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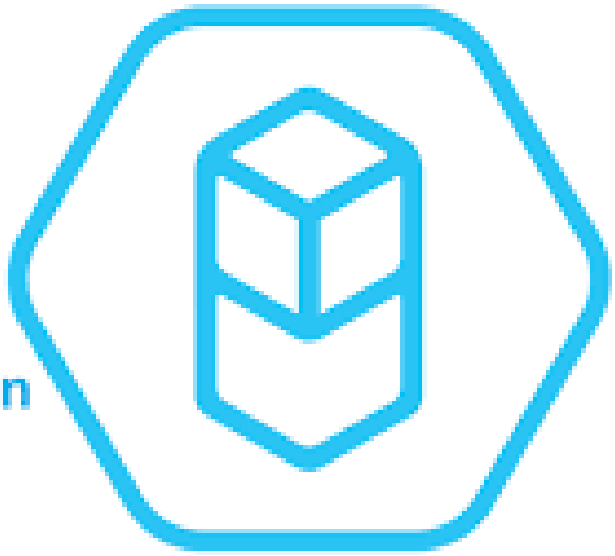

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IAI SPECIAL EDITION

RESEARCH ARTICLE

Influence of dispersing solvent on curcumin dissolution from solid dispersions prepared using hydroxypropyl methylcellulose-polyvinylpyrrolidone K30

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Keywords
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Abstract

Background: Preparation of lipophilic compounds into solid dispersion formulations (SDs) has been credited with increasing their dissolution rate. Understanding the role of the dispersing solvent is crucial to the SDs preparation. Drug/carrier-solvent immiscibility may decrease the dissolution rate. **Aim**: This work aimed to study the effect of different dispersing solvents on a curcumin dissolution. **Method**: A solvent evaporation method was used in the SD preparation. The formulation was prepared at 30% w/w drug load contained *Curcuma longa* and a carrier mixture of Hydroxy Propyl Methylcellulose (HPMC)/ Polyvinylpyrrolidone K30 (PVP K30). As for the dispersing solvent, the study used ethanol, ethyl acetate, and ethanol/ethyl acetate solvent mixture. The dissolution profile was obtained and analysed for the dissolution-efficiency (DE). **Result**: The DE values of 38.5%, 37.8%, and 32.0% were obtained using ethanol, ethyl acetate, and ethanol-ethyl acetate mixture. **Conclusion**: The results show that there is a significant impact of using different SD solvents on curcumin dissolution.

Introduction

Curcuminoids are natural polyphenolic compounds. Curcuminoid is the collective name for three components of *Curcuma longa,* i.e. curcumin, dimethoxy curcumin, and bis-dimethoxy curcumin. Within this group of curcuminoids, curcumin is the major compound (Nelson *et al.*, 2017). Numerous shreds of evidence have been reviewed on the therapeutic potential of curcumin, especially the ones related to its anti-oxidant and anti-inflammatory properties (Tabrizi *et al*., 2019). However, its poor bioavailability after oral administration limits the function of curcumin in a clinical setting (Gupta, Patchva, & Aggarwal, 2012).

Many reasons have been proposed to account for the poor oral bioavailability of curcumin, e.g., instability issue and rapid metabolism. However, poor water solubility and dissolution are the most reported description of its poor bioavailability for curcumin. The strong inter-and intra-molecular hydrogen bonding between curcumin molecules contributes to its remarkably low solubility and dissolution rate in water (Qi, Chang, & Zhang, 2008).

The study applied the technical method of solid dispersions (SDs) to improve the solubility of curcumin. Thus, it also increases the absorption of the drug in the gastrointestinal tract. SDs are defined as the dispersion of one or more active ingredients in a hydrophilic matrix, and it is prepared by fusion or solvent evaporation method employing lyophilisation, spray drying, or vacuum rotary evaporator (Leuner & Dressman, 2000). The mechanism underpinning solubility enhancement in SDs might be due to particle size reduction, improved wetting, an opportunity of dispersion at a molecular level, or through amorph formation (Janssens & Van den Mooter, 2010).

SDs produced via the solvent evaporation method involve dissolving lipophilic drugs and the carriers in a solvent or solvent mixture, followed by an evaporation method. Drug release during a dissolution study can be

rationally correlated with the variant of dispersing solvents or solvent mixtures used before the evaporation step (Rizi *et al.*, 2011). It was reported by Chen and colleagues (2018) that the dissolution rate of felodipine was affected by the solvent type; the highest dissolution rate was achieved by dispersing the drug in ethanol-dichloromethane compared to the organic solvent alone (Chen *et al*., 2018). Understanding drug-carriers-solvent miscibility is necessary because liquid-liquid phase separation can occur in the drying step, which might lead to crystal formation resulting in poor water solubility and dissolution. Therefore, this study aimed to investigate the impact of different organic solvents (ethanol, ethyl acetate and ethanol-ethyl acetate solvent mixture) on curcumin dissolution in SD formulations of *C. longa* extract-PVP K30/HPMC.

Materials and methods

Curcumin as a reference standard (USP) with a purity of 98% was obtained from Sigma-Aldrich (St. Louis, United States). *C. longa* extract was given by PT Phytochemindo Reksa Bogor, Indonesia. PVP K30 was provided by PT Konimex, Solo, Indonesia. HPMC and PVP K30 were supplied by PT Konimex (Solo, Indonesia). Pro-analytical grades of methanol, ethanol, ethyl acetate, Sodium lauryl sulfate (SLS), and sodium dihydrogen phosphate were obtained from Merck (Darmstadt, Germany). Water was prepared using a Milli-Q IQ water purification system.

Preparation of the solid dispersions formulation (SDs)

Ethanol, ethyl acetate, and ethanol/ethyl acetate mixture of 1/1 (v/v) were used as the dispersing solvents to prepare the drug-carrier mixtures. The carrier was a PVP K30/HPMC mixture in a 2:1 weight ratio. Table I shows the composition of solid dispersions preparation. The final concentration of the dissolved material (*C. longa* + PVPK30/HPMC) was 11.1 mg/mL, while the drug load was designed for 30% (w/w) of curcumin as calculated in the dried product.

Table I: The composition used in the solid dispersion preparation

Formula	System	*C. longa* extract (g)	PVP K30 (g)	HPMC (g)	Organic solvent (ml)	Water (ml)
1	E	1.500	2.334	1.166	375	75
2	E-Ac	1.500	2.334	1.166	375	75
3	E/E-Ac (1/1)	1.500	2.334	1.166	187.5:187.5	75

E = ethanol; **E-Ac** = ethyl acetate.

The Buchi Rotavapor R-300 evaporated the solvent (Buchi, Flawil, Switzerland) at 50°C and vacuum pump setting of 175 mbar for ethanol or ethanol-ethyl acetate mixture and 240 mbar for ethyl acetate. The obtained samples were subsequently dried in a vacuum oven at 50°C for another 24 hours. The dried product was grounded in a mortar and sieved using 60 mesh (Kaewnopparat *et al*., 2009). After that process, the yield was determined. The dried SD sample was stored in a desiccator until use. The drug load of the SD formulations was determined by dissolving the dried SD samples in methanol followed by detection in a UV-Vis spectrophotometry (Shimadzu 1800, Shimadzu Co. Ltd., Kyoto, Japan) at 420.5nm. The curcumin content was quantified based on a calibration sample in which it demonstrates the linear equation of y = 0.1278x + 0.0246 at the correlation coefficient of 0.9990.

Preparation of Physical Mixture (PM) sample

The control experiment used the PM sample. To prepare the PM sample, *C. longa* extract and PVPK30/HPMC at a 2:1 weight ratio were simply mixed using mortar and pestle. The powder was sieved through 60 mesh size before use (Kaewnopparat *et al*., 2009).

Dissolution study

In this study, the SD and PM formulations were tested on a SOTAX AT7 USP type II dissolution tester. The dissolution test was performed in 900 mL of 0.5% SLS in 20mM sodium phosphate buffer at 37 ± 0.5°C with 75rpm agitation. In order to maintain a sink condition, 5.0mL of dissolution medium was sampled at regular intervals. It was detected using a UV-Vis spectro-photometer at 430nm (Shimadzu 1800, Shimadzu Co. Ltd., Kyoto, Japan). Plotting the absorbance against the calibration equation of y = 0.1556x + 0.0043 yielded the curcumin concentration. The dissolution profile obtained in the 150 minutes study was analysed using a dissolution efficiency (DE) approach based on the equation below.

$$DE_t = \frac{\int_{t1}^{t2} y.\,dt}{y_{100}.\,t}) \times 100\%$$

DE_t: Dissolution efficiency at a time (t); y: Area under the curve of the dissolved drug at time t; y_{100}.t: Rectangle area where 100% of drug dissolved at time t

Results

Different solvents resulted in yield variation. The yield of SD products were 62.8%, 75.6%, and 66.0% for ethanol, ethyl acetate, and ethanol/ethyl acetate (1:1).

The colour of dried powder varied according to different solvents (Figure 1). Ethanol results in brownish-yellow colour (Figure 1a), ethyl acetate and ethanol-ethyl acetate mixture result in yellow colour (Figure 1b,c).

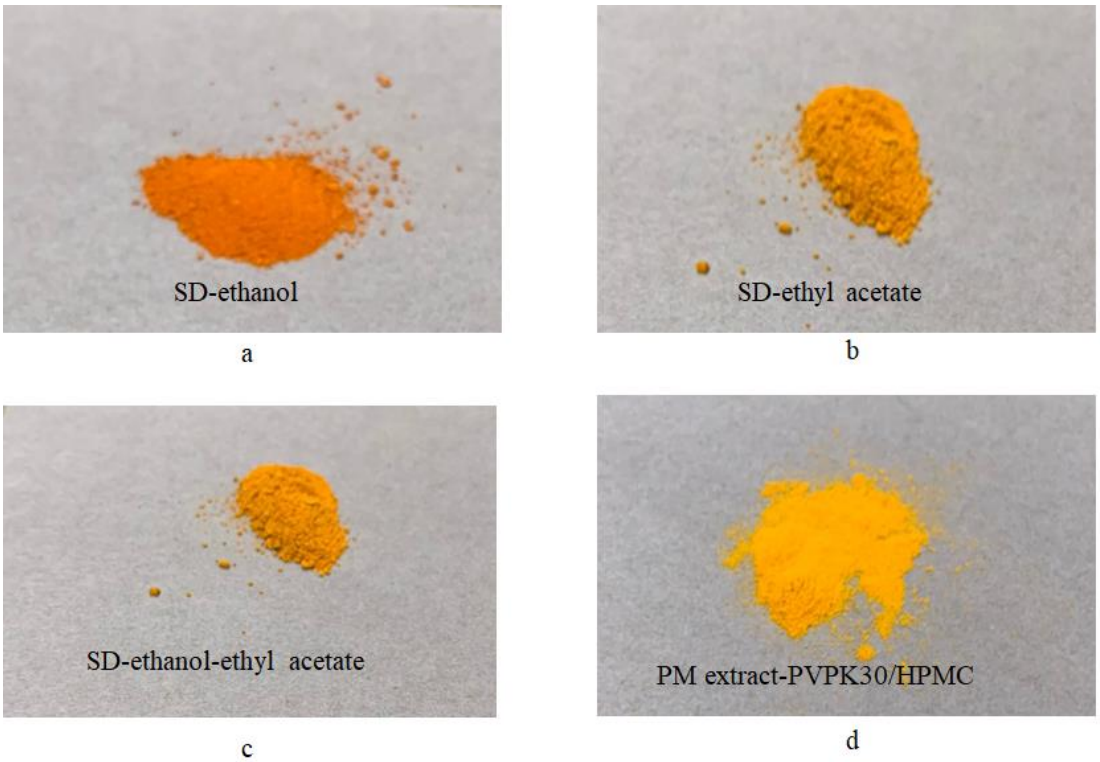

Figure 1: The SDs powder resulted from different solvents, i.e a) ethanol, b) ethyl acetate, c) ethanol/ethyl acetate (1:1). Physical mixture (PM) serves as a control experiment (d)

Drug load

Table II presents the drug load data as recovery values. The percentage assay values, calculated based on the recovery test at which the obtained curcumin contents were divided by the theoretical values and multiplied by 100%. The PM, which was used as control formulation, demonstrated a drug load of 91.34 ± 0.24% w/w of curcumin. Varied recovery values were observed depending on the organic solvent used in the solubilisation process in the SD preparation.

Table II: Drug load of the formulation presented as recovery value

Formulation/solvent	Recovery (%)	SD (%)
PM	91.34	0.24
E-OH	85.88	0.45
E-Ac	92.15	2.09
E-OH/E-Ac (1:1)	110.66	0.33

PM = Physical Mixture ; E-OH = ethanol; E-Ac = ethyl acetate; Data were obtained from three replications.

Dissolution

Figure 2a shows the dissolution profile of curcumin from the SD formulation prepared by ethanol, ethyl acetate, ethanol/ethyl acetate mixture of 1:1 volume ratio, and the PM formulation. Up to 150 minutes of monitoring, the SDs formulation in the binary carrier of PVP K30/HPMC at a weight ratio of 2:1 was able to increase curcumin dissolution as compared to the PM formulation. Using different organic solvents to disperse *C. longa* extract in the SD processing step resulted in variation in the amount of curcumin released in the dissolution media. DE_{150} was used to judge the release profile (Figure 2b). SD prepared using ethanol, ethyl acetate, and ethanol/ethyl acetate mixture of 1:1 volume ratio demonstrates DE_{150} of 38.46±0.08%, 37.83±3.68%, and 31.98±1.13%. The DE_{150} values resulted from ethanol and ethyl acetate as the SD solvent does not differ significantly (p>0.05).

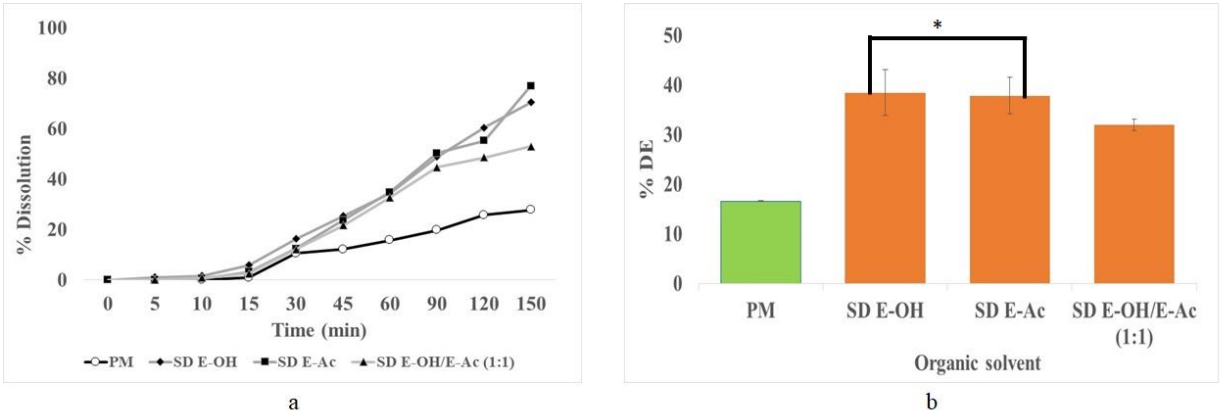

Figure 2: Dissolution profile (a) and DE150 (b) values. *No significant difference; Data is presented as mean and SD of n =3

Discussion

The solvents used in the preparation step, as reported in the SD preparations, were varied, such as ethanol, methanol, dichloromethane and acetone and it was found that the solvent type affected the physicochemical properties and dissolution of lipophilic drugs (Dohrn *et al*., 2021). Among them, ethanol was reported as the most popular solvent. Furthermore, in a more specific mechanism, it was suggested the drug release as observed in the dissolution study could be affected by the interaction of drug-solvent through the opportunity of being a proton donor and/or a proton acceptor to facilitate the miscibility of drug carries in a selected solvent. The previous research reported that the solvent type could affect the physicochemical properties of the SDs product as well as the dissolution behaviour (Krstić *et al*., 2020). The effect of the miscibility of drug-polymer in different organic solvents as dispersing solvent on the physical properties and stability of SD Naproxen-PVP K25 was studied; acetone was reported as the best dispersing solvent over methanol and acetone-methanol blend in the preparation of the SD (Paudel & Van den Mooter, 2012).

This study investigated the influence of solvents used to solubilise the lipophilic compound (curcumin) on the physical characteristic of SD curcumin-PVP K30/HPMC. Using different types of solvents, the SD preparation resulted in a various percentage yield. Ethanol resulted in the lowest yield compared to ethyl acetate or ethanol/ethyl acetate mixture. The use of ethyl acetate as the solvent in the preparation of SD formulation obtained the highest yield.

Figure 1 depicts the colour of the dried SDs product. The SDs powder produced in ethanol showed a more vivid tint of brownish-yellow colour. Turmeric's orange hue comes from curcumin and other curcuminoids. The pH of ethyl acetate is 6.5, while the pH of ethanol is 7.0. Curcumin can be decomposed to ferulic acid and feruloyl methane in neutral or alkaline circumstances, with feruloyl methane forming a brownish-yellow condensation result (Tonnesen & Karlsen, 1985). The SD produced in ethanol revealed a brownish-yellow colour (Figure 1), which could indicate a shift in the chemical structure of curcumin when the pH level changes, particularly when it becomes more alkaline. The lowest drug load (85.9% w/w) in SD produced in ethanolic solution could be attributed to modest curcumin degradation during the preparation.

To accurately compare the dissolution profile, the DE_{150} value obtained from the 150 minutes dissolution study was employed and is presented in Figure 2b. Preparation into the solid dispersions formulation using a PVP K30/HPMC as binary mixture carrier enhances the dissolution rate of curcumin compared to the physical mixture formulation (Figure 2a and Figure 2b). Ethanol is the common solvent employed in the SDs preparation using solvent evaporation method since ethanol is relatively safe as ethanol is in the Joint FAO/WHO Expert Committee on Food Additive (JEFCA) list as a suitable solvent for extraction (FAO, 2006). Furthermore, ethanol belongs to class III of the Food and Drug Administration (FDA) solvent list, considered as low toxicity potential to humans. Ethyl acetate is another member of class III solvent on the FDA list of solvent classification (Martin *et al.,* 2013).

In this study, using ethyl acetate as a solvent in the solubilisation process for the SD preparation of curcumin-PVP K30/HPMC results in a similar dissolution rate to that prepared with ethanol (Figure 2b). However, when these organic solvents were mixed at a 1:1 volume ratio of ethanol/ethyl acetate, the dissolution profile decreased as can be seen in the DE_{150} value of 32.0%.

The lower DE_{150} value of the SD-ethanol/ethyl acetate solvent mixture might be due to the less solubility of

curcumin-PVP K30/HPMC in the ethanol/ethyl acetate at 1:1 volume mixture (Krstić *et al.*, 2020).

Conclusion

The solid dispersions approach using a mixture of the binary carrier of PVP K30/HPMC in a solvent evaporation method increases the dissolution of curcumin compared to the physical mixture formulation. The use of various organic solvents to solubilise the lipophilic compound curcumin affects the dissolution behaviour of curcumin. Ethyl acetate results in higher yield, recovery value in drug loading evaluation, and dissolution profile of curcumin as indicated by the DE_{150} value.

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