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Preparation of Indomethacin Solid Dispersion Tablets Using Lactose and Polyvinylpyrrolidone as Single and Combined Water-Soluble Carriers

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ABSTRACT: Indomethacin solid dispersions were prepared by coprecipitation method using lactose and polyvinylpyrrolidone (PVP K30) as single and combined water-soluble carriers. The prepared coprecipitates were incorporated into tablets by direct compression process. Dissolution studies revealed that higher dissolution enhancing effect was derived from the solid dispersion tablets of single carrier as compared to the tablets of combined carriers. Disintegration retarding effect of PVP was responsible for less dissolution enhancing effect of the table of combined carriers. Statistical analysis was employed to identify the effect of lactose and PVP on disintergration and dissolution of indomethacin tablets. It was found that lactose and PVP exhibited interaction effect on tablet disintergration, both in physical mixture and coprecipitate tablets. Whereas, the interaction effect of lactose and PVP on tablet dissolution was not observed in the physical mixture tablets but was recognized in the coprecipitate tablets. The significant relationship between tablet disintegration time and dissolution was also established. Contour plots illustrated the effects of lactose and PVP on indomethacin tablet disintergration and dissolution were drawn.

KEY WORDS: Combined water-soluble carriers, Coprecipitates, Multiple regression, Statistical analysis

INTRODUCTION

Solid dispersion has been widely investigated as a ool to increase dissolution of poorly water-soluble drugs 1). By dispersing a poorly soluble drug within an inert oluble carrier, the drug dissolution can be significantly mproved. The increased dissolution is due to reduction in rug particle size down to molecular or colloidal level (2, 3). Various water-soluble carriers have been utilized to ncrease drug dissolution. These carriers include water-oluble polymers (such as polyethylene glycols and olyvinylpyrrolidone), sugars (such as dextrose, mannitol, nd sorbitol), soluble acids, and surfactants. In preparing oid dispersion, these carriers were commonly used as sin-le carrier but their uses as combined water-soluble carriers vere also recognized (4-6).

Combined water-soluble carriers were demonstrated o yield more drug dissolution enhancement than single water-soluble carriers (4-6). Dextrose, polyethylene glycol (PEG 4000), and polyvinylpyrrolidone (PVP K30) were studied as single and combined carriers (dextrose-PEG 4000 and dextrose-PVP K30) in preparing indomethacin solid dispersions by coprecipitation technique (5). By using appropriate ratio of combined carriers, it was demonstrated that the indomethacin tablets prepared from coprecipitates of combined carriers yielded faster dissolution than the tablets prepared from coprecipitates of single carriers.

The objective of this investigation was to employ lactose and PVP K30 as single and combined carriers for preparing indomethacin coprecipitates aiming to enhance indomethacin dissolution from indomethacin tablets prepared from the coprecipitates. Statistical analysis using multiple regression was applied to compare the effects of single and combined carriers on indomethacin tablet disintergrations and dissolutions. These effects were also explained by contour plots.

MATERIALS AND METHODS

Materials

The following chemicals were supplied by commercial sources: indomethacin (Batch. no. 89-06-03, Vertex Chemical Company, Hong Kong), lactose (supplied by Pharmaceutical Science Ltd., Thailand), polyvinylpyrrolidone (PVP K30, supplied by Pharmaceutical Science Ltd., Thailand), microcrystalline cellulose (Avicel PH 101^R, Lot No. 20325, Ming Tai Chemical, Co., Ltd., Taiwan R.O.C.), spray-dried lactose (supplied by Pharmaceutical Science Ltd., Thailand), silicon dioxide (Aerosil^R, supplied by Pharmaceutical Science Ltd., Thailand), magnesium stearate (supplied by Pharmaceutical Science Ltd., Thailand), absolute ethanol (supplied by Government Pharmaceutical Organization, Thailand), monobasic phosphate sodium (Fluka-Garantie, Switzerland), sodium hydroxide (Ajak Chemicals, Australia).

Equipment

The following equipment was used: analytical balance (Sartorious, Model A200S, Germany), single stroke tabletting machine (Viuhang Engineering, Thailand). pH meter (Schott Co., Model CG 840, Germany), disintegrator (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 carriers, as listed in Table 1, were dissolved in 60 ml of absolute ethanol. For lactose, it was firtly dissolved in 10 ml of distilled water and then was incorporated into the ethanolic solution of drug or drug and PVP to make the final volume of 60 ml. The solution was mixed thoroughly and the solvent was 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 coprecipitates was then pulverized and screened through a 40 mesh sieve and kept in a desiccator.

Preparation of indomethacin physical mixtures

The amounts of the drug and carrier(s) as indicated in Table 1 were thoroughly mixed for 5 minutes using a mortar and a pestle. The mixture was then screened through a 40 mesh sieve and stored in a desiccator.

Preparation of indomethacin tablets

Indomethacin tablets were prepared by direct compression according to the formulations listed in Table 2. All the excipients were screened through a 40 mesh sieve and then mixed with the coprecipitates or the physical mixtures by geometric dilution for 10 minutes. The obatined mixtures were directly compressed into tablets using a single stroke tabletting machine to yield the tablets having diameter of 9 mm and hardness of 4-6 kp. The control tablet containing indomethacin powder was also prepared.

Table 1 Quantities of Indomethacin and Carrier(s) Used in Preparing Coprecipitates and Physical Mixtures.

Coprecipitate or Physical Mixture	Indomethacin (g)	Lactose (g)	PVP K30 (g)
1:0 drug:carrier	3.75	–	–
1:(0.0+1.0) drug:(lactose+PVP)	3.75	–	3.75
1:(0.2+0.8) drug:(lactose+PVP)	3.75	0.75	3.00
1:(0.4+0.6) drug:(lactose+PVP)	3.75	1.50	2.25
1:(0.6+0.4) drug:(lactose+PVP)	3.75	2.25	1.50
1:(0.8+0.2) drug:(lactose+PVP)	3.75	3.00	0.75
1:(1.0+0.0) drug:(lactose+PVP)	3.75	3.75	–

Table 2 Formulations of Indomethacin Tablets (Per Tablet).

Formulation	Control	P1 C1	P2 C2	P3 C3	P4 C4	P5 C5	P6 C6
Indomethacin (mg)	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Lactose (mg)	–	–	5.0	10.0	15.0	20.0	25.0
PVP K30^{R} (mg)	–	25.0	20.0	15.0	10.0	5.0	0.0
Spray-dried lactose (mg)	210.5	210.5	210.5	210.5	210.5	210.5	210.5
Avicel PH 101^{R} (mg)	30.0	30.0	30.0	30.0	30.0	30.0	30.0
Magnesium stearate (mg)	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Aerosil (mg)	7.5	7.5	7.5	7.5	7.5	7.5	7.5

Note: P = Physical mixture tablet formulation
C = Coprecipitate tablet formulation

Table 3 Average Disintegration times of Indomethacin Tablets Containing Lactose and PVP K30 in Various Ratios.

Indomethacin:lactose:PVP	Disintegration time (average ± S.D.) (minutes)	
	Physical mixture	Coprectipitate
1:0:0 (Control tablet)	0.76 ± 0.11	–
1:0:1	12.73 ± 1.72	4.70 ± 1.38
1:0.2:0.8	13.69 ± 1.25	13.29 ± 1.62
1:0.4:0.6	11.48 ± 1.02	14.98 ± 1.17
1:0.6:0.4	11.70 ± 0.72	12.56 ± 1.18
1:0.8:0.2	3.79 ± 1.67	10.07 ± 2.40
1:1:0	1.28 ± 0.15	0.85 ± 0.19

Disintegration studies

The disintegration studies of the indomethacin tablets ere conducted by a USP type disintegrator using distilled ater as medium. The temperature of the medium was aintained at 37±1 °C throughout the experiment. Each verage disintegration time was obtained from 6 tablets.

Dissolution studies

Dissolution studies of indomethacin tablets were per-rmed by USP type I dissolution apparatus according to e dissolution of indomethacin capsule, USP XXII & NF VII (7). Seven hundred and fifty milliliters of a mixture 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 basket was adjusted to rotate at 100 rpm. Ten milliliters of dissolution medium was withdrawn at various time intervals up to 90 minutes 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.

RESULTS AND DISCUSSION

Disintegration studies

Table 3 demonstrates the average disintegration times of the indomethacin tablets. For 1:1 indomethacin:lactose

tablets, there was no difference in disintegration time between the tablets of coprecipitate and physical mixture ($\alpha = 0.01$). However, the 1:1 indomethacin:PVP tablet of coprecipitate exhibited faster disintegration time than the 1:1 indomethacin:PVP tablet of physical mixture ($\alpha = 0.01$).

For the 1:1 indomethacin: (lactose+PVP) tablets, there were no differences between the disintegration times of the coprecipitate and physical mixture tablets containing lactose:PVP in the ratios of 0.2:0.8 and 0.6:0.4, respectively ($\alpha = 0.01$). But in the ratios of 0.4:0.6 and 0.8:0.2 lactose:PVP, the tablets of coprecipitates yield slower disintegration times than the tablets of pysical mixtures in both ratios ($\alpha = 0.01$).

The disintegration time of the control tablet was fast and close to those of the 1:1 indomethacin:lactose tablets.

For the physical mixture tablets, higher amount of PVP resulted in retardation of tablet disintegration from the lactose:PVP ratio of 1.0:0.0 up to the ratio 0.6:0.4, then from the ratio of 0.6:0.4 to the ratio of 0.0:1.0 the disintegration retarding effect of PVP was absent. Similarly, in the coprecipitate tablets, higher amount of PVP also resulted in disintegration retarding effect from the lactose:PVP ratio of 1.0:0.0 to 0.4:0.6, then the effect was disappeared. In contrast, from the lactose:PVP ratio of 0.4:0.6 to the ratio of 0.0:1.0, the disintegration times of the coprecipitate tablets were decreased. These results indicated that the effects of the amount of PVP or lactose on the indomethacin physical mixture and coprecipitate tablets were complicated. Hence, the interaction effects between lactose and PVP on the indomethacin tablet disintegrations, both in the physical mixture and coprecipitate tablets, were expected.

In order to evaluate the main effects of lactose or PVP and the interaction effects of lactose and PVP on the physical mixture and coprecipitate tablets, a multiple regression computer program was applied to analyse the disintegration data. Therefore, the disintegration data of the physical mixture tablets and of the coprecipitate tablets were subjected to multiple regression. Two variables were established, these were the fraction of lactose (X_1) and the fraction of PVP (X_2) utilized in preparation of the indomethacin solid dispersions or physical mixtures. Hence, the ranges of X_1 and X_2 being studied were 0.0-1.0. By multiple regression, various relationships between disintegration time (D.T.) and the two variables (X_1 and X_2) were established. These relationships were evaluated basing on their correlation coefficient (R^2) as shown in Table 4, and the most appropriate relationship was selected to represent the most possible relationship between the disintegration time and the two variables. From Table 4, it was demonstrated that the disintegration time of the physical mixture tablets was function of lactose (X_1) and interaction between lactose and PVP (X_1X_2) or function of PVP (X_2) and interaction between lactose and PVP (X_1X_2), as shown by the R^2 value of 0.931127. Similarly, the disintegration time of the coprecipitate tablets was function of X_1 and X_1X_2 or X_2 and X_1X_2 as confirmed by the R^2 value of 0.969119.

By multiple regression, the equations represented the relationship between the tablet disintegration time of the physical mixture tablets ($D.T._p$) or coprecipitate tablets ($D.T._c$) and the two variables, X_1 and X_2, were derived as following.

$$D.T._p = -12.390000X_1+17.924107X_1X_2 +12.916786 \quad (1.1)$$

or

$$D.T._p = 12.390000X_2+17.924107X_1X_2 +0.526786 \quad (1.2)$$

$(R^2 = 0.931127)$

$$D.T._c = -4.475714X_1+47.218750X_1X_2 +5.350357 \quad (2.1)$$

or

$$D.T._c = 4.475714X_2+47.218750X_1X_2 +0.874643 \quad (2.2)$$

$(R^2 = 0.969119)$

From the disintegration time equation of 1.1 and 2.1, it was demonstrated that the negative effect (disintegration enhancing effect) of lactose (X_1) on D.T. was observed in the tablets having PVP (X_2) in low content but did not exist the tablet of high PVP (X_2) content. At low X_2 content the negative effect of X_1 on D.T. exceeded the positive interaction effect of X_1X_2 while at high X_2 content the negative effect of X_1 was overcome by the positive interaction effect of X_1X_2. As a water-soluble polymer, PVP exhibited both wetting effect and sticky effect, the latter effect was due to high viscosity of PVP upon dissolved (2). In the case of low PVP content, the wetting effect and sticky effect were not much difference. Hence, the negative effect of lactose on D.T. was obviously observed. However, when PVP content was high the sticky effect was much higher than the wetting effect. As the result, the negative effect of lactose on D.T. was absent. This trend was observed both in the

physical mixture and coprecipitate tablets, but the interaction effect seemed to be higher in the coprecipitate tablets.

High amount of PVP presented in the tablets containng of 1:1 indomethacin:PVP was expected to result in slow ablet disintegration time. This was true in the tablet of ɔhysical mixture with the average disintegration time of 12.73 minutes. But the unexpected faster disintegration ime of 4.70 minutes was observed in the tablet of ɔoprecipitate. The water-soluble polymer, PVP, as it dis-ɔlved might impart a solubilizing or wetting effect on the drug. In 1:1 indomethacin:PVP coprecipitate, the molecules ɔf drug were intimately encircled by the PVP. Thereby, the vetting effect of PVP on the drug was believed to be higher n the coprecipitate than in the physical mixture. This rea-on was responsible for faster disintegration time of the ablet of 1:1 drug:PVP coprecipitate as compared to the ablet of 1:1 drug:PVP physical mixture.

In the 1:1 indomethacin:lactose tablets, there was no ifference between the disintegration times of the physical ɔixture and the coprecipitate tablet ($\alpha = 0.01$). This result ɔdicated that lactose did not impart additional wetting ffect on the drug in the coprecipitate tablets as compared ɔ the physical mixture tablets. The interaction effect of ɑctose and PVP (X_1X_2) on D.T., as shown in equations 1.2 nd 2.2, implied the effects of PVP on D.T. at low and high ɔntents of lactose were different. The positive effect (dis-ɑtegration retarding effect) of PVP on D.T. was higher at igh lactose content than at low lactose content. Since ctose was a sugar (8) therefore it could cause visous envi-ɔnment around the tablet upon dissolved. In the tablet of gh lactose content, this viscous effect was high enough to ɔntribute to the disintegration retarding effect of PVP ·sulting in more positive effect of PVP on D.T. In contrast, e viscous effect was low in the tablet of low lactose and ss contributing effect due to lactose was observed.

Dissolution studies

The results of dissolution studies are illustrated in ɑble 5, Figure 1, and Figure 2. Coprecipitation technique sulted in faster and more complete drug dissolution from e indomethacin tablets as compared to physical mixing ɔhnique. The indomethacin tablets prepared from the precipitates of combined carriers, lactose and PVP, ex-bited less dissolution enhancement than the tablets pre-red from the coprecipitates of single carrier. Therby, the e of lactose and PVP as combined water-soluble carrier d not provide any advantage over the use of single car-

Table 4 Correlation Coefficients (R^2) of Various Relationships between Tablet Disintegration Time (D.T.), Percentage of Drug Dissolved at the 20th Minute (C_{20}), Time for 80% Drug Dissolved (T_{80}) and the Two Variables, the Fraction of Lactose (X_1) and PVP (X_2).

Effect(s) Included	R^2 of Physical Mixture Tablets for D.T.	C_{20}	T_{80}
X_1	0.790037	0.869271	0.841401
X_2	0.790037	0.869271	0.841401
X_1X_2	0.141091	0.021643	0.028176
X_1 and X_1X_2	0.931127	0.886906	0.869577
X_1 and X_1X_2	0.931127	0.886906	0.869577
Effect(s) Included	**R^2 of Coprecipitate Tablets for D.T.**	**C_{20}**	**T_{80}**
X_1	0.092316	0.167459	0.246476
X_2	0.092316	0.167459	0.246476
X_1X_2	0.876803	0.676758	0.667817
X_1 and X_1X_2	0.969119	0.844181	0.937987
X_1 and X_1X_2	0.969119	0.844181	0.937987

rier, lactose or PVP, in increasing drug dissolution from indomethacin tablets.

USP XXII & NF XVII established indomethacin dissolution requirement of 80% drug dissolved within 20 minutes for the solid dosage form (7). But the control tablet gave only 68% indomethacin dissolution within 20 minutes which was lower than the official requirement. The higher amount of PVP presented in the tablets of physical mixtures caused increasing disintegration times and consequently decreasing drug dissolutions as demonstrated in Table 5 and Figure 1, 2.

In order to establish the relationship between the dissolution of the physical mixture tablets or coprecipitate tablets and the two variables, X_1 and X_2, two dissolution parameters were set. These parameters were the percentage of drug dissolved at the time of 20 minutes (C_{20}) and the time required for 80% drug dissolved (T_{80}). Then, the multiple regression computer program was used to construct the relationship between the C_{20} or T_{80} and the two variables,

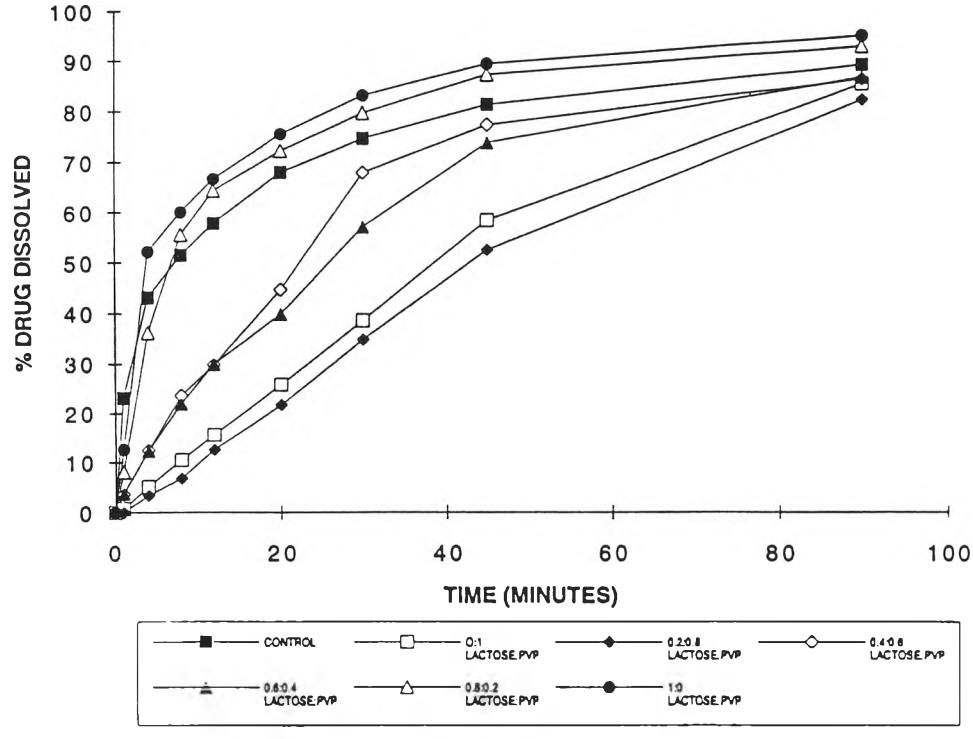

Figure 1 Dissolution profiles of indomethacin physical mixture tablets.

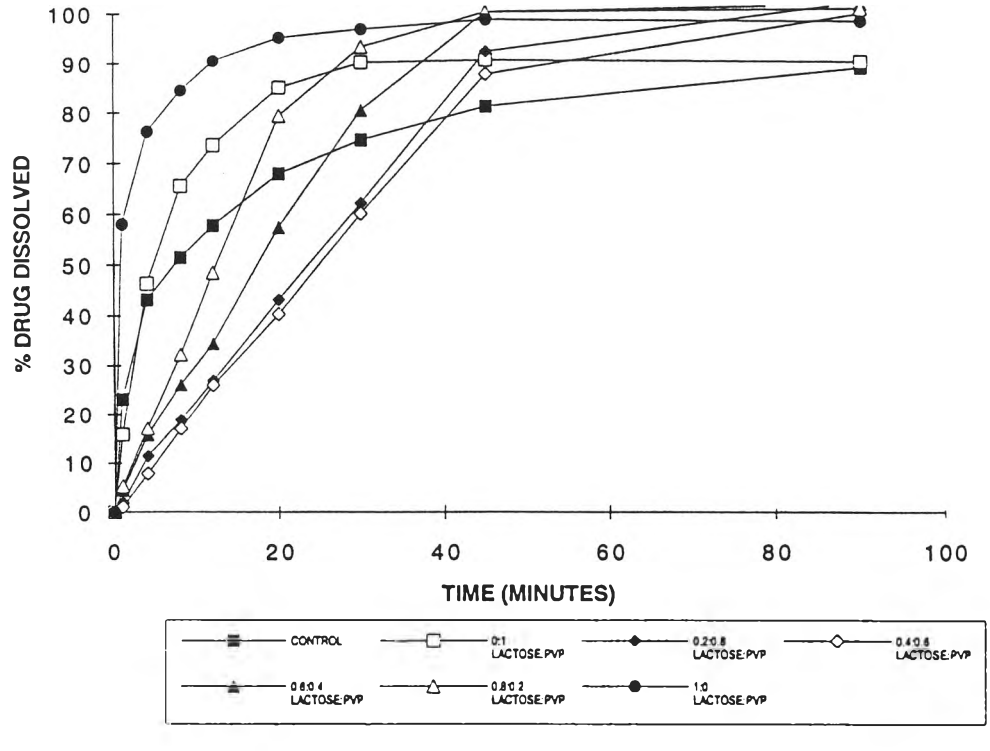

Figure 2 Dissolution profiles of indomethacin coprecipitate tablets.

X_1 and X_2. Various functions were built as shown in Table 4 and the appropriate function, according to the highest R^2 value, was selected. The following equations represented the selected models of C_{20} and T_{80} as function of X_1 and X_2.

$$C_{p20} = 56.514286X_1 - 33.142857X_1X_2 + 22.808571 \quad (3.1)$$

or

$$C_{p20} = -56.514286X_2 - 33.142857X_1X_2 + 79.322857 \quad (3.1)$$

($R^2 = 0.836906$)

$$C_{c20} = 25.197143X_1 - 173.361607X_1X_2 + 77.279643 \quad (4.1)$$

or

$$C_{c20} = -25.197143X_2 - 173.361607X_1X_2 + 102.476786 \quad (4.2)$$

($R^2 = 0.844181$)

Where C_{p20} and C_{c20} were C_{20} of the physical mixture tablet and coprecipitate tablets, respectively.

$$T_{p80} = -62.0X_1 + 38.839286X_1X_2 + 83.821429 \quad (5.1)$$

or

$$T_{p80} = 62.0X_2 + 38.839286X_1X_2 + 21.821429 \quad (5.2)$$

($R^2 = 0.869577$)

$$T_{c80} = -17.714286X_1 + 107.589286X_1X_2 + 20.178571 \quad (6.1)$$

or

$$T_{c80} = 17.714286X_2 + 107.589286X_1X_2 + 2.464286 \quad (6.2)$$

($R^2 = 0.937987$)

Where T_{p80} and T_{c80} were T_{80} of the physical mixture tablet and coprecipitate tablets, respectively.

Table 5 The Dissolution Parameters of Indomethacin Tablets Containing Lactose and PVP K30 in Various Ratios.

Indomethacin Tablet Containing	C_{20} (%)	T_{80} (**minute**)
1:0 drug:carrier (control)	67.95	42
1:(0.0+1.0) drug:(laclose+PVP)		
physical mixture	25.76	80
coprecipitate	85.13	17
1:(0.2+0.8) drug:(lactose+PVP)		
physical mixture	21.75	87
coprecipitate	43.12	39
1:(0.4+0.6) drug:(laclose+PVP)		
physical mixture	44.69	59
coprecipitate	40.29	40
1:(0.6+0.4) drug:(lactose+PVP)		
physical mixture	39.91	66
coprecipitate	57.44	33
1:(0.8+0.2) drug:(laclose+PVP)		
physical mixture	72.21	30
coprecipitate	79.38	20
1:(1.0+0.0) drug:(lactose+PVP)		
physical mixture	75.56	26
coprecipitate	95.22	5

Table 6 The t-values for the Effects of X_1, X_2, and X_1X_2 on D.T., C_{20}, and T_{80} of the Physical Mixture and Coprecipitate Tablets.

Effect(s)	t-values for physical mixture tablets D.T.	C_{20}	T_{80}
X_1	–5.866250	4.780772	–4.399314
X_2	5.866250	–4.780772	4.399314
X_1X_2	2.479055	–0.819010	0.805052
Effect(s)	**t-values for coprecipitate tablets D.T.**	**C_{20}**	**T_{80}**
X_1	–2.994727	1.795877	–3.307549
X_2	2.994727	–1.795877	3.307549
X_1X_2	9.229299	–3.609422	5.868282

D.F. = 3 : $t(\alpha = 0.005) = 12.924$, $t(\alpha = 0.001) = 10.213$, $t(\alpha = 0.0025) = 7.453$, $t(\alpha = 0.005) = 5.841$
$t(\alpha = 0.010) = 4.541$, $t(\alpha = 0.025) = 3.182$, $t(\alpha = 0.05) = 2.353$, $t(\alpha = 0.10) = 1.638$

To consider the significant effects of X_1, X_2, and X_1X_2 on C_{20} and T_{80} of the physical mixture and coperecipitate tablets as derived in the equations listed above, the t-value of each effect was computed by a statistical computer program as demonstrated in Table 6.

By examining the effect of X_1, X_2, and X_1X_2 on C_{20} and T_{80} of the physical mixture tablets; it was recognized that the significant effects on C_{20} and T_{80} were derived from X_1 ($\alpha = 0.010$ and 0.025) or X_2 ($\alpha = 0.010$ and 0.025), while the effect of X_1X_2 was insignificant. However, it was found that C_{20} and T_{80} of the coprecipitate tablets were significantly influenced by X_1 ($\alpha = 0.10$ and 0.025), X_2 ($\alpha = 0.10$ and 0.025), and X_1X_2 ($\alpha = 0.025$ and 0.005). This result hinted that the dissolution of the physical mixture tablets depended on the content of lactose or PVP. The same positive effect of lactose and the same negative effect of PVP on C_{20} were observed at low and high contents of PVP and lactose, respectively. Similarly, the negative effect of lactose and positive effect of PVP on T_{80} were not different at low and high contents of PVP and lactose, respectively. Whereas, the significant effect of X_1X_2 on C_{20} or T_{80} of the coprecipitate tablets indicated that the effect of lactose or PVP on dissolution was not the same at low and high content of PVP or lactose. The positive effect of lactose on C_{20} and the negative effect of lactose on T_{80} were found at low content of PVP but did not exist at high PVP content. In contrast, the negative effect of PVP on C_{20} and the positive effect of PVP on T_{80} was more significant at high content of lactose than at low content of lactose.

In solid dispersion tablets, PVP could impart two effects consisting of drug dissolution enhancing effect due to solid dispersion and tablet disintegration retarding effect. The latter effect also resulted in dissolution retardation. At low PVP content the dissolution enhancing effect was prominent while at high PVP content the disintegration retarding effect was prominent. Therefore, the positive effect of lactose on dissolution was present at low PVP content but was absent at high PVP content.

As mentioned, lactose was a sugar and upon dissolving it could induce viscous environment to tablet. This viscous environment was significant in the case of high lactose content, resulting in additional dissolution retarding effect. Hence, the negative effect of PVP (dissolution retarding effect) on C_{20} was more prominent at high content of lactose than at low lactose content.

The same explanation could be used to explain the effects of X_1, X_2, and X_1X_2 on T_{80} considering that T_{80} was inverse proportion to C_{20}.

Relationship between disintegration and dissolution

In order to study the relationship between tablet disintegration and dissolution, the data of D.T. and C_{20} was searched for an appropriate model. Different models were built and their R^2 were compared. These models were demonstrated as the follwing.

Physical mixture tablets

$$C_{20} = -4.220876\ D.T. + 85.105803 \quad (R^2 = 0.933894) \quad (7.1)$$

$$C_{20} = 2.449391\ D.T. - 0.448791\ D.T.^2 + 71.762237 \quad (R^2 = 0.982916) \quad (7.2)$$

$$C_{20} = -0.287383\ D.T.^2 + 77.020750 \quad (R^2 = 0.976442) \quad (7.3)$$

Coprecipitate tablets

$$C_{20} = -3.886434\ D.T. + 103.328197 \quad (R^2 = 0.864765) \quad (8.1)$$

$$C_{20} = 1.139120\ D.T. - 0.319400\ D.T.^2 + 92.404221 \quad (R^2 = 0.936187) \quad (8.2)$$

$$C_{20} = -0.250410\ D.T.^2 + 95.268207 \quad (R^2 = 0.932690) \quad (8.3)$$

From the R^2 of the above relationships, it was clearly evident that the C_{20} of the physical mixture and cprecipitate tablets were function of D.T. and $D.T.^2$ or $D.T.^2$ according to equations 7.2 or 7.3 and 8.2 or 8.3, respectively. Therefore, it was possible to calculate the required D.T. of the physical mixture and coprecipitate tablets resulting in the C_{20} of 80%. According to the equations 7.3 and 8.3, the D.T. of not more than 7.81 minutes for the coprecipitate tablet was considered as the required D.T., while it was infeasible for the physical mixture tablet to yield C_{20} of 80%.

Contour plots

In order to view the effects of lactose and PVP on the D.T., C_{20}, and T_{80} of the coprecipitate tablets, the contour plots of the equations 2.1, 4.1, and 6.1 were drawn as shown in Figure 3, 4, and 5. From the contour plots, the values of D.T., C_{20}, and T_{80} obtained by varying X_1 and X_2 in the range of 0.0-1.0 were identified. These contour plots also demonstrated the effects of X_1 on D.T., C_{20}, and T_{80} at low and high contents of X_2 and vice versa. The superimposed contour polot of D.T., C_{20}, and T_{80} equations, as demonstrated in Figure 6, was used to identify the value of X_1 and X_2 that would yield the required constrains of D.T., C_{20}, and T_{80}. For the required D.T. of not more than 30 minutes and C_{20} of not less than 80%, the various ratio of X_1 and X_2 that would yield the predetermined T_{80} could be selected.

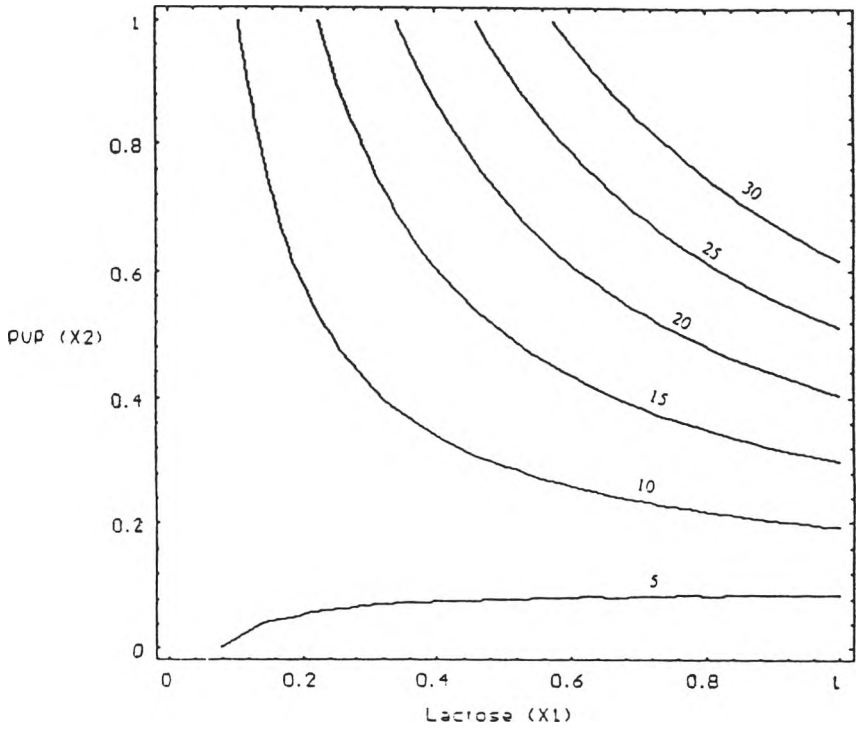

Figure 3 The contour plot for D.T. (minutes) as function of lactose (X_1) and PVP K30 (X_2)

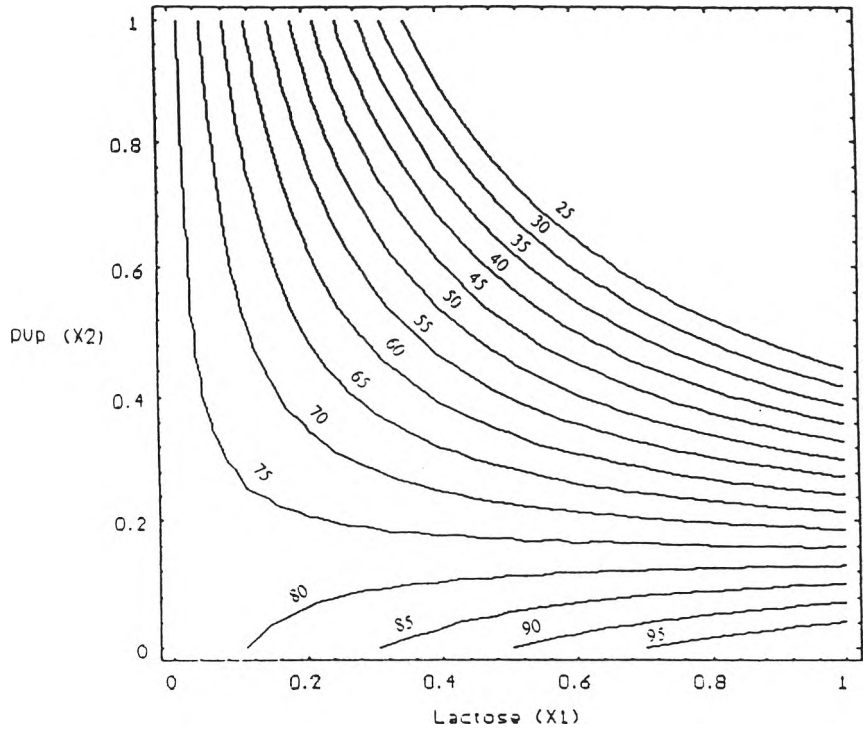

Figure 4 The contour plot for C_{20} (%) as function of lactose (X_1) and PVP K30 (X_2)

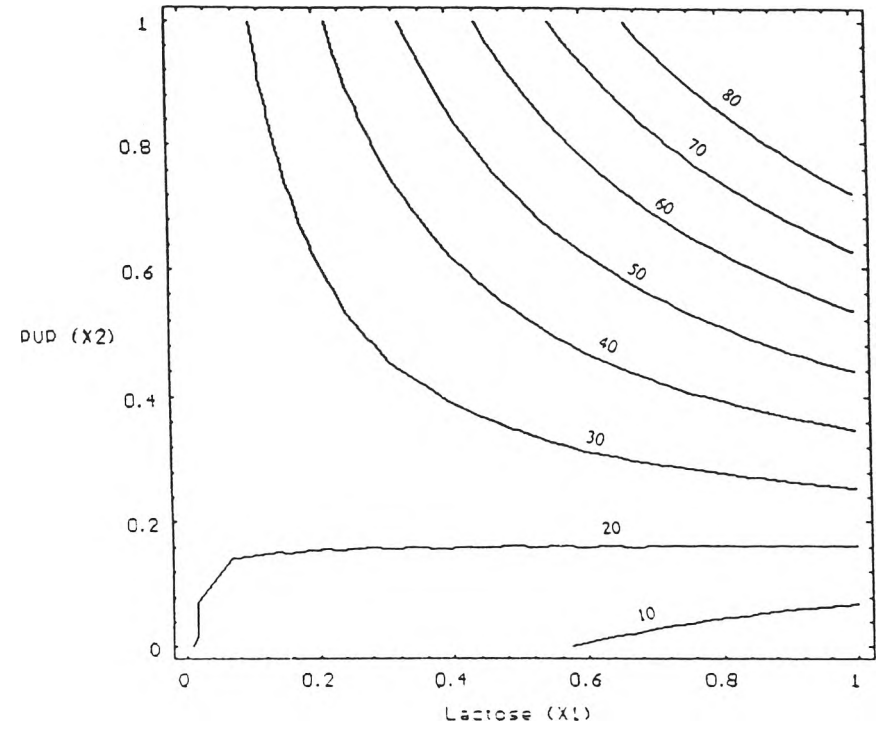

Figure 5 The contour plot for T_{80} (minutes) as function of lactose (X_1) and PVP K30 (X_2)

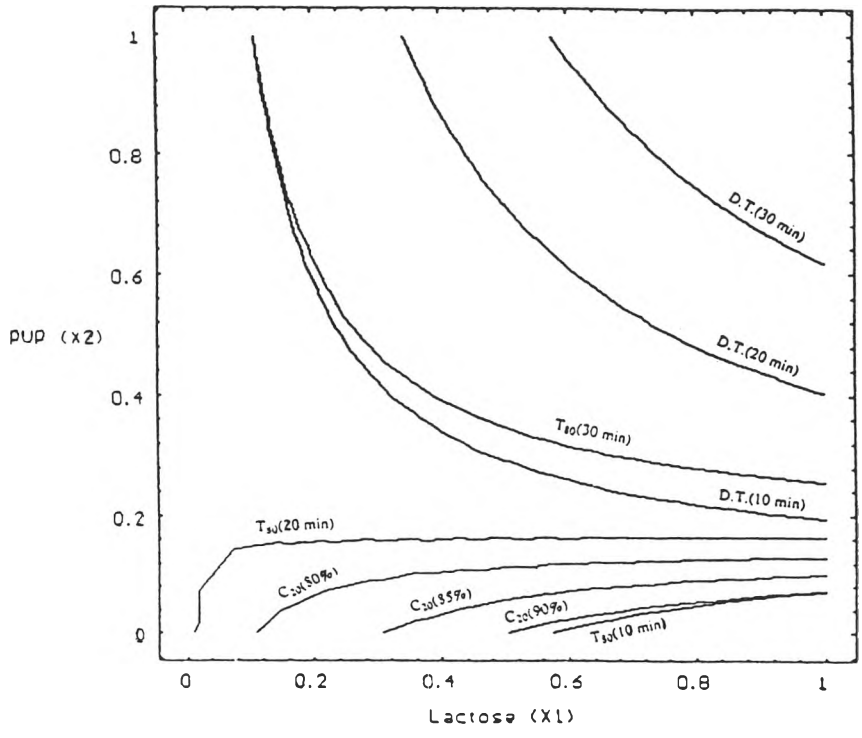

Figure 6 The superimposed contour plot for D.T., C_{20}, and T_{80} as functions of lactose (X_1) and PVP K30 (X_2)

CONCLUSION

This investigation demonstrated the effect of lactose and PVP K30 as single and combined water-soluble carriers on indomethacin tablet disintegration and dissolution. Their use as single carrier was found to yield higher indomethacin dissolution enhancement than their use as combined carriers. The interaction effect of lactose and PVP on retardation of tablet disintegration was beleived to be a reason for less dissolution enhancement of the combined carriers. The statistical analysis, by the aid of multiple regression, was shown to be useful in evaluating the main effects and interaction effects of lactose and PVP on tablet disintegration time and dissolution. The contour plots were also helpful in location the right ratio of lactose per PVP resulting in the required disintegration time and dissolution of the indomethacin coprecipitate tablets. The use of combined water-soluble carriers would be useful if the carrier of disintegration retarding effect such as PVP, was avoided. Since the latter effect tended to counter the dissolution enhancing effect of the combined carriers. For indomethacin tablets prepared from both physical mixture and coprecipitate tablets, the relationships between their C_{20} or T_{80} and disintegration time were represented by polynomial equation. The significance of the established relationship between tablet disintegration time and C_{20} could be benefit as a guideline to produce the indomethacin tablets of required dissolution.

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การเตรียมยาเม็ดอินโดเมธาซินโซลิดดิสเพอร์ชันโดยใช้แลคโตสและโพลีไวนิลไพโรลิโดนตามลำพัง และร่วมกันเป็นตัวพาที่ละลายน้ำได้

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บทคัดย่อ: อินโดเมธาซินโซลิดดิสเพอร์ชันเตรียมโดยวิธีการตกตะกอนร่วม โดยใช้แลคโตสและโพลีไวนิล-ไพโรลิโดน (PVP K30) ตามลำพังและร่วมกันเป็นตัวพาชนิดละลายน้ำได้ นำตะกอนร่วมที่เตรียมได้ไปทำเป็นยาเม็ดโดยกระบวนการตอกโดยตรง จากการศึกษาการละลายตัวพบผลของการเพิ่มการละลายเกิดขึ้นในยาเม็ดโซลิดดิสเพอร์ชันที่เตรียมจากการใช้ตัวพาเดี่ยว มากกว่าที่เกิดขึ้นในยาเม็ดโซลิดดิสเพอร์ชันที่เตรียมจากการใช้ตัวพาร่วม ผลของ PVP ในการยับยั้งการแตกตัวของยาเม็ด เป็นสาเหตุที่ทำให้ยาเม็ดที่เตรียมจากตัวพาร่วมมีการเพิ่มอัตราการละลายที่ต่ำกว่า เมื่อทำการวิเคราะห์เชิงสถิติเพื่อพิจารณาผลของแลคโตสและ PVP ที่มีต่อการแตกตัวและการละลายตัวของยาเม็ดอินโดเมธาซิน พบว่าแลคโตสและ PVP มีผลแบบ interaction ต่อการแตกตัวของยาเม็ด ทั้งยาเม็ดที่เตรียมจากของผสมทางกายภาพและยาเม็ดที่เตรียมจากตะกอนร่วม ในขณะที่ไม่พบผลแบบ interaction ของแลคโตสและ PVP ต่อการละลายตัวของยาเม็ดที่เตรียมจากของผสมทางกายภาพ แต่พบในยาเม็ดที่เตรียมจากตะกอนร่วม นอกจากนั้นยังพบความสัมพันธ์อย่างมีนัยสำคัญระหว่างเวลาที่ใช้ในการแตกตัวของยาเม็ดและการละลายตัวของยาเม็ด สามารถอธิบายผลของแลคโตสและ PVP ที่มีต่อการแตกตัวและการละลายตัวของยาเม็ดอินโดเมธาซินได้จากกราฟแบบ contour plot

กุญแจคำ: ตัวพาร่วมที่ละลายน้ำได้, ตะกอนร่วม, การถดถอยแบบพหุคูณเชิงเส้น, การวิเคราะห์ผลเชิงสถิติ