30.9 ± 8.0
20	0.5 ± 0.1	51.2 ± 5.7	24.7 ± 6.9
30	0.2 ± 0.1	23.3 ± 4.2	70.1 ± 13.5
CB			
5	2.2 ± 0.2	285.8 ± 32.4	9.4 ± 1.2
10	0.7 ± 0.1	102.7 ± 13.2	6.6 ± 0.9
15	0.4 ± 0.5	28.0 ± 9.5	8.7 ± 2.1
ZO			
5	1.9 ± 0.2	239.8 ± 26.2	10.1 ± 1.6
10	1.2 ± 0.2	155.3 ± 17.6	8.3 ± 0.0
20	0.7 ± 0.1	126.1 ± 9.1	5.5 ± 1.1
25	0.5 ± 0.1	117.1 ± 10.8	5.9 ± 2.5
PM			
5	2.5 ± 0.2	320.6 ± 41.7	8.7 ± 0.9
10	0.9 ± 0.2	73.8 ± 15.5	34.4 ± 7.1
20	0.2 ± 0.1	23.3 ± 4.8	39.2 ± 7.9

It appeared that for all ODFs prepared an increase in extract load resulted in a decreased tensile strength. A higher extract load led to an increased brittleness of the ODFs and hence decreased the force necessary to break or tear the ODFs.

The Young's modulus decreased with increasing extract load for ODFs containing the extracts PN, CB, ZO and PM. For ODFs containing the extract LS a dose-dependent increase was found.

For the extracts LS, PN and ZO a dose dependent decrease in elongation at break was observed, but dose dependency was not found for CB. Glycerol was used in ODFs containing 15 mg CB enhancing elasticity of the ODFs.

In case of PM, different film forming agents were used for different extract loads. The influence of extract load on mechanical properties is therefore not only dose-dependent but also dependent on the formulation used.

Water content has an influence on the mechanical properties of the ODFs. As mentioned in Paragraph 3.2.3. a high water content will lead to sticky films, whereas a low water content will yield brittleness. No clear relationship between water content and the mechanical properties was observed in this study.

Summarized, an increased extract load seems to have influence on the mechanical properties resulting in a decrease in tensile strength, Young's modulus and elongation at break. However, this was not applicable for all extracts. Overall it can be concluded that the ODFs prepared showed good handling properties.

3.2.5. Dynamic vapor sorption

For ODFs containing 5 mg of extract a change in mass below 10 wt.% was observed up to 50% RH (Fig. 2). The uptake of moisture increased rapidly at higher RH values. For ODFs containing an active pharmaceutical ingredient it was found that a moisture content above 10 wt.% increased the stickiness of the ODFs (Visser et al., 2015a). It is to be expected that water uptake will also result in increased stickiness of the ODFs containing herbal extracts.

Storage of the ODFs should be carried out at a relative humidity below 50%. In Indonesia where the humidity can be far above 50% extra attention should be paid to the packaging material and storage conditions. Laminate packaging material with a water and oxygen barrier and good seal integrity might be suitable. The

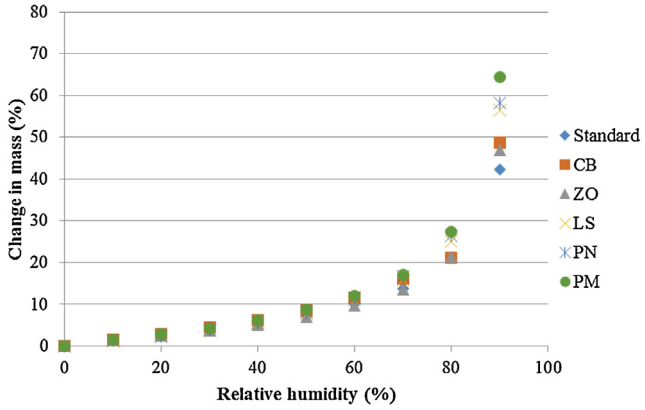

Fig. 2. Change in mass curves of a plain ODF (referred to as 'standard' and prepared from the standard casting solution) and of ODFs each containing 5 mg of plant extract.

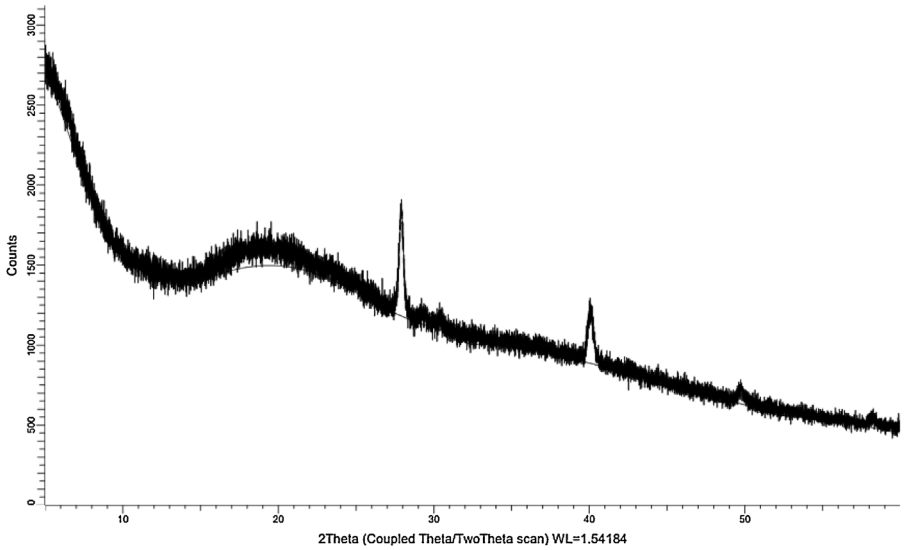

Fig. 3. XRPD pattern of PM extract.

packaging alone is not sufficient enough to protect the ODFs against heat. This could be achieved by climate controlled storage of the ODFs. This, however, applies to ODFs in general.

Despite the different compositions of the ODFs the water sorption was almost similar up to 80% RH. At 90% RH differences were seen. An increased water sorption was seen in ODFs containing 5 mg LS, PN and PM. This was however not reflected in a faster disintegration time compared to ODFs containing ZO or CB. This unpredictable behaviour was also seen in ODFs containing 10 mg extract.

Water uptake is also correlated with disintegration behaviour of ODFs (Preis et al., 2013; Visser et al., 2015a).

3.2.6. Measurement of residual ethanol

The presence of ethanol in oral preparations should be avoided. In the preparation of the ODFs with herbal extracts ethanol was needed as a co-solvent to dissolve the extracts and to lower the viscosity of the casting solution. According to the ICH guidelines (2011) an amount of 50 mg/day corresponding with 5000 ppm is acceptable without justification (ICH guidelines).

All ODFs had a residual ethanol amount far below the limitations of 5000 ppm. Thus the residual amount of ethanol can be considered as safe to the patient. In general values varied between 2 and 8 ppm.

3.2.7. Evaluation of crystallinity with XRPD

XRPD patterns of PM and ZO extracts from the supplier DLBS showed an amorphous halo with some sharp peaks. These sharp peaks may be ascribed to crystallization of (yet unknown) constituents of the extracts and for ZO; also to recrystallization of microcrystalline cellulose and silicon dioxide which were added to the extract as filler during the manufacturing process. Fig. 3 shows a typical XRPD of the herbal extract PM. The XRPD patterns of the other extracts from the supplier DLBS also showed an amorphous halo with some very small sharp peaks, indicating limited crystallinity. In the XRPD patterns of all ODFs containing

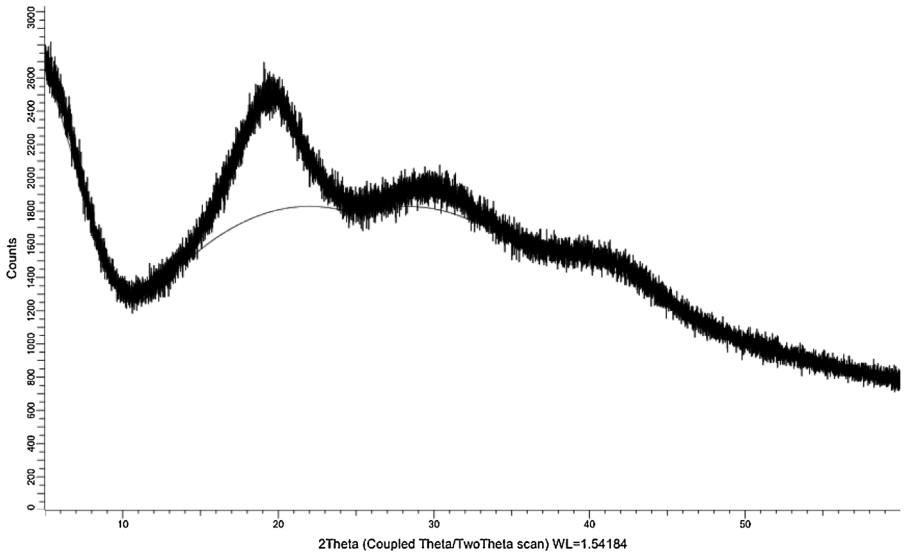

Fig. 4. XRPD pattern of an ODF containing 10 mg PM extract.

Table 7
Rf values of the extracts (as documented by DLBS and as measured) and of ODFs containing extract.

Extract	LS	PN	CB	ZO	PM
DLBS Rf 254 nm	Black spot at ±0.50–0.60	Black spot at ±0.50–0.60			Black spot at ±0.1 and ±0.6
DLBS Rf 366 nm	Black spot at ±0.50–0.60	Brown spot at ±0.50–0.60	Blue fluorescence spot at ±0.6	Brownish spots at ±0.30, ±0.40, ±0.45 and ±0.65	Black spot at ±0.1 and ±0.6
DLBS Rf visible light			Green spot at ±0.5 and yellow spot at ±0.6	Brownish spots at ±0.30, ±0.40, ±0.45 and ±0.65	Brownish-yellow spot at ±0.1
Extract Rf 254 nm	Black spot at ±0.50–0.60				Black spot at ±0.1 and ±0.6
Extract Rf 366 nm	Black spot at ±0.50–0.60	Brownish to black spot at ±0.5–0.6	Blue fluorescence spot at ±0.6		Black spot at ±0.1 and ±0.6
Extract Rf visible light		Brownish to black spot at ±0.5–0.6	Green spot at ±0.5 and yellow spot at ±0.7	Brownish spots at ±0.30, ±0.40, ±0.45 and ±0.65	Brownish to yellow spot at ±0.1
ODF Rf 254 nm	Black spot at ±0.50–0.60				Black spot at ±0.1 and ±0.6
ODF Rf 366 nm	Black spot at ±0.50–0.60	Brownish to black spot at ±0.5–0.6	Blue fluorescence spot at ±0.6		Black spot at ±0.1 and ±0.6
ODF Rf visible light		Brownish to black spot at ±0.5–0.6	Green spot at ±0.5 and yellow spot at ±0.7	Brownish spots at ±0.30, ± 0.40, ±0.45 and ±0.65	Brownish to yellow spot at ±0.1

the five different extracts up to an extract load of 20 mg only an amorphous halo was observed indicating no crystallinity. Fig. 4 represents an XRPD of an ODF with PM. At higher extract loads a few small peaks appeared in the XRPD patterns indicating some recrystallization.

3.2.8. Qualitative profiling of herbal extracts and ODFs containing herbal extracts with TLC

TLC profiles of the original extracts were compared to TLC profiles of the ODFs containing the extracts. For the extract loaded ODFs, solid phase extraction was needed to separate the active components from ingredients of the film-forming material that disturbed the elution process in the TLC analysis. The Rf-values of the original extract and the ODFs containing extract are listed in Table 7. The different spots and their Rf-values found in our study with extracts and ODFs containing extracts corresponded with the data documented by DLBS. The profile of each extract obtained from the OFDs was similar to that of the corresponding unprocessed extract. This indicates that the extracts remained their integrity during the preparation of the ODFs. Fig. 5 shows a typical example of the TLC profile of ZO extract and ODFs containing ZO.

4. Conclusion and perspective

In conclusion, suitable ODFs can be prepared with extracts of LS, PN, CB, ZO and PM. For each extract and extract load the standard casting solution containing the film forming agents HPMC and carbomer 974P needed to be adapted by using the co-solvent ethanol, surfactant benzalkonium chloride or filler silicon dioxide. For LS and PN and the higher extract loads of PM a new casting solution was developed containing the film forming agent HPC.

In case of ZO the fillers microcrystalline cellulose and silicon dioxide needed to be removed prior to ODF preparation. The fillers led to an unacceptable appearance of the ODFs.

Many herbal extracts have an unpleasant, (mainly) bitter taste, therefore taste masking is needed. According to the test panel the taste of the extracts was successfully masked by the addition of sucralose and flavour. All ODFs had an acceptable surface pH, showed fast disintegration time, complied with the requirements of the uniformity of mass and showed good handling properties. The analytical profiling with TLC yielded the similar patterns for the original extract and the ODF prepared thereof, meaning that the ODFs can be used for the same indication as the extract itself.

There was one important limitation in incorporation extracts in ODFs. The maximum extract load was limited and varied per extract. For *jamu* relatively high extract loads are needed to achieve a therapeutic level. The extract load can be increased by increasing the casting height and/or increasing the size of the ODF, keeping in

Fig. 5. TCL profile of ZO extract (left) and ODFs containing ZO (middle and right).

mind that a thicker and larger ODF may be less favorable in terms of patient (or user) acceptance.

Herbal extracts contain many ingredients such as phenols, alkaloids, flavonoids, terpenoids, tannins and other typical secondary metabolites. These main active ingredients as well as other plant constituents may influence the consistency of the casting solution and the ODFs prepared thereof. In this study no clear relationship was found between major groups of secondary metabolites present in the extract and the quality of the ODF.

The ODFs appeared to be physically stable after 18 months of storage, reflected in unchanged disintegration properties. A preliminary shelf life for that period seems justified, although further (chemical) analysis should be carried out to confirm this.

All ODFs should be adequately stored and appropriately packaged to protect them against humid conditions. In this study benzalkonium chloride was used at low and safe concentration to act as a surfactant to obtain a better spread over the release liner. Benzalkonium chloride can also serve as a preservative.

Conflict of interest

None.

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