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Application of Freeze-Drying Technique in Preparing Indomethacin-Lactose Solid Dispersion

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ABSTRACT: Indomethacin (ID) solid dispersions were prepared by coprecipitation method using lactose as a water-soluble carrier. Two techniques, simple evaporation and freeze-drying techniques, were used to prepare 1:1 and 1:5 indomethacin:lactose coprecipitates. Dissolution studies of the prepared ID coprecipitates and ID powder were performed. The coprecipitates yielded higher drug dissolution than the ID powder. The freeze-drying technique provided more drug dissolution enhancing effect than the simple evaporation technique. As higher ratio of lactose was utilized, higher dissolution enhancing effect was obtained in the evaporated coprecipitates but was not observed in the freeze-dried coprecipitates. The 1:1 ID:lactose freeze-dried coprecipitate and 1:5 ID:lactose evaporated coprecipitates were formulated into tablets. Factorial design and statistical analysis were applied to study the effects of coprecipitation technique, dicalcium phosphate dihydrate (DCP) content, and tablet hardness on tablet disintegration and dissolution. The significant effects on tablet disintegration derived from coprecipitation technique and tablet hardness. While coprecipitation technique, DCP content, and their interaction imparted significant effects on tablet dissolution. As an insoluble direct compressible filler, DCP was not suitable to be used in preparing fast release solid dispersion tablet.

KEY WORDS: Coprecipitate, Freeze-dry, Factorial design, Multiple regression

INTRODUCTION

Indomethacin was recognized as a poorly water-soluble drug (1). Hence, the accepted official indomethacin solid dosage form was capsule (2). Solid dispersion was an approach to improve dissolution of a poorly water-soluble drug and thereby its absorption and therapeutic efficacy (3). By solid dispersion, the drug was dispersed as molecules or colloids within an inert solid water-soluble carrier. Upon exposure to dissolution medium, the carrier dissolved quickly and the drug molecules or colloids were suddenly released and exposed to the medium, resulting in fast drug dissolution. Lactose was found to be useful as a water-soluble carrier in preparing indomethacin solid dispersion by coprecipitation using simple evaporation technique (4). However, the simple evaporation technique resulted in sticky mass of coprecipitate causing the problem in handle. Additional problems were also derived from this technique, including solvent handling and pulverizing problems (3, 5). Another technique, freeze dry, could be used to prepare the coprecipitate without the prementioned problems (6). By freeze drying, the obtained coprecipitate mass was less sticky and easily processed into powder. This technique was also suitable to prepare the coprecipitate in large scale.

The objective of this investigation was to employ freeze drying technique to prepare fast release indomethacin solid dispersion by using lactose as a water-soluble carrier. The dissolution enhancing effect of this technique was also compared to the effect derived from the simple evaporation technique. In order to obtain some useful information, as a guideline to develop the solid dispersion into tablet dosage form, the influences of some tablet formulation variables on dissolution enhancing effect of the prepared solid dispersion were investigated. Statistical analysis using multiple regression was applied to identify the significance of each investigated formulation variable.

MATERIALS AND METHODS

Materials

The following chemicals were obtained from commercial sources: indomethacin (Batch No. 89-06-03, Vertex Chemical Company, Hong Kong), lactose (supplied by Pharmaceutical Science Ltd., Thailand), dicalcium phosphate dihydrate (supplied by Pharmaceutical Science Ltd., Thailand), magnesium sterate (supplied by Pharmaceutical Science Ltd., Thailand), absolute ethanol (supplied by Government Pharmaceutical Organization, Thailand), monobasic phosphate sodium (Fluka Garantie, Switzerland), sodium hydroxide (Ajax Chemicals, Australia).

Equipment

The following equipment was used: analytical balance (Sartorius, Model A200S, Germany), freeze dryer (Labconco Co., Model Lyph-Lock 12L, U.S.A.), single stroke tabletting machine (ViuHang Engineering, Thailand), pH meter (Schott Co., Model CG 840, Germany), disintegration apparatus (K.S.L. Engineering Co., Ltd., USP type, Thailand), hardness tester (Dr. Schleuniger Co., Type THP-4M, Switzerland), dissolution apparatus (Pharma Test Co., Model TW II, Germany), and UV spectrophotometer (Milton Roy, Co., Spectronic 3000 Array, U.S.A.)

Methods

Preparation of indomethacin coprecipitates

Weighed amounts of indomethacin and lactose, as listed in Table 1, were dissolved in 50 ml of absolute ethanol and 10 ml of distilled water, respectively. Then, the lactose solution was incorporated into the ethanolic solution of drug to make the final volume of 60 ml. To prepare indomethacin coprecipitate by simple evaporation technique, the solution was mixed thoroughly and allowed to evaporate continuously on a water bath at 70 °C with continuous stirring. The resulted coprecipitate was stored in an incubator at 60 °C for 48 hours to eliminate the remaining solvent. The dry coprecipitate was then pulverized and screened through a 40 mesh sieve. To prepare indomethacin coprecipitate by freeze-drying technique, the mixture solution of drug and lactose was filled in an aluminium tray and placed on a shelf within a chamber of a freeze dryer. Then, the freeze-drying process was run until the dry coprecipitate was obtained. The dry coprecipitate was passed through a 40 mesh sieve. The evaporated and freeze-dried coprecipitates were kept in a desiccator.

Dissolution studies

Dissolution studies of indomethacin powder and coprecipitates, equivalent to 25 mg of indomethacin, were performed by USP type II dissolution apparatus according to the dissolution of indomethacin capsule, USP XXII & NF XVII (7). Seven hundred and fifty milliliters of a mixture of distilled water and pH 7.2 phosphate buffer (4:1) was used as dissolution medium. The medium was maintained at 37±1 °C and the paddle was adjusted to rotate at 50 rpm. Ten milliliters of dissolution medium was withdrawn at various time intervals up to 1 hour and assayed for drug content by spectrophotometer at 318 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium.

Table 1 Amounts of Indomethacin and Lactose Used in Preparing Solid Dispersions.

	Simple evaporation		Freeze-dry	
	Indomethacin	lactose	Indomethacin	lactose
1:1 Indomethacin:lactose	15 g	15 g	15 g	15 g
1:5 Indomethacin:lactose	15 g	75 g	15 g	75 g

Table 2 Experimental Design of Indomethacin Coprecipitate Tablets.

Formulation	Process	Variable level DCP	Hardness
I	−1	−1	−1
II	1	−1	−1
III	−1	1	−1
IV	1	1	−1
V	−1	−1	1
VI	1	−1	1
VII	−1	1	1
VIII	1	1	1

Formulation	Process	DCP (mg/tablet	Hardness (kp)
I	Evaporation	130	2.5
II	Freeze-dry	130	2.5
III	Evaporation	200	2.5
IV	Freeze-dry	200	2.5
V	Evaporation	130	6.0
VI	Freeze-dry	130	6.0
VII	Evaporation	200	6.0
VIII	Freeze-dry	200	6.0

Table 3 Tablet Formulations of Indomethacin Coprecipitate Tablets.

Ingredient	Amount per tablet
Coprecipitate equivalent to indomethacin	2.5 mg
DCP	130 or 200 mg
Magnesium stearate	0.75 %
Aerosil^{R}	1 %
Hardness	2.5 or 6.0 kp

Experimental design

Factorial design was used as an experimental design to study the effects of the investigated formulation variables on dissolution of indomethacin tablets prepared from the coprecipitates. The effects of three variables; coprecipitation technique (simple evaporation or freeze-drying technique), content of dicalcium phosphate dihydrate (DCP), and level of tablet hardness, on disintegration and dissolution of coprecipitate tablets were studied. By factorial design, eight tablet formulations were established, as demonstrated in Table 2.

Preparation of indomethacin tablets

Indomethacin tablets were prepared by direct compression according to the formulations listed in Table 3. All the excipients were screened through a 40 mesh sieve and then mixed with the coprecipitates (1:5 ID:lactose evaporated coprecipitates or 1:1 ID:lactose freeze-dried coprecipitates) by geometric dilution for 10 minutes. The obtained mixtures were directly compressed into tablets using a single stroke tabletting machine to yield the tablets having diameter of 9 mm and hardness of 2.5 or 6.0 kp according to the experimental design.

Tablet disintegration studies

The disintegration studies of the indomethacin tablets were conducted by a USP type disintegration apparatus using distilled water as medium. The temperature of the medium was maintained at 37±1 °C throughout the experiment. Each average disintegration time was obtained from 6 tablets.

Tablets dissolution studies

Dissolution studies of indomethacin tablets were performed by USP type I dissolution apparatus according to the dissolution of indomethacin capsule, USP XXII & NF XVII (7). The basket was adjusted to rotate at 100 rpm. Ten milliliters of dissolution medium was withdrawn at various time intervals up to 1 hour and assayed for drug content by spectrophotometer at 318 mm.

RESULTS AND DISCUSSION

Dissolution profiles of indomethacin (ID) powder evaporated coprecipitates (1:1, and 1:5 ID:lactose), and freeze-dried coprecipitates (1:1 and 1:5 ID:lactose) are demonstrated in Figure 1. Among the coprecipitates, it was clearly demonstrated that the dissolution of the 1:1 ID:lactose freeze-dried coprecipitate was the fastest, followed by the 1:5 ID:laclose freeze-dried coprecipitate, the 1:5 ID:lactose evaporated coprecipitate, and the 1:1 ID:lactose evaporated coprecipitate, respectively. Comparing to the indomethacin powder, higher drug dissolutions were obtained from the coprecipitates at all time intervals. An exception was found in the 1:1 ID:lactose evaporated coprecipitate. In the latter case, the coprecipitate provided faster dissolution in the

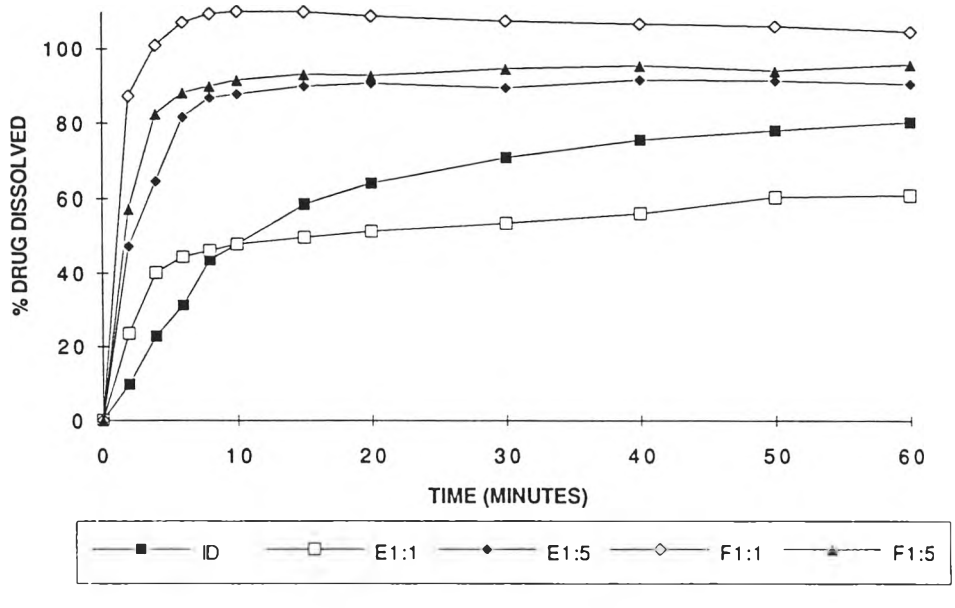

Figure 1 Dissolution profiles of indomethacin powder (I.D.), 1:1 ID:lactose (E1:1) and 1:5 ID:lactose (E1:5) evaporate coprecipitates, 1:1 ID:lactose (F1:1) and 1:5 ID:lactose (F1:5) freeze-dried coprecipitates.

first ten minutes. However, the ID powder showed faster dissolution in the last fifty minutes.

For the simple evaporation technique, increasing lactose ratio from 1:1 ID:lactose to 1:5 ID:lactose resulted in higher drug dissolution. In solid dispersion, increasing water-soluble carrier content would result in more dissolution enhancing effect (8). However, the dissolution of 1:5 ID:lactose freeze-dried coprecipitate was lower than the dissolution of 1:1 ID:lactose freeze-dried coprecipitate. Since the solubility of lactose in absolute ethanol was low (9). Therefore when the amount of lactose in the ID-lactose freeze-dried hydroalcoholic liquid was increased from 15 g to 75 g, most of them would precipitated out during the operation of the freeze dryer. The 1:5 ID:lactose freeze-dried coprecipitate, thereby, consisted of the precipitated lactose and the solid dispersion of ID in lactose. Hence, the resulted ID solid dispersion was not truly the 1:5 ID:lactose solid dispersion but was believed to be the solid dispersion of ID in lactose of similar extent as the 1:1 ID:lactose freeze-dried solid dispersion. Lower dissolution of the 1:5 ID:lactose freeze-dried coprecipitate, as compared to the 1:1 ID:lactose freeze-dried coprecipitate, was likely to attribute from the presence of lactose in higher amount. Lactose as a sugar, if presented in high amount, would provide viscous environment around the drug upon dissolving. The induced viscous environment could retard drug diffusion and hence causing less drug dissolution from the 1:5 ID:lactose freeze-dried coprecipitate.

Table 4 Disintegration Times (D.T.) and Percentages of Drug Dissolved at the 20th Minute (C_{20}) of the Indomethacin Coprecipitate Tablets.

Formulation	D.T. (minutes)	C_{20} (%)
I	4.74	12.68
II	16.46	17.49
III	9.85	17.26
IV	21.65	14.54
V	13.36	11.54
VI	58.96	17.66
VII	37.92	17.10
VIII	51.47	14.63

Table 5 The t-values for the Main Effects and Interaction Effects of X_1, X_2, and X_3 on Tablet Disintegration and Dissolution.

Variable	t-value	
	D.T.	C_{20}
X_1	2.572985	5.415094
X_2	0.851852	3.924528
X_3	3.392779	–0.98113
X_1X_2	–0.99625	–15.07547
X_1X_3	1.108932	1.471698
X_2X_3	0.210707	0.849057

D.F. = 4 : $t(\alpha = 0.0005) = 8.610$, $t(\alpha = 0.001) = 7.173$, $t(\alpha = 0.0025) = 5.598$, $t(\alpha = 0.005) = 4.604$, $t(\alpha = 0.01) = 3.747$, $t(\alpha = 0.025) = 2.776$, $t(\alpha = 0.05) = 2.133$, $t(\alpha = 0.10) = 1.533$, $t(\alpha = 0.25) = 0.741$

From the dissolution studies, the 1:5 ID:lactose evaporated coprecipitate and the 1:1 ID:lactose freeze-dried coprecipitate were chosen to develop into tablet dosage form. In order to obtain some useful information for development of the solid dispersion into tablet, the influences of some tablet formulation variables on dissolution enhancing effect of the coprecipitates were investigated. Therefore, a factorial design was used as an experimental design to study the effects of three variables; coprecipitation technique (X_1) the amount of dicalcium phosphate dihydrate (X_2), and tablet hardness (X_3), on disintegration and dissolution of the ID coprecipitate tablets.

Disintegration times and dissolution profiles of the prepared ID coprecipitate tablets are demonstrated in Table 4 and Figure 2, respectively. The data of disintegration time was submitted to multiple regression to establish the relationship between the disintegration time and the three investigated variables. The disintegration time equation was then derived as the following.

$$D.T. = 10.33375X_1 + 3.42125X_2 + 13.62625X_3 - 3.99625X_1X_2 + 4.45375X_1X_3 + 0.84625X_2X_3 + 26.80125 \quad (1)$$

$(R^2 = 0.954794)$

The validity of the equation was confirmed by the R^2 value of 0.954794. The significance of the main effects of X_1, X_2, X_3 and the interaction effects of X_1X_2, X_1X_3, X_2X_3 were considered from t-values as shown in Table 5.

From the disintegration time equation, it was demonstrated that D.T. was function of coprecipitation technique, X_1, ($\alpha = 0.05$) and tablet hardness, X_3, ($\alpha = 0.025$). Changing tablet component from 1:5 ID:lactose evaporated coprecipitate to 1:1 ID:lactose freeze-dried coprecipitate resulted in higher D.T. Therefore, the freeze-drying process even though provided the coprecipitate of higher dissolution as compared to the simple evaporation process but it yielded the coprecipitate tablets of higher disintegration time. As expect, increasing tablet hardness also resulted in higher D.T.

In order to establish the relationship between the dissolution and the investigated variables, the percentage o drug dissolved at the time of 20th minute (C_{20}) was determined as a criteria. USP XXII & NF XVII establishec indomethacin dissolution requirement of 80% drug dissolvec within 20 minutes for the solid dosage form (7). Table 4 lists the C_{20} of the ID coprecipitate tablets. It was clearly shown that the C_{20} of all the ID tablet formulations were

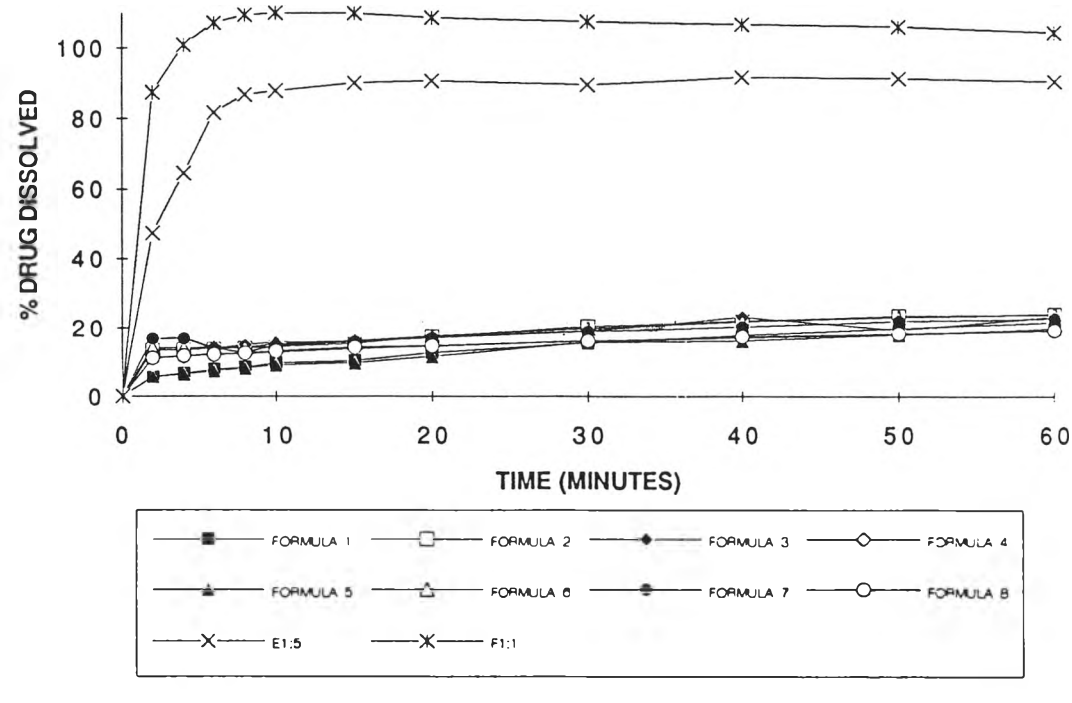

Figure 2 Dissolution profiles of indomethacin coprecipitate tablets as compared to 1:5 ID: lactose evaporated coprecipitat (E1:5) and 1:1 ID:lactose freeze-dried coprecipitate (F1:1).

very low and did not meet the requirement indicating a problem in the tablet formulation. By multiple regression, the relationship between the C_{20} and X_1, X_2, and X_3 was derived as the following.

$$C_{20} = 0.7175X_1 + 0.5200X_2 - 0.1300X_3 - 2.105X_1X_2 + 0.1950X_1X_3 + 0.1125X_2X_3 + 15.3625 \quad (R^2 = 0.996439)$$

From the C_{20} equation, it was demonstrated that C_{20} depended on X_1 ($\alpha = 0.005$), X_2 ($\alpha = 0.010$), and X_1X_2 ($\alpha = 0.005$). However, the dissolutions of all the prepared ID tablets were very low, ranging from the C_{20} of 11.54-17.66%. Therefore, this equation was no mean to obtain the requirement of 80% drug dissolved within 20 minutes.

As compared to the 1:5 ID:lactose evaporated coprecipitate and 1:1 ID: lactose freeze-dried coprecipitate, the tablets of the coprecipitates exhibited much lower dissolutions. This result indicated that the designed tablet formulations were not appropriate formulations. DCP, as a direct compressible filler, was reported to retard drug dissolution due to its hydrophobic nature (10). Hence, the use of this hydrophobic filler in the tablet formulations caused retardation in the dissolution enhancing effect of the coprecipitates. The compression of the coprecipitates into tablets was also another factor causing reduction in the dissolution enhancing effect of the solid dispersion. The tablets needed extra time to disintegrate into the coprecipitate powders and hence more time was required for drug dissolution.

Dangprasirt et al (4) prepared tablet containing 1:1 ID:lactose evaporated coprecipitate by using spray-dried lactose as a direct compressible filler and microcrystalline cellulose (Avicel PH 101^R) as a tablet disintegrant. The employed tablet formulation (per tablet) was listed as the following.

Indomethacin	25	mg
Lactose (as carrier)	25	mg
Spray-dried lactose	210.5	mg
Avice PH 101^R	30.0	mg
Magnesium stearate	0.2	mg
Aerosil^R	7.5	mg
Hardness	4-6	kp

The D.T. and C_{20} of this ID tablet formulation were 0.85 minute and 95.22%, respectively. Since spray-dried lactose was a water-soluble direct compressible filler; therefore, the use of a water-soluble filler along with a disintegrant resulted in the solid dispersion tablet of fast disintegration and high dissolution.

It would be noticed that by using freeze-drying technique in preparing ID solid dispersion, in addition to its convenience and ability to prepare at large-scale level, the amount of the carrier being used was also reduced. Lower amount of the applied carrier was benefit in the case of selecting a direct compressible filler. The direct compressible filler of low dilution potential such as spray-dried lactose could be used since the total amount of the drug-carrier was not high providing an additional advantage of less production cost. Although the freeze-drying process would yield the solid dispersion tablets of slow disintegration but this shortcoming could be overcome by the incorporation of a disintegrant in the tablets.

CONCLUSION

From this investigation, the freeze-drying technique was demonstrated to be useful to develop indomethacin coprecipitate with improvement in drug dissolution. The coprecipitate prepared by freeze-drying technique yielded faster dissolution than the one obtained by simple evaporation technique. However; when the freeze-dried coprecipitate was prepared into tablet, the use of tablet excipient would be carefully considered. The water-insoluble direct compessible filler, DCP, was found to retard drug dissolution. As the consequence, the use of DCP in the ID coprecipitate tablet would be avoided. In order to maintain the dissolution enhancing effect of the coprecipitation technique upon tabletting, the use of a water-soluble compressible filler and a disintegrant in the table formulation was suggested.

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การใช้เทคนิคการทำให้แห้งแบบเยือกแข็งในการเตรียมอินโดเมธาซิน-แลคโตสโซลิดดิสเพอร์ชัน

เพียรกิจ แดงประเสริฐ, ศันสนีย พงษ์วัย, วสันต์ ลิ้มพงศานุรักษ์ และโชคชัย ตรีกริชวัฒนา

ภาควิชาเภสัชอุตสาหกรรม คณะเภสัชศาสตร์ มหาวิทยาลัยรังสิต

บทคัดย่อ: อินโดเมธาซิน (ID) โซลิดดิสเพอร์ชันเตรียมขึ้นด้วยวิธีตกตะกอนร่วม โดยใช้ lactose เป็นตัวพาที่ละลายน้ำได้ ทำการเตรียมตะกอนร่วมของ 1:1 และ 1:5 ID:lactose โดยใช้เทคนิค 2 ประการ คือ เทคนิคการระเหยธรรมดา และเทคนิคการทำให้แห้งแบบเยือกแข็ง จากนั้นนำตะกอนร่วมของอินโดเมธาซินและผงยาอินโดเมธาซินไปศึกษาการละลายตัว พบว่าตะกอนร่วมของอินโดเมธาซินมีการละลายตัวของยามากกว่าผงยาอินโดเมธาซิน และเทคนิคการทำให้แห้งแบบเยือกแข็งให้ผลในการเพิ่มอัตราการละลายมากกว่าเทคนิคการระเหยธรรมดา ในการเตรียมตะกอนร่วมพบว่าเมื่อเพิ่มปริมาณของ lactose จะสังเกตเห็นผลการเพิ่มการละลายที่สูงขึ้นในตะกอนร่วมที่เตรียมจากการระเหย แต่ยังไม่พบผลดังกล่าวในตะกอนร่วมที่เตรียมจากเทคนิคการทำให้แห้งแบบเยือกแข็ง นำตะกอนร่วมของ 1:1 ID:lactose ที่เตรียมจากการทำให้แห้งแบบเยือกแข็ง และตะกอนร่วมของ 1:5 ID:lactose ที่เตรียมจากการระเหยไปตั้งตำรับเตรียมเป็นยาเม็ด จากนั้นศึกษาหาผลของเทคนิคที่ใช้ในการเตรียมตะกอนร่วม ปริมาณของ dicalcium phosphate dihydrate (DCP) และความแข็งของยาเม็ด ที่มีต่อการแตกตัวและการละลายตัวของยาเม็ด พบว่าเทคนิคที่ใช้ในการเตรียมตะกอนร่วมและความแข็งของยาเม็ด มีผลอย่างมีนัยสำคัญต่อการแตกตัวของยาเม็ด ในขณะที่เทคนิคที่ใช้ในการเตรียมตะกอนร่วม ปริมาณของ DCP และ interaction ของปัจจัยทั้งสองดังกล่าวมีผลอย่างมีนัยสำคัญต่อการละลายตัวของยาเม็ด และพบว่าไม่เหมาะสมที่จะใช้ DCP เป็นสารเพิ่มปริมาณที่ตอกอัดได้ในตำรับยาเม็ดที่เตรียมจากโซลิดดิสเพอร์ชันที่ต้องการให้ตัวยาละลายอย่างรวดเร็ว