การเพิ่มการละลายของเคอร์คูมินด้วยระบบก่ออิมัลชันด้วยตนเองรูปแบบของแข็ง
Dissolution Improvement of Curcumin by Solid Self-emulsifying Drug Delivery System (Solid-SEDDS)

นิพนธ์ต้นฉบับ **Original Article**

ศุภชัย ชุ่มชื่น และ ธนู ทองนพคุณ*
สาขาวิชาเทคโนโลยีเภสัชกรรม คณะเภสัชศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ จ.นครนายก 26120
*** Corresponding author:** thanu@g.swu.ac.th
วารสารไทยเภสัชศาสตร์และวิทยาการสุขภาพ2564;16(3):255-262.

Supachai Chumchuen and Thanu Thongnopkoon*
Department of Pharmaceutical Technology, Faculty of Pharmacy, Srinakharinwirot University, Nakhonnayok 26120 Thailand
*** Corresponding author:** thanu@g.swu.ac.th
Thai Pharmaceutical and Health Science Journal 2021;16(3):255-262.

บทคัดย่อ

วัตถุประสงค์: เพื่อเพิ่มอัตราการละลายของเคอร์คูมินโดยการเตรียมเป็นระบบก่ออิมัลชันด้วยตนเองรูปแบบของแข็ง (solid self-emulsifying drug delivery system, solid-SEDDS) โดยทดสอบกับสารดูดซับหลายชนิด **วิธีการศึกษา:** ศึกษาส่วนประกอบที่เหมาะสมของระบบ SEDDS โดยใช้แผนภาพไตรภาคเทียม โดยเลือกศึกษาน้ำมัน 2 ชนิด ได้แก่ คาไปรลิก คาปริก ไตรกลีเซอไรด์ (Myritol® 318) และน้ำมันมะกอก (olive oil) โดยใช้พอลิซอร์เบต 80 และพรอพิลีน ไกลคอล (PG) เป็นสารลดแรงตึงผิวและตัวทำละลายร่วมในระบบตามลำดับ จากนั้นบรรจุเคอร์คูมินลงในระบบ SEDDS ที่มีสมบัติเหมาะสมและกำหนดให้เป็น cur-SEDDS แล้วศึกษาขนาดอนุภาคของหยดอิมัลชันเมื่อนำระบบไปกระจายในตัวกลางที่เป็นน้ำปราศจากไอออน คัดเลือก cur-SEDDS ที่มีสมบัติเหมาะสมเพื่อนำไปบดผสมกับสารดูดซับ 4 ชนิด ได้แก่ คอลลอยด์ดัล ซิลิกอน ไดออกไซด์, แลกโตส โมโนไฮเดรต, ไดเบสิก แคลเซียม ฟอสเฟต และแคลเซียม คาร์บอเนต เพื่อเตรียมเป็น SEDDS รูปแบบของแข็ง (solid-SEDDS) จากนั้นศึกษาการละลายของเคอร์คูมินรูปแบบ solid-SEDDS ในของเหลวกระเพาะอาหารจำลอง (pH 1.2) โดยใช้เครื่องทดสอบการละลายประเภท 2 ตามเภสัชตำรับสหรัฐอเมริกา **ผลการศึกษา:** ระบบ cur-SEDDS ที่ประกอบด้วย Myritol® 318 : polysorbate80 : PG หลายอัตราส่วนให้อนุภาคหยดอิมัลชันที่มีขนาดเล็กในระดับนาโนเมตรได้เมื่อกระจายระบบในน้ำปราศจากไอออน ได้คัดเลือกระบบ cur-SEDDS ของ Myritol® 318 : polysorbate80 : PG ที่อัตราส่วน 3:5:2 โดยน้ำหนักเพื่อใช้บดผสมกับสารดูดซับให้ได้เป็น solid-SEDDS พบว่าคอลลอยด์ดัล ซิลิกอน ไดออกไซด์สามารถดูดซับดีที่สุด แต่พบว่าระบบสามารถปลดปล่อยเคอร์คูมินได้เพียงร้อยละ 20 ภายในเวลา 120 นาที ซึ่งต่างกับ solid-SEDDS ที่ใช้ไดเบสิก แคลเซียม ฟอสเฟต และแลกโตส โมโนไฮเดรตเป็นสารดูดซับที่ปลดปล่อยเคอร์คูมินได้รวดเร็วถึงกว่าร้อยละ 90 ภายใน 120 นาที ทั้งนี้ไม่ศึกษาการละลายของ solid-SEDDS ที่ใช้แคลเซียม คาร์บอเนตเป็นสารดูดซับ เนื่องจากพบว่าเคอร์คูมินอาจเสื่อมสลายในตัวอย่างดังกล่าว **สรุป:** ส่วนประกอบของระบบ SEDDS และชนิดของสารดูดซับที่ใช้ในการเตรียม solid-SEDDS มีความสำคัญอย่างมากต่อรูปแบบการละลายของสารสำคัญที่ใส่เข้าไปในระบบ

คำสำคัญ: เคอร์คูมิน, คอลลอยด์ดัล ซิลิกอน ไดออกไซด์, แคลเซียม คาร์บอเนต, ไดเบสิก แคลเซียม ฟอสเฟต, แลกโตส โมโนไฮเดรต, พอลิซอร์เบต 80, พรอพิลีน ไกลคอล, ระบบก่ออิมัลชันด้วยตนเองรูปแบบของแข็ง

Abstract

Objective: To improve the dissolution of curcumin by developing solid self-emulsifying drug delivery system (solid-SEDDS) using various solid carriers. **Methods:** The study began with the optimization of the SEDDS composition using pseudoternary phase diagrams. Two types of oil, i.e. caprylic capric triglyceride (Myritol® 318) and olive oil, were used to determine the suitable oil for these systems. Polysorbate80 and propylene glycol (PG) were used as surfactant and cosolvent, respectively. The SEDDS with acceptable properties were loaded with curcumin to form cur-SEDDS and then characterized for droplet size after reconstitution in an aqueous medium. The suitable cur-SEDDS formulations were selected to grind with various solid carriers, including colloidal silicon dioxide, lactose monohydrate, dibasic calcium phosphate and calcium carbonate, to create solid-SEDDS. The dissolution study was carried out in simulated gastric fluid (pH 1.2) using USP dissolution apparatus II. **Results:** Various ratios of cur-SEDDS containing Myritol® 318 : polysorbate80 : PG provided satisfying properties, including droplet size of the reconstituted emulsion in nanometer ranges. The cur-SEDDS of Myritol® 318 : polysorbate80 : PG with a weight ratio at 3:5:2 was selected to mix with solid carriers. Colloidal silicon dioxide had the highest adsorption ability but the obtained solid-SEDDS retarded the dissolution rate of curcumin, which only 20% of the drug was released in 120 min. In contrast, curcumin solid-SEDDS using dibasic calcium phosphate and lactose monohydrate as solidifying agents could be rapidly released for up to 90% within 120 min. The solid-SEDDS using calcium carbonate as solidifying agent was excluded from the dissolution study since it showed a sign of curcumin degradation. **Conclusion:** This study emphasized the importance of SEDDS composition and type of solid carrier of solid-SEDDS for the dissolution behavior of the incorporated active ingredients.

Keywords: curcumin, colloidal silicon dioxide, calcium carbonate, dibasic calcium phosphate, lactose monohydrate, polysorbate80, propylene glycol, solid self-emulsifying drug delivery system

Editorial note
Manuscript received in original form: March 12, 2021;
Revised: May 28, 2021;
Accepted in final form: September 1, 2021;
Published online: September 26, 2021.

Journal website: http://ejournals.swu.ac.th/index.php/pharm/index

Introduction

Dissolution improvement for poorly water-soluble drugs still has been a challenging issue in pharmaceutical researches because many active pharmaceutical ingredients and 40% of new pharmaceutical candidates in the drug discovery pipeline have problems with their aqueous solubility.[1] Various techniques have been employed to enhance the dissolution behavior of those compounds, for instance, solid dispersion, particle size reduction,

amorphization and complexation with β-cyclodextrin. A self-emulsifying drug delivery system (SEDDS) is one of the promising techniques used to enhance the dissolution of poorly water-soluble drugs.[1-3] SEDDS is a thermodynamically stable solution composing of proper proportions of oil, surfactant, cosurfactant and dissolved drug which could spontaneously form oil-in-water emulsion after dispersing in water with a suitable mixing manner. Regarding the ingestion of SEDDS, an emulsion containing drug incorporated in finely oil droplets could be formed after the system is contacted with gastrointestinal fluid with the help of gastrointestinal motility. Incorporating a poorly water-soluble drug in oil droplets with their size within nanometer ranges together with the presence of surfactants to stabilize the systems leads to an increase in the surface area of the drug to be dissolved readily in gastrointestinal fluid prior to absorption.[1-5] The nature of SEDDS is a lipid-based formulation in liquid form, suggesting the limited stability and the difficulty in using compared with solid dosage forms. Thus, there have been several studies focusing on the solidification of SEDDS by adsorbing these systems on solid carriers to create solid-SEDDS.[1,2,6,7] Silicon dioxide in colloidal form is usually the first choice to be an adsorbent for SEDDS since its high specific surface area could adsorb liquids effectively.[2,6]

Curcumin is a yellowish polyphenolic pigment extracted from the rhizome of *Curcuma longa* Linn. (Family: Zingiberaceae). Curcumin has been generally used as a spice, dietary supplement and traditional medicine in Asia. Curcumin shows numerous pharmaceutical activities, including antioxidant, cardioprotective, anti- diabetic, anti-inflammatory and anti-cancer activities.[8-13] However, it possesses several limitations particularly for the very low aqueous solubility (11 ng/mL in pH 5.0 buffer)[10] and pH-dependent instability, leading to ultimately restricted bioavailability.[11,12] Curcumin has keto-enol tautomerism. Its keto form is more stable in acidic and neutral pH conditions while it rapidly undergoes hydrolytic degradation in alkaline solution.[13] According to its limitations, many approaches have been employed to improve the dissolution behavior and stability of curcumin, e.g. solid dispersion, particle size reduction, solid lipid nanoparticles and polymeric nanoparticles.[14,15]

In this study, curcumin SEDDS (cur-SEDDS) were prepared using different types of oil, i.e. caprylic capric triglyceride and olive oil, which can solubilize a given amount of curcumin based on our preliminary study and the previous report.[16] Polysorbate80 and propylene glycol (PG) were used as surfactant and cosolvent in these systems, respectively. Polysorbate80 is a surfactant which generally used in oral liquid dosage forms, suggesting the safety for ingestion as an ingredient of these lipid-based formulations.[17] PG is a versatile ingredient that could be used as solvent, cosolvent and preservative in liquid preparations.[17] Herein, the use of PG as a cosolvent in SEDDS, instead of using cosurfactant, possibly avoids the gastrointestinal irritation from cosurfactants that are normally used in SEDDS upon ingestion. A pseudoternary phase diagram was applied to optimize the suitable proportions of three components, i.e. oil, polysorbate80 and PG, before loading curcumin. To create solid self-emulsifying drug delivery systems (solid-SEDDS) of curcumin, the solidification technique used in this study was a physical grinding between cur-SEDDS and solid carriers by mortar and pestle because it is a simple, sufficiently effective, and practical technique and can be easily applied for industrial application by using a proper mixing machine. Four types of solid carriers, namely lactose monohydrate, calcium carbonate, dibasic calcium phosphate and colloidal silicon dioxide, were used to adsorb cur-SEDDS and form solid-SEDDS. Colloidal silicon dioxide is usually utilized as an adsorbent in solid-SEDDS because of its large specific surface area, leading to efficient adsorption.[2,6] Lactose monohydrate is widely used as a water-soluble filler in solid dosage forms, whereas dibasic calcium phosphate is a water-insoluble filler possessing good flowability.[17] Calcium carbonate is frequently used as an adsorbent in solid formulations containing oil or having hygroscopic tendency.[17] The fillers generally used in solid dosage forms, i.e. lactose monohydrate, dibasic calcium phosphate and calcium carbonate, are the promising candidates for applying as a solid carrier in solid-SEDDS of curcumin because of their well-defined properties. The solid-SEDDS prepared using these fillers as solid carriers might be directly manipulated for processing into solid dosage forms, e.g. tablet and capsule.

Methods

Materials

Curcumin powder (79% purity) was purchased from Sigma- Aldrich (Saint Louis, MO, USA) . Colloidal silicon dioxide (Cab-O-Sil®) was bought from Technochemical

(Bangkok, Thailand). Calcium carbonate, lactose monohydrate, dibasic calcium phosphate (Emcompress®), caprylic capric triglyceride (Myritol® 318), polysorbate80 and olive oil were purchased from P.C. Drug Center (Bangkok, Thailand). Propylene glycol (PG) was bought from SL Quality Supply (Bangkok, Thailand). All chemicals were used as received.

Preparation of curcumin SEDDS (cur-SEDDS) and solid-SEDDS of curcumin

Caprylic capric triglyceride (Myritol® 318) and olive oil were used as oil phases in the systems. Polysorbate80 and PG were used as surfactant and cosolvent, respectively. According to the pseudoternary phase diagram in Figure 1, each component was weighed and mixed by vortex mixer (700 rpm) for 30 sec to obtain the total weight of 3 g of SEDDS formulations. The appearance and physical characteristics of each formulation were visually determined. The SEDDS formulations showing a clear or homogenously mixed characteristic were selected for further curcumin loading. To create cur-SEDDS, 20 mg of curcumin was accurately weighed and then incorporated into the selected SEDDS (3 g) by vortexing for 30 sec. The satisfying cur-SEDDS could be determined by visual inspection for the clarity and homogeneity of the curcumin dissolved in the systems and they were then characterized for droplet size of the systems emulsified in deionized water.

The cur-SEDDS with suitable properties was solidified by grinding with four types of solid carrier, i.e. colloidal silicon dioxide, dibasic calcium phosphate, lactose monohydrate and calcium carbonate. 1 g of cur-SEDDS was weighed and placed in a glass mortar. 1 g of a solid carrier was gradually added each time to mix thoroughly with cur-SEDDS by a pestle until homogenous dried powder with satisfied flowing behavior was obtained. The weight ratios between cur-SEDDS and solid carriers used to form homogenous dried powder of solid-SEDDS were recorded.

Hausner ratio was investigated to determine the flowability of solid-SEDDS and it was used to judge the proper weight ratios of cur-SEDDS to solid carriers. Since the quantity of the prepared solid-SEDDS powder was limited, the Hausner ratio was therefore examined with a modified method. The solid-SEDDS sample was first sieved through a sieve with an opening orifice of 0.42 mm. 10 g of solid-SEDDS was filled into a 25-mL measuring glass cylinder and then gently tapped to remove the powder sticking to the cylindrical wall. The unsettled apparent volume (V_o) of the powder was recorded.

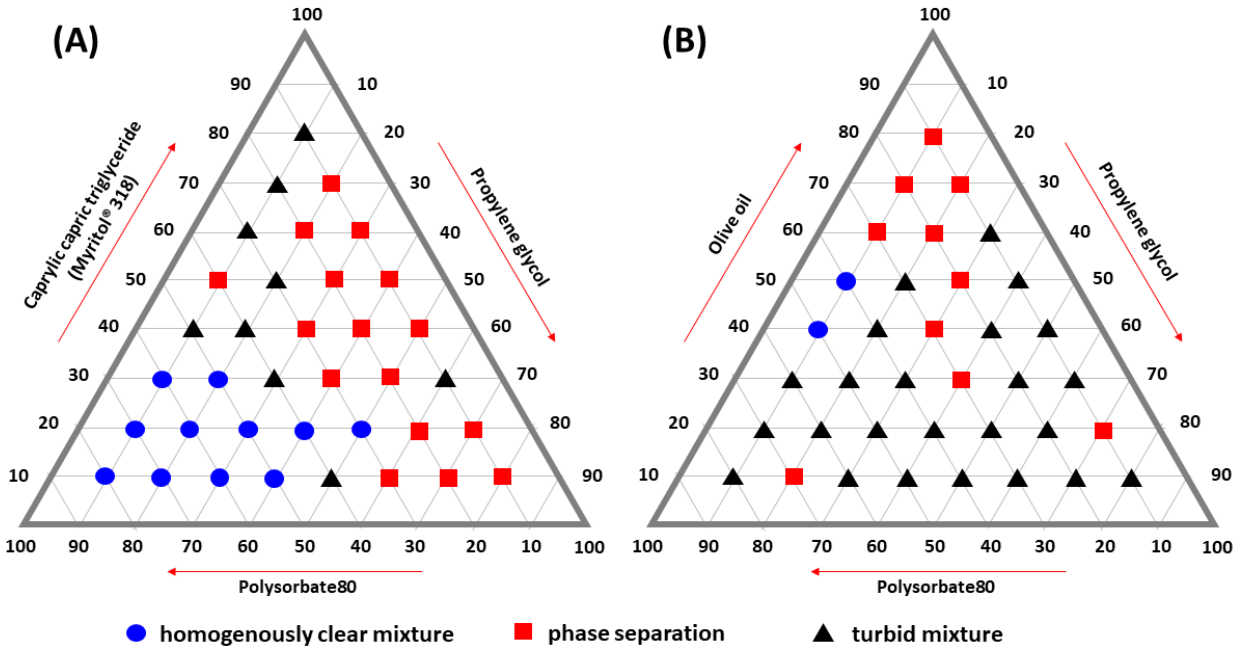

Figure 1 Pseudoternary phase diagrams of the SEDDS using caprylic capric triglyceride (Myritol®318) (A) and olive oil (B) as the oil phase. Both systems contained polysorbate80 and propylene glycol (PG) as surfactant and cosolvent, respectively. The scale presents the percentage of weight ratio of each component.

Then, the powder filled-cylinder was tapped manually with the height of 2 cm from the bench surface until the powder volume was unchanged and the powder volume was recorded as the final volume (V_f). The Hausner ratio was calculated by equation (1). The addition of solid carriers to cur-SEDDS to form dried powder of solid-SEDDS was ended up when the Hausner ratios of the obtained solid-SEDDS were comparable to those of the unprocessed solid carriers.

$$\text{Hausner ratio} = V_o / V_f \quad (1)$$

Droplet size measurement of reconstituted cur-SEDDS

50 µL of cur-SEDDS was dispersed in 10 mL of deionized water and mixed using a vortex mixer for 30 sec. The obtained dispersion was left for 5 min to eliminate the bubbles prior to the measurement for droplet size using dynamic light scattering (Zeta-sizer®, Malvern, Nano-ZS, United Kingdom) at 25 ˚C. The droplet size was reported as an average diameter with standard deviation and polydispersity index (PDI). In order to study the effect of the reconstituted medium, pH 1.2 simulated gastric fluid (SGF) was used instead of deionized water to imitate the incident after ingestion.

Dissolution study of solid-SEDDS

2 mg of the unprocessed curcumin and solid-SEDDS containing an equivalent weight of curcumin for 2 mg were accurately weighed for dissolution analysis. The dissolution study was performed using a USP dissolution apparatus type II (paddle) (Vankel®, VK750D, USA) with 500 mL of pH 1.2 simulated gastric fluid (SGF) as a medium at 37.0 ± 0.5 ˚C. The paddle speed was set at 50 rpm. 5 mL of an aliquot sample was withdrawn at specific time intervals until 120 min with compensation of an equal volume of fresh medium. The sample was analyzed to determine curcumin absorption using a UV-visible spectrophotometer (Shimadzu®, UV-1601, Japan) operated at 432 nm and the dissolved curcumin concentration was calculated using a predetermined standard curve. Each dissolution test was carried out in triplicate.

Results and Discussions

Preparation of curcumin SEDDS (cur-SEDDS)

Although SEDDS can be easily prepared by gentle mixing three components, i.e. oil, surfactant and cosurfactant, without the need for any special equipment. The optimization of the suitable ratios of those three components is relatively difficult and time-consuming. Herein, caprylic capric triglyceride and olive oil were used as oil phase, whereas polysorbate80 and propylene glycol were used as surfactant and cosolvent, respectively, in the SEDDS formulations. In general, one surfactant and one cosurfactant are employed to form SEDDS. In this study, PG was used and specified as a cosolvent since it can satisfactorily solubilize curcumin according to the preliminary study. The pseudoternary phase diagrams of the prepared SEDDS are shown in Figure 1.

It was found that the use of caprylic capric triglyceride (Myritol® 318) was more efficient to form the homogenously transparent SEDDS at the various ratios of the three components compared with the systems using olive oil. Both caprylic capric triglyceride and olive oil are classified as polar oil but the oil polarity index of caprylic capric triglyceride (21.3 mN/m) is higher than that of olive oil (16.9 mN/m) indicating that caprylic capric triglyceride is less polar than olive oil.[18] Thus, caprylic capric triglyceride may be better miscible in the systems containing PG which is a semipolar solvent, leading to the ability to form SEDDS with good homogeneity at various ratios of the components (represented as blue circles in Figure 1). The limited miscibility between polysorbate and PG with fixed oil has also been reported.[17]

20 mg of curcumin was loaded into 3 g of the selected SEDDS by simple dispersion using a vortex mixer to create SEDDS of curcumin (cur-SEDDS) prior to reconstitution into deionized water to form emulsion by vortexing. All cur-SEDDS samples were in dark yellowish color with transparent characteristic, indicating the complete dissolution of curcumin in the systems. This result might be due to a good curcumin solubility in polysorbate80 (13.53 mg/mL) and curcumin can be partially dissolved in PG (solubility in PG 1.60 mg/mL).[19] The reconstituted emulsions of cur-SEDDS were investigated for droplet size and polydispersity index (PI) and the results are summarized in Table 1. The results showed that the cur-SEDDS containing the total weight ratios of polysorbate80 and PG of more than 80% led to the formation of smaller droplet size (less than 100 nm) of the reconstituted emulsion with a narrow size distribution by showing small PDI values. It might be said that the droplet size of the reconstituted emulsion increased when the concentration of polysorbate80 in the systems was decreased, and PG can be effectively used together with polysorbate80 to emulsify the oil droplets. Therefore, the concentration of surfactant had an important

role to emulsify and stabilize the obtained emulsion, conforming to the previous reports.[20,21] On the other hand, the cur-SEDDS using olive oil showed a larger droplet size in several microns with higher PDI values. This might be due to the lower concentrations of polysorbate80 in those systems, resulting in inadequate emulsifying ability. The incomplete emulsification of oil droplets due to lower surfactant concentration would result in higher interfacial tensions, consequently forming larger droplets.[20] In addition, the solubility of curcumin in caprylic capric triglyceride (1.85 mg/g of caprylic capric triglyceride) is higher than that of curcumin in olive oil (0.45 mg/g of olive oil).[16] The lower solubility of curcumin in olive oil might speed up the formation of a saturated solution of curcumin, leading to the rapid precipitation of curcumin as larger particles in the dispersing medium. Therefore, the SEDDS using olive oil was excluded for further studies because of the formation of large droplets of the emulsified SEDDS.

Table 1 Droplet size in average (nm) ± standard deviation (SD) and polydispersity index (PDI) of emulsified cur-SEDDS in deionized water and pH 1.2 simulated gastric fluid (SGF).

Composition of SEDDS (20 mg of curcumin loaded)	Ratio (by weight)	Deionized water		pH 1.2 SGF	
		Droplet size (nm)	PDI	Droplet size (nm)	PDI
Myritol® 318 : polysorbate80 : PG	1 : 8 : 1	14.79 ± 0.16	0.198 ± 0.014	-	-
	1 : 7 : 2	23.59 ± 1.90	0.323 ± 0.010	32.73 ± 0.40	0.512 ± 0.013
	1 : 5 : 4	23.65 ± 0.11	0.412 ± 0.003	103.83 ± 31.66	0.318 ± 0.163
	2 : 7 : 1	25.38 ± 0.21	0.354 ± 0.004	-	-
	1 : 6 : 3	36.71 ± 0.87	0.468 ± 0.004	-	-
	2 : 5 : 3	77.77 ± 0.75	0.466 ± 0.005	-	-
	3 : 6 : 1	126.73 ± 1.77	0.258 ± 0.006	130.43 ± 0.60	0.258 ± 0.009
	3 : 5 : 2	154.03 ± 1.85	0.305 ± 0.050	164.10 ± 2.01	0.285 ± 0.037
	2 : 6 : 2	157.20 ± 1.55	0.231 ± 0.007	-	-
	2 : 4 : 4	183.47 ± 2.25	0.408 ± 0.012	-	-
	2 : 3 : 5	235.60 ± 14.66	0.621 ± 0.108	-	-
Olive oil : polysorbate80 : PG	5 : 4 : 1	3850.67 ± 550.53	0.436 ± 0.504	-	-
	4 : 5 : 1	4411.00 ± 2144.76	0.862 ± 0.214	-	-

To imitate the gastrointestinal condition, simulated gastric fluid (SGF) was used as a medium for emulsifying cur-SEDDS. The results showed that the droplet size of the emulsified samples was slightly increased in SGF, implying the effect of acidity and electrolyte (potassium chloride) in dispersing medium. However, this effect was more pronounced in the system with low surfactant concentration. Therefore, the increase in droplet size in SGF might involve with the presence of electrolyte which then affected the saturated behavior of curcumin because there was a lack of data involving the instability of each SEDDS component in an acid medium. These results suggested that the bioavailability of curcumin in these cur-SEDDS upon ingestion might be affected when the formulations reach the gastrointestinal fluid.

Solidification of cur-SEDDS to form solid-SEDDS

In order to solidify the cur-SEDDS, four types of solid carriers, namely colloidal silicon dioxide, lactose monohydrate, dibasic calcium phosphate and calcium carbonate, were chosen to grind with cur-SEDDS by using a glass mortar and pestle until dried powder samples with acceptable flowability determined by Hausner ratio were obtained. The suitable weight ratio of cur-SEDDS and the solid carrier was recorded when the Hausner ratio of solid-SEDDS was comparable to that of the intact solid carrier. The lower Hausner ratio indicates better flowability or less cohesiveness in powder. The Hausner ratio of less than 1.25 suggests that the obtained powder has passable flowability and efficiency for industrial production.[20] As summarized in Table 2, the results revealed that colloidal silicon dioxide had the best adsorption ability among the others by showing the least amount to produce the dried powder sample. This result can confirm the findings of the previous reports about the good adsorption property of colloidal silicon dioxide which was attributable to the large specific surface area of colloidal particles.[2,6] On the other hand, the amounts of lactose monohydrate and dibasic calcium phosphate to properly adsorb cur-SEDDS and form dried powder were high, i.e. 18 and 22 times of the cur-SEDDS weight, respectively. This might be due to the relatively lower surface area and the higher bulk density of these two solid carriers (0.5 - 0.8 g/cm^3 for lactose monohydrate and 0.915 g/cm^3 for dibasic calcium phosphate)[17] as compared with colloidal silicon dioxide, leading to the need of a higher weight to adsorb cur-SEDDS adequately. Regarding the difficulty of the grinding process, it was found that the bulkiness of colloidal silicon dioxide (bulk density of 0.029 - 0.042 g/cm^3) hindered the mixing by grinding technique as it can be seen by using a longer period to mix homogenously. In contrast to lactose monohydrate and dibasic calcium phosphate, the dense and better flowing behavior of these two solid carriers, especially for dibasic calcium phosphate, can ease the grinding process. Additionally, the solid-SEDDS using dibasic calcium phosphate possessed the low Hausner ratio, suggesting the good flowability of this powder. These results might be used to consider for practically industrial manufacturing. For calcium carbonate, it can be seen that the weight ratio to form dried

powder was interestingly low and it can be mixed with cur-SEDDS easily by grinding. However, the obtained cur-SEDDS powder using calcium carbonate was in brownish instead of yellowish color like the others (Figure 2), indicating the possible degradation of curcumin in this sample. This might be due to the alkalinity of calcium carbonate (pH of aqueous dispersion = 9.0)[17] which could affect the curcumin stability[13], whereas pH of colloidal silicon dioxide, lactose monohydrate and dibasic calcium phosphate was 3.8 - 4.2 (aqueous dispersion), 4.0 - 6.5 (aqueous solution) and 7.4 (slurry), respectively.[17] According to the presumably chemical degradation, the cur-SEDDS powder using calcium carbonate was excluded for dissolution study.

Table 2 Weight ratios of cur-SEDDS* to solid carriers to create solid-SEDDS.

Solid carrier	Ratio (by weight)	Hausner ratio		Mixing capability
		Solid-SEDDS	Intact solid carrier	
Colloidal silicon dioxide	1:2	1.36	1.39	Difficult
Lactose monohydrate	1:18	1.93	2.05	Easy
Dibasic calcium phosphate	1:22	1.05	1.07	Very easy
Calcium carbonate	1:7	1.02	1.05	Easy

* The cur-SEDDS was the cur-SEDDS containing Myritol® 318 : polysorbate80 : PG at the weight ratio of 3:5:2.

Dissolution study of solid-SEDDS

For dissolution study in simulated gastric fluid (pH 1.2), solid-SEDDS of curcumin containing Myritol® 318 : polysorbate80 : PG at the weight ratio of 3:5:2 was mainly selected to perform dissolution study because this ratio possessed a lower proportion of surfactant, i.e. polysorbate80, which was presumed to be safer for ingestion, but still provided the reconstituted system with acceptable droplet size and polydispersity index. According to the dissolution profiles in Figure 3, the results showed that the intact curcumin had the lowest dissolution rate as its dissolution was lower than 2% within 120 min. This result was in agreement with the previous reports and confirmed the problematic solubility of curcumin.[22,23] The dissolution of curcumin from the solid-SEDDS using colloidal silicon dioxide as a solid carrier reached 20% within 120 min, whereas those from the solid-SEDDS using lactose monohydrate and dibasic calcium phosphate as solid carriers reached approximately 90% within 120 min. The superior dissolution of curcumin from solid-SEDDS using lactose monohydrate as a solid carrier might involve with the hydrophilic nature of lactose monohydrate which can be dissolved in the dissolution medium and rapidly released the adsorbed cur-SEDDS, leading to the improved dissolution of curcumin. Regarding the solid-SEDDS using dibasic calcium phosphate, the high density and discrete behavior of dibasic calcium phosphate powder resulted in the rapid sinkage of a powder sample in the dissolution medium. In addition, dibasic calcium phosphate can be partly dissolved in the acidic dissolution medium (pH 1.2 SGF) which may promote the dissolution of curcumin. On the other hand, the relatively low dissolution rate of curcumin from solid-SEDDS

Figure 2 Solid-SEDDS of curcumin using colloidal silicon dioxide (A), lactose monohydrate (B), dibasic calcium phosphate (C) and calcium carbonate (D) as solid carriers.

using colloidal silicon dioxide might be due to the agglomeration and hydrophobicity of the colloidal powder since the agglomerated powder floated on the surface of the dissolution medium could be observed particularly in the first 30 minutes. The dissolution profile of curcumin from solid-SEDDS containing the weight ratio of Myritol® 318 : polysorbate80 : PG at 1:7:2 with the use of dibasic calcium phosphate as the solid carrier was performed to investigate the influence of the weight ratio of SEDDS compositions on the dissolution behavior. It can be seen that the dissolution rate of curcumin from this sample was relatively close to those from the samples containing the weight ratio of Myritol® 318 : polysorbate80 : PG at 3:5:2 in the first 10 minutes and the dissolution can be achieved approximately to 60% within 120 min. The slightly slower dissolution rate at the later period might be explained by the high affinity of curcumin to attach on or inset into the particles of the solid carrier which resulted from the use of a higher proportion of polysorbate80 (1:7:2) in the solid-SEDDS sample. This result also indicated that the droplet size of the reconstituted SEDDS might not significantly impact the dissolution of the incorporated active ingredients. These results suggested that the dissolution behavior of the poorly water-soluble drug loaded in solid-SEDDS can be affected by the ratio of SEDDS components and the type of solid carriers.

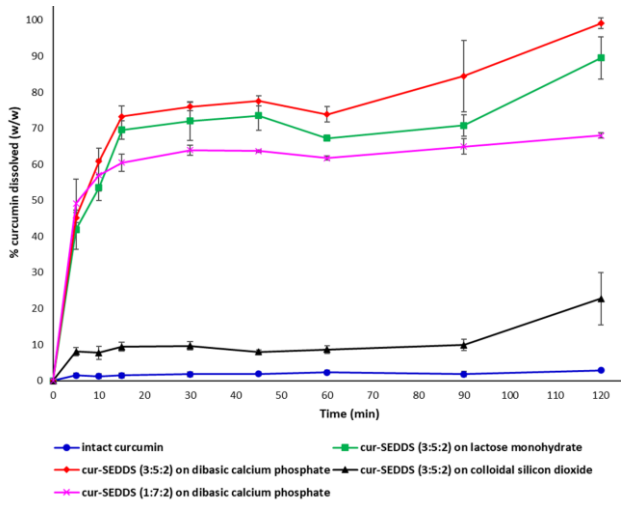

Figure 3 Dissolution profiles in simulated gastric fluid (pH 1.2) of curcumin from cur-SEDDS adsorbed on different solid carriers compared with the intact curcumin.

Conclusion

The dissolution of curcumin was improved by incorporating curcumin into SEDDS prior to solidifying to form a solid-SEDDS by grinding with various solid carriers. Developing solid-SEDDS from typically liquid-SEDDS can create value-added SEDDS, and the solid-SEDDS can be further created to various solid dosage forms, e.g. tablet, capsule. The results showed that several ratios of Myritol® 318 : polysorbate80 : PG could be used to prepare SEDDS containing curcumin (20 mg) with satisfied physical properties particularly for the droplet size of the aqueous dispersed samples which were in a nanometer size range. The proportion of each component in SEDDS distinctly affected the droplet size of the reconstituted samples. The increase in surfactant, i.e. polysorbate80, concentration led to the smaller droplet size. The acidity of dispersing medium influenced the droplet size of the reconstituted cur-SEDDS particularly for those containing a low surfactant concentration. According to the dissolution behavior of solid-SEDDS, it can be seen that the type of solid carrier affected the dissolution of curcumin from solid-SEDDS. Dibasic calcium phosphate was the most effective solid carrier for improving the curcumin dissolution and it can be mixed with cur-SEDDS effortlessly by simple grinding even though a high quantity was needed to form dried powder as compared to the other solid carriers. Therefore, oil type, percentage of each SEDDS component, and type of solid carrier were the important parameters that impacted the properties of the prepared solid-SEDDS. This technique is one of the promising approaches to improve the dissolution of poorly water-soluble drugs and it can be supposedly utilized for commercial production.

Acknowledgment

The authors would like to acknowledge the Faculty of Pharmacy, Srinakharinwirot University for chemical expenditure support.

Conflict of interest

The authors report no declarations of interest.

References

1. Tang B, Cheng G, Gu JC, Xu CH. Development of solid self-emulsifying drug delivery systems: preparation techniques and dosage forms. *Drug Discov Today* 2008;13:606-612.

2. Gonçalves A, Nikmaram N, Roohinejad S, Estevinho BN, Rocha F, Greiner R, McClements DJ. Production, properties, and applications of solid self-emulsifying delivery systems (S-SEDS) in the food and pharmaceutical industries. *Colloids Surf A* 2018;538:108-126.
3. Ujhelyi Z, Vecsernyés M, Fehér P, Kósa D, Arany P, Nemes D, Sinka D, Vasvári G, Fenyvesi F, Váradi J, Bácskay I. Physico-chemical characterization of self-emulsifying drug delivery systems. *Drug Discov Today Technol* 2018;27:81-86.
4. Vasconcelos T, Marques S, Sarmento B. Measuring the emulsification dynamics and stability of self-emulsifying drug delivery systems. *Eur J Pharm Biopharm* 2018;123:1-8.
5. Rohrer J, ZupanČiČ O, Hetényi G, Kurpiers M, Bernkop-Schnürch A. Design and evaluation of SEDDS exhibiting high emulsifying properties. *J Drug Deliv Sci Technol* 2018;44:366-372.
6. MandiĆ J, Pobirk AZ, VreČer F, Gašperlin M. Overview of solidification techniques for self-emulsifying drug delivery systems from industrial perspective. *Int J Pharm* 2017;533(2):335-345.
7. Kazi M, Al-Qarni H, Alanazi FK. Development of oral solid self-emulsifying lipid formulations of risperidone with improved *in vitro* dissolution and digestion. *Eur J Pharm Biopharm* 2017;114:239-249.
8. Das RK, Kasoju N, Bora U. Encapsulation of curcumin in alginate-chitosan-pluronic composite nanoparticles for delivery to cancer cells. *Nanomedicine* 2010;6(1):153-60.
9. Bhawana, Basniwal RK, Buttar HS, Jain VK, Jain N. Curcumin nanoparticles: preparation, characterization, and antimicrobial study. *J Agric Food Chem* 2011;59(5):2056-2061.
10. Kadota K, Okamoto D, Sato H, Onoue S, Otsu S, Tozuka Y. Hybridization of polyvinylpyrrolidone to a binary composite of curcumin/α-glucosyl stevia improves both oral absorption and photochemical stability of curcumin. *Food Chem* 2016;213:668-674.
11. Mehanny M, Hathout RM, Geneidi AS, Mansour S. Exploring the use of nanocarrier systems to deliver the magical molecule; Curcumin and its derivatives. *J Control Release* 2016;225:1-30.
12. Tapal A, Tiku PK. Complexation of curcumin with soy protein isolate and its implications on solubility and stability of curcumin. *Food Chem* 2012; 130(4):960-965.
13. Priyadarsini KI. The chemistry of curcumin: from extraction to therapeutic agent. *Molecules* 2014;19(12):20091-20112.
14. Prasad R, Patsariya R, Dalvi SV. Precipitation of curcumin by pressure reduction of CO_2-expanded acetone. *Powder Technol* 2017;310:143-153.
15. Dey S, Sreenivasan K. Conjugation of curcumin onto alginate enhances aqueous solubility and stability of curcumin. *Carbohydr Polym* 2014; 99:499-507.
16. Takenaka M, Ohkubo T, Okadome H, Sotome I, Itoh T, Isobe S. Effective extraction of curcuminoids by grinding turmeric (*Curcuma longa*) with medium-chain triacylglycerols. *Food Sci Technol Res* 2013; 19(4):655-659.
17. Rowe RC, Sheskey PJ, Quinn ME. Handbook of pharmaceutical excipients. 6th ed. London. Pharmaceutical Press, 2009.
18. Hloucha M, Kuesters E, Schorb J, Nieendick C, Winzek M, Seidler S. BASF SE., assignee. Oil concentrates for cosmetic compositions. United States Patent US 20160279041A1. 2016 Sep 29.
19. Sharma V, Pathak K. Effect of hydrogen bond formation/replacement on solubility characteristics, gastric permeation and pharmacokinetics of curcumin by application of powder solution technology. *Acta Pharm Sin B* 2016;6(6):600-613.
20. Huang J, Wang Q, Sun R, Li T, Xia N, Xia Q. A novel solid self-emulsifying delivery system (SEDS) for the encapsulation of linseed oil and quercetin: Preparation and evaluation. *J Food Eng* 2018;226:22-30.
21. Quan G, Wu Q, Zhang X, Zhan Z, Zhou C, Chen B, Zhang Z, Li G, Pan X, Wu C. Enhancing *in vitro* dissolution and *in vivo* bioavailability of fenofibrate by solid self-emulsifying matrix combined with SBA-15 mesoporous silica. *Colloids Surf B Biointerfaces* 2016;141:476-482.
22. Uchiyama H, Nogami S, Katayama K, Hayashi K, Kadota K, Tozuka Y. Jelly containing composite based on α-glucosyl stevia and polyvinylpyrrolidone: Improved dissolution property of curcumin. *Eur J Pharm Sci* 2018;117:48-54.
23. Paradkar A, Ambike AA, Jadhav BK, Mahadik KR. Characterization of curcumin-PVP solid dispersion obtained by spray drying. *Int J Pharm* 2004;271:281-286.