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Formulation and evaluation of orally disintegrating film (ODF) containing piperine-succinic acid cocrystal

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ABSTRACT

Piperine is a type of alkaloid found in plants of the Piperaceae family, including *Piper nigrum* and *Piper longum*, which has numerous pharmacological properties and is being developed as a nutraceutical. However, its poor solubility makes delivering in effective doses for therapeutic purposes challenging. To overcome this limitation, the cocrystals of piperine and succinic acid was prepared, which are more soluble, and then formulated into orally disintegrating films (ODFs) for better delivery. The cocrystals were formed using the slurry method, while the ODFs were made using the solvent-casting method with different concentrations of hydroxypropyl methylcellulose (HPMC) and polyethylene glycol (PEG) 400. The resulting films were evaluated for various parameters, such as their organoleptic characteristics, weight and thickness uniformity, pH, moisture content, swelling properties, and disintegration time. The results showed that the ODF with 6% HPMC as a film-forming polymer and 0.6% PEG 400 as a plasticizer loaded with 10 mg of piperine in the form of piperine-succinic acid cocrystal was the best formula. This ODF formulation disintegrated in less than one minute and was found to be a good film with uniform content.

Keywords: Cocrystal piperine-succinic acid, orally disintegrating film, solvent casting, disintegration time

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INTRODUCTION

Piperine ($C_{17}H_{19}NO_3$) is one of the secondary metabolites of the alkaloid group, which is famous for its spicy taste. Piperine is present in the fruit and roots of *Piper nigrum* and *Piper retrofractum*, both of which belong to the Piperaceae family (Chopra et al., 2017; Tiwari et al., 2020; Vasaravirama & Upender, 2014). These alkaloids have shown that they have many benefits for health (Gorgani et al., 2017). Piperine has antihyperlipidemic, antioxidant, antibacterial, analgesic, anti-inflammatory, hepatoprotective, antifungal, antimicrobial, antidepressant, and anticancer activities (Umadevi et al., 2013; Vijayakumar et al., 2004; Zarai et al., 2013). Piperine is widely used as traditional medicine, especially to improve memory for the elderly and to support intelligence in children (Katiyar et al., 2016; Umadevi et al., 2013; Vijayakumar et al., 2004; Zarai et al., 2013). Piperine is one of the natural ingredients that can be classified as a nutraceutical substance with health benefits in the form of preclusion and disease treatment (Dudeja & Gupta, 2017; Smilkov et al., 2019). Nutraceuticals can also be taken as dietary supplements (Télessy, 2018).

The pharmacological effect of piperine in pharmaceutical preparations is underutilized because piperine is practically insoluble at approximately 40 mg/L in water (Vasaravirama & Mahesh Upender, 2014). Piperine is classified in BCS class II based on its characteristics in the Biopharmaceutical Classification System (BCS) classification, indicating that it has low solubility in water and high permeability (Oladimeji et al., 2018). Solubility is one of the essential physicochemical properties to predict the gastrointestinal absorption rate of active drug substances that will affect bioavailability (Alatas et al., 2019; Aungst et al., 2002).

Various techniques are employed to address the challenge of enhancing drug solubility and dissolution rates. Several methods have been found effective in improving the solubility and dissolution rate of piperine. These include the formation of inclusion complexes (Ezawa et al., 2018), the use of nanosuspensions (Zafar et al., 2019), and the formation of multicomponent crystals with several coformers: succinic acid, nicotinic acid, and saccharin (Sari et al., 2019; Zaini, Afriyani, et al., 2020; Zaini, Riska, et al., 2020). These methods have been successful in addressing the challenge of low solubility and dissolution rate of piperine, which has significant implications in improving its therapeutic potential. Previously, Zaini reported the formation of piperine-succinic acid multicomponent crystals by the slurry method. In developing this multicomponent crystal, succinic acid was chosen as a conformer to improve piperine's solubility and dissolution rate. The solubility of piperine was found to be 3.9 times higher when it was in the form of a piperine-succinic acid cocrystal at a 2:1 molar ratio compared to its intact form. Additionally, the dissolution rate of piperine was also observed to be doubled in the cocrystal form (Zaini, Afriyani, et al., 2020).

Oral solid dosage forms are the most commonly available drugs on the market (Siddiqui et al., 2011). Oral administration is the most convenient and preferred route for drug delivery due to its various benefits over other routes. However, it is a known fact that many patients, particularly the elderly, pediatrics, and those with medical conditions such as dysphagia, find it difficult to swallow tablets, which can pose a choking hazard. The use of tablets becomes considerably difficult due to this, leading to a necessity to create alternative forms that can accommodate the requirements of these patients (Bhyan et al., 2011; Kalyan & Bansal, 2012; Ouda et al., 2020).

Oral dissolving tablets (ODT) and orally disintegrating films (ODF) are innovative drug delivery systems designed to address challenges associated with tablet usage. They are designed to dissolve or disintegrate easily in the mouth, enabling effective drug delivery. Orally disintegrating film (ODF) formulations offer improved patient comfort and adherence. The primary benefits of this type of medication are quick disintegration upon contact with the tongue, moistening by saliva, and the discharge of the active drug substance from the dosage form. Compared with other oral preparations, ODF usually results in increased bioavailability and a faster action onset since it can be directly absorbed in blood vessels in the mouth and avoid first-pass metabolism (Irfan et al., 2016; Lee et al., 2017).

ODF preparations mainly contain active substances, film-forming polymers, plasticizers, and several additional components. In general, ODF is formulated by utilizing hydrophilic polymers that facilitate fast disintegration when they come in contact with saliva (Irfan et al., 2016). The plasticizer used in the

formulation must also be compatible with the type of film-forming polymer (Patil & Shrivastava, 2014; Sharma & Kaur, 2015). The choice of the film-forming polymer has a specific effect on the quality of the film formed. In previous research, it was shown that several polymers, such as tragacanth, chitosan, gelatin, and acacia, showed a sticky film that was difficult to remove from the mold. Polymers such as HPMC can form good films because they produce films that are transparent, strong, flexible, and easy to withdraw from the mold (Febriyenti et al., 2008). Many studies comparing HPMC with other polymers have shown that HPMC polymers can form films that are more flexible, smoother, transparent, and have a faster drug disintegration time (Abd & Mostafa, 2018; Pahare et al., 2013). The selection of plasticizers that reduce the transition temperature and increase viscosity makes the film flexible and reduce the fragility of the film so that it is not easily broken can affect the quality of the ODF preparation (Abd & Mostafa, 2018; Febriyenti et al., 2008; Sharma & Kaur, 2015). Several studies found that the combination of HPMC as a film-forming agent and PEG 400 as a plasticizer was a suitable choice of materials. The combined polymer and plasticizer can form an optimal formula (Ito et al., 2016; Sheskey et al., 2020).

There are several methods available to produce orally disintegrating films (ODF), including hot melt extrusion, electrospraying, and electrospinning, but the most commonly used method is solvent casting. This method is highly preferred because it is suitable for water-soluble polymers, does not require exposure to high temperatures, making it an ideal choice for heat-sensitive ingredients, provides excellent thickness uniformity, and results in clear and physically stable films compared to other methods (Febriyenti et al., 2008; Sharma & Kaur, 2015). Thus, this research aimed to formulate piperine-succinic acid cocrystal formula into an ODF formula with several piperine-compatible excipients, HPMC as the film-forming polymer, and PEG 400 as the plasticizer.

MATERIALS AND METHODS

Materials

Piperine (BOC Sciences, USA), succinic acid (Merck, Germany), ethyl acetate (Merck, Germany), ethanol pro analysis (Merck, Germany) hydroxypropyl methylcellulose/ HPMC (Ashland, USA), polyethylene glycol/PEG 400 (Clariant, USA), sorbitol (Roquette, France), nipagin (Ueno Fine Chemicals, Japan), citric acid (Merck, Germany), menthol (Anhui Province, China), phosphate buffer 6,8, and distilled water.

Methods

Preparation of PSA (Piperine-Succinic Acid) cocrystal

The synthesis of PSA cocrystals with a 2:1 molar ratio using the slurry method previously described by Zaini. The method involved grinding precise amounts of piperine (0.078 g) and succinic acid (0.0170 g) in a mortar with ethanol, resulting in a powder referred to as the liquid-assisted grinding (LAG) sample. The LAG sample was then added to a mixture of piperine, succinic acid, and ethyl acetate in a sealed glass container and stirred for more than 24 hours using a magnetic stirrer. The PSA cocrystals were obtained by filtration and stored in a desiccator until further analysis (Zaini, Afriyani, et al., 2020).

Characterization of PSA cocrystal by differential scanning calorimetry (DSC)

The thermal properties of piperine, succinic acid, and the cocrystal were analyzed using a DSC apparatus (Shimadzu DSC-60 Plus, Japan) calibrated with indium. About 4 mg of each sample was loaded into an aluminum pan and subjected to a temperature range of 30°C to 250°C at a heating rate of 10°C/min. (Zaini, Riska, et al., 2020).

Optimization of orally disintegrating film formula

The base film formulation was improved by creating six different formulations that contained varying amounts of HPMC, the polymer used in film formation, and PEG 400, the plasticizer. Table 1 displays the entire set of formulas used.

Table 1. Formulation orally disintegrating film base

Formulation	F1	F2	F3	F4	F5	F6
HPMC (mg)	400	600	400	600	400	600
PEG 400 (mg)	60	60	120	120	180	180
Sorbitol (mg)	300	300	300	300	300	300
Menthol (mg)	20	20	20	20	20	20
Nipagin (mg)	2	2	2	2	2	2
Citric acid (mg)	10	10	10	10	10	10
Aquadest (g)	Ad 10	Ad 10	Ad 10	Ad 10	Ad 10	Ad 10

Each formula was subjected to organoleptic evaluation and disintegrating time to determine the best formula. To manufacture an ODF loaded with PSA cocrystal (ODF-PSA Cocrystal), the cocrystal was added, which is equivalent to 10 mg of piperine.

Preparation of ODF-PSA cocrystal

The ODF-PSA cocrystal was formed by solvent casting method using a petri dish. All materials needed are weighed. Distilled water was used to dissolve citric acid, sorbitol, and polyethylene glycol 400 (mixture A). HPMC was soaked in mixture A and stirred homogeneously. Menthol and nipagin were dissolved and stirred in 50% ethanol (mixture B) until homogeneous, and also PSA cocrystal was in 50% ethanol (mixture C) stirred until homogeneous. Mixtures A, B, and C are mixed in one container and stirred until thick gel-like liquid forms. The gel pH value was measured and adjusted if needed to meet the range of 6.8-7.2. Subsequently, the mixture was left to stand to eliminate any trapped air bubbles, before being poured into molds and dried in an oven at 40 °C. The dried film was then taken out of the mold and cut into 2x2 cm dimensions.

Evaluation of ODF-PSA cocrystal

Organoleptic characteristics

The organoleptic characteristics of the ODF preparation were determined visually, including the film's shape, taste, color, homogeneity, odor, and texture (Bala et al., 2013; Kalyan & Bansal, 2012).

Measurement of film weight and thickness uniformity

Measurement of weight uniformity was carried out for six films by weighing films one by one using a micrometer screw gauge that had been calibrated, and the weight of each film should not deviate significantly from the average weight (Galgatte et al., 2013). To determine the thickness of the film, measurements were taken at the center and the four corners. The mean thickness and weight of the film were then computed, with a requirement for the standard deviation to be lower than 5%. (Asija et al., 2013; Irfan et al., 2016).

pH measurement

To determine the pH of the film preparation, a pH meter was used after calibration with buffer solutions. Both the solution and dry film were assessed, with each dry film sample being dissolved in 3 mL of distilled water. The acceptable pH range for the ODF was determined to be between 6.8 and 7.2 (Chandra et al., 2010; Kalyan & Bansal, 2012).

Moisture content

To determine the moisture content of the films, a moisture balance test was performed at a temperature of 105°C. The acceptable moisture content level for the orally disintegrating film (ODF) was found to be less than 10% (Bala et al., 2013).

Swelling index

To assess the swelling index of the film, a wired basket was utilized, and a simulated liquid with a pH equivalent to that of saliva (pH 6.8 phosphate buffer) was used. Initially, the film was weighed, and the weight was recorded as Wo. The film was placed in the basket and allowed to soak in 15 mL of buffer for five seconds. The soaked film was subsequently weighed (Wt), and this process was repeated until the film broke (Chandra et al., 2010; Irfan et al., 2016). Three films for each formula were subjected to measurements. The swelling index (SI) was calculated using equation 1.

$$SI = \frac{Wt-Wo}{Wo} x100\% \ldots\ldots \quad (1)$$

Disintegrating time

Measurements of disintegrating time were carried out on three films for each formula. There are two methods to determine the disintegrating time of film preparations the slide frame method and the petri dish method were used in this evaluation (Bala et al., 2013; Chandra et al., 2010). The slide frame method is done by placing the film on a petri dish in a horizontal position, dripping it with 6.8 phosphate buffer, and then counting the disintegrating time until the film is perforated (Asija et al., 2013). Meanwhile, the petri dish method is carried out by placing the film on a petri dish and then adding 2 mL of 6.8 phosphate buffer solution onto the film until its destroyed by agitation in an orbital shaker at 30-50 rpm (Asija et al., 2013).

Content uniformity test

One sheet of ODF-PSA Cocrystal dissolved in 100 mL ethanol p.a in a volumetric flask. This solution the diluted to obtain a concentration of 4 µg/mL in a 10 mL volumetric flask. The amount of piperine in each ODF was analyzed with spectrophotometry UV-Vis and measured at λ 342.2 nm. Tests were carried out for ten sheets of ODF. The average drug content for ten sheets of ODF-PSA cocrystal was calculated. The content uniformity should meet the 6th edition of Farmakope Indonesia (Indonesia Pharmacopoeia) requirement, in which the acceptability value (NP) must be less than 15 (Kementerian Kesehatan RI, 2020).

RESULT AND DISCUSSION

Differential scanning calorimetry (DSC) analysis is a valuable technique for examining the thermal transitions and physical properties of polymeric materials. By utilizing DSC, it is possible to estimate the fusion of materials and calculate associated values such as entropy and enthalpy (Singh & Singh, 2022). Based on the formed DSC thermogram, the melting point of piperine-succinic acid cocrystal (109.31°C), intact piperine (131.63°C), and succinic acid (189.74°C) can be seen in Figure 1. The PSA cocrystal has a lower melting point (109.31°C) compared to intact piperine (131.63°C). The lower melting point indicates a weaker intermolecular bond within the cocrystal, which causes the lattice energy to be frailed and often correlated to the increase of the solubility (Zaini, Afriyani, et al., 2020). The thermogram confirmed that the PSA cocrystal was formed in this research.

The base is the key to the quality of the ODF. The base formula optimization was carried out to determine the optimum ODF base by some physical properties evaluation. The optimization results obtained at F1, F3, and F5 were sticky, thin, and wet masses that could not be removed from the mold; thus, they were unable to form a film to be evaluated. The result showed that 4% HPMC in the ODF base formula failed to form a good film, which is in the range of HPMC used as film former 2-20%. Moreover, a combination of HPMC with PEG 400 as a plasticizer can increase the water intake by the ODF (Sheskey et al., 2020). The film of F2, F4, and F6 can be seen in Figure 2, forming a smooth, flexible, not sticky, and transparent film, although F6 was slightly thicker than the other formula.

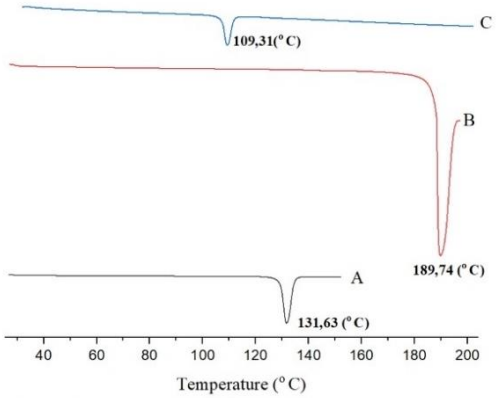

Figure 1. Thermogram overlay of piperine (A), succinic acid (B), and piperine-succinic acid cocrystal (C)

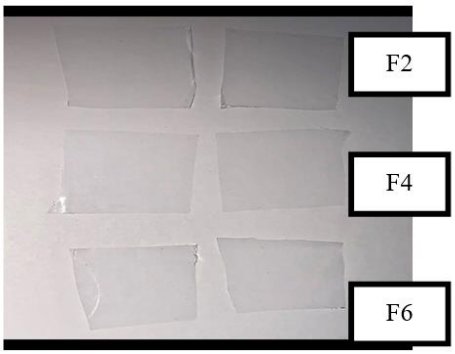

Figure 2. F2, F4, and F6 film optimization

The evaluation of the disintegrating time of the film was used to determine how fast the film could be dissolved when used by the patient. The requirement for the film to disintegrate should be less than 1 minute when placed on the tongue (Han et al., 2019). In this study, two distinct methodologies were employed to investigate the disintegration time of the orally disintegrating film (ODF) base. Specifically, the petri dish method and the slide dish method were utilized to assess the rate of disintegration of the ODF base. The Petri dish method imitates the process when the film is placed into the mouth and then crushed by the movement of the tongue. Meanwhile the slide dish method, the film is placed in a petri dish and then dripped with 6.8 phosphate buffer on the film until the film forms a hole to emulate the film when it is inserted into the mouth without any movement of the tongue (Patil & Shrivastava, 2014). The average disintegrating time of the optimization film formula can be seen in Table 2.

Table 2. Disintegration time data for ODF base F2, F4, and F6

Formula	Average disintegrating time of petri dish method ± SD (seconds)	Average disintegrating time of slide dish method ± SD (seconds)
F2	36.74 ± 0.31	40.38 ± 0.80
F4	40.89 ± 0.78	43.30 ± 0.94
F6	49.04 ± 1.25	46.28 ± 0.39

Based on the evaluation results in Table 2, the fastest disintegrating times were given by F2. The formula shows a correlation between disintegrating time and the difference in the concentration of the

plasticizer, in which the less plasticizer used in the formula will, the slower disintegrating time. This phenomenon is most plausibly attributed to the impact of an elevated concentration of plasticizer on the film's strength (Cilurzo et al., 2010; Patil & Shrivastava, 2014). The results also showed that the disintegrating time in the petri dish method and the slide had significant differences in the time needed for each formula to break. However, F2 showed a faster disintegration time in both tests. Based on the organoleptic and disintegration time evaluation results that have been carried out for each formula, the F2 was selected to be loaded with PSA cocrystal.

The sensory evaluation of PSA cocrystal films is a crucial stage in the development process, as these films will stay in the mouth for an extended period of time. The product must have acceptance criteria for the patient, including a non-bitter taste, an attractive shape, and a smooth and homogeneous surface (Siddiqui et al., 2011). The results of the organoleptic examination of piperine-succinic acid cocrystal films can be seen in Table 3.

Table 3. Data from organoleptic examination of ODF-PSA cocrystal

F2	Color	Odor	Homogeneity	Texture	Taste
Cocrystal piperine-succinic acid	Yellowish white	Typical	Homogeneous	Smooth, flexible, not sticky	Spicy sweet

Table 3 shows that the ODF-PSA cocrystal has a yellowish-white color caused by the active substance of the cocrystal and has a characteristic piperine odor. The texture of the film is smooth, flexible, and not sticky, and the film has a sweet taste and a slightly spicy sensation. Therefore, in terms of film characteristics, it is to the requirements (Abd & Mostafa, 2018; Bala et al., 2013). A picture of the cocrystal films of piperine-succinic acid can be seen in Figure 3.

Figure 3. The appearance of F2 ODF base loaded with PSA cocrystal

The homogeneity of the weight of the film was assessed with an analytical balance, while the thickness of the film was determined using a micrometer. The test was carried out on six sheets of film (Kalyan & Bansal, 2012). The results of the assessment of the weight and thickness consistency of the piperine-succinic acid cocrystal films can be seen in Table 4.

Table 4. Evaluation data of orally disintegrating film loaded with piperine-succinic acid cocrystal

Evaluation	Result
Weight (g)	0.0823 ± 0.001[a]
Thickness (mm)	0.142 ± 0.0016 [a]
Solution pH	6.86 ± 0.004 [a]
Moisture content (%)	7.933 ± 0.311 [a]
Swelling index at 15 s (%)	142.92 ± 4.58 (fully dissolved at 20 s)[b]
Petri dish disintegration time (s)	41.367 ± 1.538 [b]
Slide dish disintegration time (s)	48.227 ± 0.352 [b]

[a] : n=6
[b] : n=3

The data shows the average film weight is 0.0823 ± 0.001 g, and the average film thickness is 0.143 ± 0.002 mm. The results of the standard deviation evaluation of weight and thickness uniformity in each formula are less than 5% of the average and show that the weight and thickness of each film in the same formula have weights and thicknesses that are not significantly different, indicating that this method produced a good uniformity in each film weight and thickness. The average ODF-PSA Cocrystal thickness was laid within the requirements of 5-200 μm (Patil & Shrivastava, 2014).

The film pH was evaluated on three sheets of film using a calibrated pH meter (Bala et al., 2013; Kalyan & Bansal, 2012). The average pH of the ODF-PSA cocrystal is 6.86 ± 0.004. This fits within the pH range in the literature from 6.8 to 7.2. ODF disintegration can be facilitated by a slightly acidic pH that increases the rate of saliva production (Patil & Shrivastava, 2014).

Moisture content testing is carried out using a moisture balance. The average moisture content of the film is 7.933 ± 0.311%, while the requirement is below 10%. It was expected that this number would form good mechanical properties of the film that are not brittle and minimize the possibility of microbial growth (Bala et al., 2013).

The swelling index evaluation was carried out using 6.8 phosphate buffer as a saliva fluid simulation. The increase in film weight was determined by weighing the film at intervals of every 5 seconds until the film was fully disintegrated (Ketul et al., 2013; Patil & Shrivastava, 2014). As shown in Table 4, the average swelling index of piperine-succinic acid cocrystal films is less than 20 seconds. This result met the requirement that the films should swell and disintegrate in less than 30 seconds so that the release of the active ingredient from the film is predicted to occur in a short time. This can be related to patient comfort, where adhesion between the film and the tongue will happen in a short amount of time (Peh & Wong, 1999).

The disintegrating time was evaluated by the petri dish method and the slide dish method. The average disintegrating time of the film using the petri dish method is 41.367 ± 1.538 seconds, and the slide dish method is 48.227 ± 0.352 seconds. Thus it also met the existing requirements, which was below one minute.

The content uniformity test was carried out to measure the drug content in the film and evaluate the uniformity of the drug in the film and whether it was within the specified content range. The piperine-succinic acid cocrystal active substance in the formulated film contains below 25 mg or 25% of the active substance (Kementerian Kesehatan RI, 2020). Ten films were subjected to the content uniformity test, where the content of each film was quantified, and the acceptance value was calculated according to the formula specified in the Indonesian Pharmacopoeia VI edition. The calculation results obtained an average percentage of piperine-succinic acid cocrystal film content of 99.8 ± 0.322%. The acceptability value (NP) of the content uniformity test was 0.773. The average value of the percentage of content uniformity and the acceptability value of the content uniformity test on the piperine-succinic acid cocrystal ODF obtained has met the criteria required by the Indonesian Pharmacopoeia edition VI, with a maximum acceptability value limit of less than or equal to 15 (Kementerian Kesehatan RI, 2020).

CONCLUSION

ODF with 6% HPMC as film-former polymer and 0.6% PEG 400 as plasticizer loaded with 10 mg piperine in the form of piperine-succinic acid cocrystal formed a good film that can be dissolved in less than 1 minute.

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