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Effect of Combined Water-Soluble Carriers on Dissolution Rates of Indomethacin Tablets Prepared by Coprecipitation Technique (ผลของตัวพาชนิดละลายน้ำได้สองชนิดประกอบกันต่...

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ORIGINAL ARTICLE

Effect of Combined Water-Soluble Carriers on Dissolution Rates of Indomethacin Tablets Prepared by Coprecipitation Technique

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Abstract

Indomethacin tablets were directly compressed from coprecipitates of drug with various ratios of combined water-soluble carriers, dextrose : polyethylene glycol (PEG) 4000, and dextrose : sodium lauryl sulfate (SLS). The disintegration and dissolution of these tablets were studied and compared to those prepared from physical mixtures and indomethacin control tablets. The results revealed that tablets containing combined water soluble carriers prepared by coprecipitation produced better dissolution than those prepared by physical mixing and consequently the control tablets. Higher amount of PEG 4000 or SLS lowered the dissolution rate because of their disintegration retarding property. This effect was prominent when coprecipitation technique was used. These two combined water-soluble carriers gave coprecipitates of higher drug dissolution rate than their individual carriers. Dextrose : SLS systems offered higher dissolution than dextrose : PEG 4000 systems. At the ratio of 0.6 : 0.4, indomethacin tablets containing dextrose : PEG 4000 or dextrose : SLS coprecipitates produced highest dissolution rate. (Th. J. Pharm. Sci., Vol 12 No.3, 225-236 (1987)).

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INTRODUCTION

Application of solid dispersion systems is one of the important method to improve dissolution, absorption and therapeutic efficacy of poorly soluble drugs (1). In these systems, one or more drugs were dispersed in inert water soluble carrier (s) or matrix at solid state prepared by fusion, coprecipitation or fusion-coprecipitation technique. It was reported that coprecipitation technique gave superior dissolution than melting technique (2). Many materials have been examined as potential carriers (3). They are classified as either sugars, soluble polymers, surfactants or soluble acids. Polyethylene glycols and polyvinyl-pyrrolidones were most reported carriers. Combined carriers of sugars or sugar with polymer or sugar with surfactant were reported to yield more improvement of the dissolution of glibencamide, hydrochlorothiazide, tolbutamide or diazepam than single carrier (4, 5, 6, 7).

Indomethacin is a very low aqueous soluble drug. It has been widely used as an anti-inflammatory analgesic in rheumatoid arthritis, spondylitis, osteoarthritis, and to a lesser extent in gout. Its absorption is reported to be formulation dependence and the drug has been classified under demonstrating clinical inequivalence among its formulations (8).

The purpose of this investigation was to applied solid dispersion technique to enhance the dissolution rates of indomethacin by using coprecipitation method. Three water-soluble carriers were utilized, dextrose, polyethylene glycol 4000 (PEG 4000) and sodium lauryl sulfate (SLS). Various ratios of dextrose : PEG 4000, dextrose : SLS were studied. The disintegration times and dissolution rates of tablets prepared from these coprecipitates and tablets of corresponding mixtures were investigated. The effect of amount and type of carriers on the disintergration and dissolution of these tablets were also studied.

MATERIALS AND METHOD

A. Chemicals - The following were obtained from commercial sources : indomethacin BP 1973[1], dextrose anhydrous USP/BP[2], polyethylene glycol 4000[1], sodium lauryl sulfate,[1] dicalcium phosphate dihydrate[1], microcrystalline cellulose (Avicel PH 102)[3], Cab-o-sil[1], absolute alcohol[4], potassium dihydrogen phosphate[5], sodium hydroxide[6].

B. Equipment - The following were used : hardness tester[a], single punch tablet machine[b], disintegration apparatus[c], dissolution apparatus USP type I[d], pH meter[e], spectrophotometer[f].

C. Preparation of Indomethacin Coprecipitates

Weighed quantities of the drug and carrier(s), presented in Table 1, were dissolved in 60 ml of absolute ethanol. The solution was mixed thoroughly and the solvent was allowed to evaporate continuously under a cold air stream. The resulting coprecipitate was placed in an incubator at 50°C overnight to eliminate the remaining solvent and then was stored in a dessicator until the dry solid coprecipitate was obtained. The dry coprecipitate was then screened through a 40 mesh sieve and kept in a dessicator.

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1. Pharmaceutical science Ltd., Part., Bangkok, Thailand.
2. Iwaki, Japan.
3. AMC Corporation Ltd., Bangkok, Thailand.
4. Merck, Germany.
5. Fluka-Garantie, Switzerland.
6. Eka Kemi, Sweden.

a. Model 2E/205, Dr. K. Schleuniger Co., Switzerland.
b. Model No.6, Viuhang Engineering, Thailand.
c. Manesty T.D. 65T170, Manesty Machines Ltd., England.
d. Model 500-230, Hansen Research Corporation, U.S.A.
e. Model 292, Pye Unicam Ltd., England.
f. Model 3600, Beckman, U.S.A.

D. Preparation of Indomethacin Physical Mixtures

The required amounts of the drug and carrier(s), as presented in Table 1, were thoroughly mixed for 5 minutes by using a motar and a pestle. The mixture was screened through a 40 mesh sieve and stored in a dessicator.

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

Coprecipitate or physical mixture	indomethacin (g)	dextrose (g)	PEG 4000 (g)	SLS (g)
1:0 drug : carrier	2.5			
1:(0.0+1.0) drug : (dextrose + PEG 4000)	2.5	—	2.5	—
1:(0.2+0.8) drug : (dextrose + PEG 4000)	2.5	0.5	2.0	—
1:(0.4+0.6) drug : (dextrose + PEG 4000)	2.5	1.0	1.5	—
1:(0.6+0.4) drug : (dextrose + PEG 4000)	2.5	1.5	1.0	—
1:(0.8+0.2) drug : (dextrose + PEG 4000)	2.5	2.0	0.5	—
1:(1.0+0.0) drug : (dextrose + PEG 4000)	2.5	2.5	—	—
1:(0.0+1.0) drug : (dextrose + SLS)	2.5	—	—	2.5
1:(0.2+0.8) drug : (dextrose + SLS)	2.5	0.5	—	2.0
1:(0.4+0.6) drug : (dextrose + SLS)	2.5	1.0	—	1.5
1:(0.6+0.4) drug : (dextrose + SLS)	2.5	1.5	—	1.0
1:(0.8+0.2) drug : (dextrose + SLS)	2.5	2.0	—	0.5
1:(1.0+0.0) drug : (dextrose + SLS)	2.5	2.5	—	—

E. Preparation of Indomethacin Tablets

The composition of indomethacin tablets was described in Table 2. The drug-carrier(s) coprecipitate or physical mixture was manually mixed with dicalcium phosphate dihydrate for 3 minutes. Microcrystalline cellulose and Cab-o-sil were then added and mixed for another 5 minutes. The obtained mixture was passed through a 40 mesh sieve and directly compressed into tablets using a single punch tablet machine to have a diameter of 9 mm and a hardness between 4-5 kps.

Table 2 Formulation of Indomethacin Tablets.

Ingredient	Weight (mg)
Indomethacin (as pure drug or drug in coprecipitates or drug in physical mixtures)	25
Microcrystalline cellulose	50
Dicalcium phosphate	145
Cab-o-sil	6

F. Disintegration Studies

The disintegration studies were conducted on test tablets using a USP XX disintegration apparatus. Water was used as disintegration medium and maintained at $37 \pm 1^\circ$ C throughout the experiment. Each average disintegration time was obtained from 6 tablets.

G. Dissolution Studies

The dissolution studies of indomethacin tablets were performed according to the dissolution of indomethacin capsules, USP XXI & NF XVI (9). Seven hundred and fifty millilitres of a mixture of distilled water and pH 7.2 phosphate buffer solution (4:1) was used as dissolution medium and maintained at $37 \pm 1^\circ$ C. The basket, containing a tablet, was adjusted to rotate at 100 rpm. Ten millilitre aliquots

of the dissolution medium were pipetted out at the intervals of time upto 1 hour, and filtered through a filter paper. About 5 ml of the first filtrate was discarded and the subsequent filtrate was used as the sample solution. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium.

Assay - Each sample solution was assayed spectrophotometrically at 318 nm for indomethacin content. The sample concentration was calculated from a standard curve.

Standard curve - Standard curve of indomethacin in dissolution medium was obtained between 10-50 mcg/ml. Absorbance at 318 nm versus concentration plots followed Beer's law.

The T_{80}, time when 80 percent of drug dissolves, and the C_{20}, concentration of drug dissolved after 20 minutes in dissolution medium, were calculated.

RESULTS

a. Dextrose - PEG 4000 systems

Disintegration studies : The average disintegration times of tablets containing drug : (dextrose + PEG 4000) were listed in Table 3. Higher amount of dextrose and lesser amount of PEG 4000 presented in the tablets caused decreasing in tablet disintegration time. Tablets containing dextrose as carrier alone produced the fastest disintegration, while tablets containing PEG 4000 alone produced the slowest. Coprecipitation technique produced slower tablet disintegration than physical mixing technique. In addition, tablet containing coprecipitates showed slower disintegration than control tablets except those containing very high amount of dextrose.

Table 3 Average Disintegration Times of Tablets Containing Various Systems of 1:1 Indomethacin: (dextrose + PEG 4000)

Indomethacin tablets containing	Average disintegration time ± S.D. (min)
1:0 drug : carrier coprecipitate	5.07 ± 0.93
1:(0.0 + 1.0) drug : (dextrose + PEG 4000) coprecipitate	22.38 ± 2.92
1:(0.0 + 1.0) drug : (dextrose + PEG 4000) physical mixture	12.84 ± 2.64
1:(0.2 + 0.8) drug : (dextrose + PEG 4000) coprecipitate	13.39 ± 2.51
1:(0.2 + 0.8) drug : (dextrose + PEG 4000) physical mixture	3.75 ± 0.92
1:(0.4 + 0.6) drug : (dextrose + PEG 4000) coprecipitate	10.30 ± 1.07
1:(0.4 + 0.6) drug : (dextrose + PEG 4000) physical mixture	2.93 ± 0.82
1:(0.6 + 0.4) drug : (dextrose + PEG 4000) coprecipitate	7.06 ± 1.68
1:(0.6 + 0.4) drug : (dextrose + PEG 4000) physical mixture	3.72 ± 1.16
1:(0.8 + 0.2) drug : (dextrose + PEG 4000) coprecipitate	3.70 ± 1.04

Indomethacin tablets containing	Average disintegration time ± S.D. (min)
1:(0.8+0.2) drug : (dextrose + PEG 4000) physical mixture	1.85±0.86
1:(1.0+0.0) drug : (dextrose + PEG 4000) coprecipitate	1.96±0.90
1:(1.0+0.0) drug : (dextrose + PEG 4000) physical mixture	1.51±0.73

* From 6 tablets

Dissolution studies : The dissolution parameters and dissolution profiles of tablets containing drug : (dextrose+PEG 4000) were demonstrated in Table 4 and Figure 1-2. The presence of these carriers in tablets clearly resulted in faster dissolution rate compared to indomethacin control tablets. All tablets containing coprecipitates yielded faster dissolution rates than tablets of corresponding physical mixtures.

Table 4 The Dissolution Parameters of Indomethacin Tablets Containing Various Systems of 1:1 Drug: (dextrose + PEG 4000)

Indomethacin tablets containing	C_{20}^{1}	C_{60}^{2}	T_{80}^{3} (min)
1:0 drug : carrier coprecipitate	35.8±2.13	70.2±1.55	>60
1:(0.0+1.0) drug : (dextrose + PEG 4000) coprecipitate	49.3±2.90	94.2±0.06	37.5
1:(0.0+1.0) drug : (dextrose + PEG 4000) physical mixture	36.8±0.55	87.7±0.09	43.5
1:(0.2+0.8) drug : (dextrose + PEG 4000) coprecipitate	73.7±1.44	97.1±0.90	24.0
1:(0.2+0.8) drug : (dextrose + PEG 4000) physical mixture	64.3±0.90	85.0±1.10	44.5
1:(0.4+0.6) drug : (dextrose + PED 4000) coprecipitate	88.9±0.44	97.2±1.17	1.50
1:(0.4+0.6) drug : (dextrose + PEG 4000) physical mixture	62.0±0.92	84.6±0.59	46.0
1:(0.6+0.4) drug : (dextrose + PEG 4000) coprecipitate	94.8±0.21	99.1±0.06	9.0
1:(0.6+0.4) drug : (dextrose + PEG 4000) physical mixture	61.5±1.67	86.6±1.03	42.5
1:(0.8+0.2) drug : (dextrose + PEG 4000) coprecipitate	76.6±0.51	90.0±1.04	25.5
1:(0.8+0.2) drug : (dextrose + PEG 4000) physical mixture	67.4±0.81	89.5±1.65	37.0
1:(1.0+0.0) drug : (dextrose + PEG 4000) coprecipitate	79.1±0.45	93.5±0.33	21.0
1:(1.0+0.0) drug : (dextrose + PEG 4000) physical mixture	67.3±0.00	86.3±0.74	40.5

[1] C_{20} = % drug dissolved obtained at the time of 20 minutes
[2] C_{60} = % drug dissolved obtained at the time of 60 minutes
[3] T_{80} = The time required for 80% drug dissolution

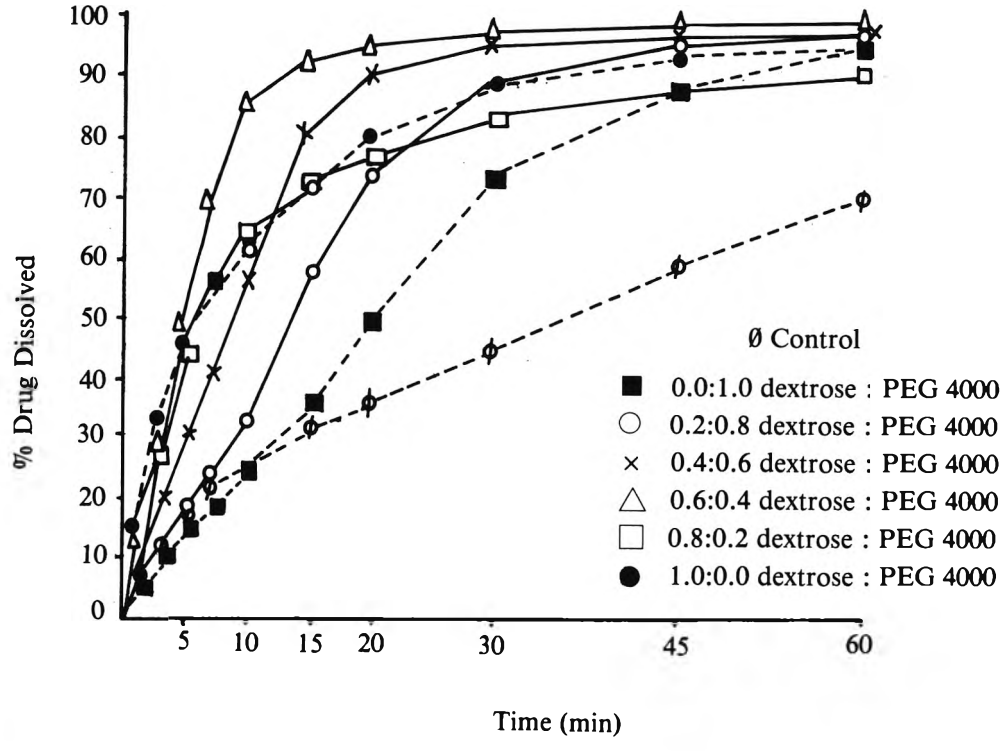

Figure 1 Dissolution profiles of tablets containing various systems of 1:1 indomethacin : (dextrose + PEG 4000) coprecipitates.

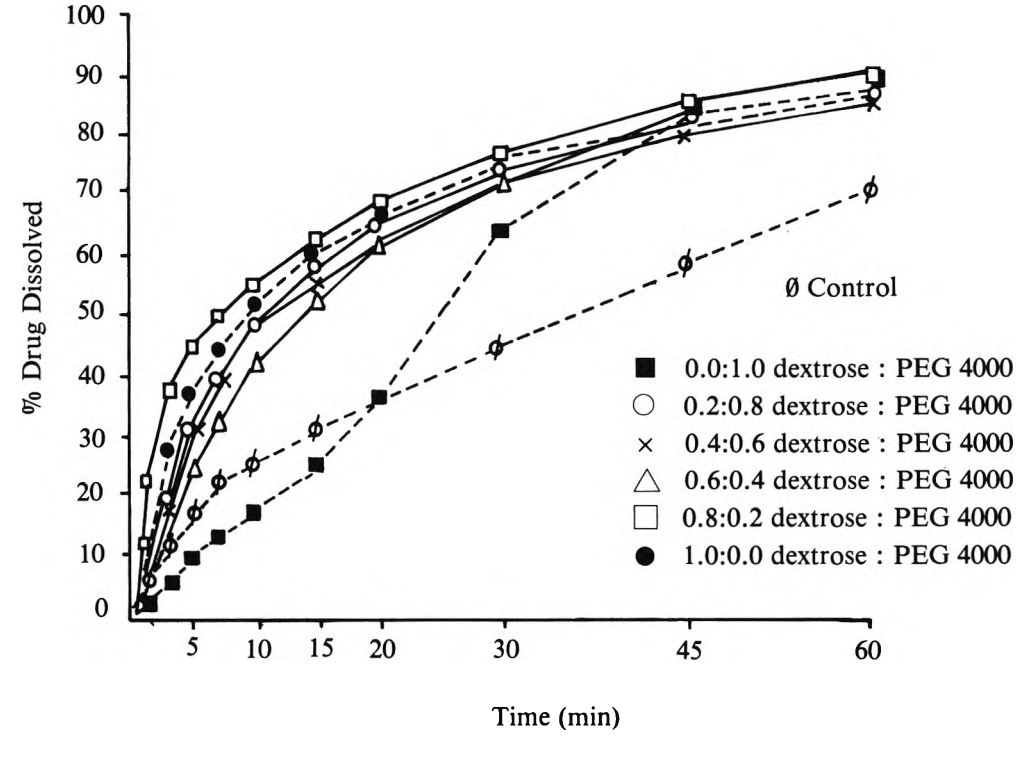

Figure 2 Dissolution profiles of tablets containing various systems of 1:1 indomethacin: (dextrose + PEG 4000) physical mixtures.

By comparing T_{80} of these tablets, the best system for improving indomethacin dissolution was the system of 1 : (0.6+0.4) drug : (dextrose + PEG 4000) coprecipitates. Among tablets containing physical mixtures, the tablets of 1 : (0.8 + 0.2) drug : (dextrose + PEG 4000) produced the fastest dissolution rate.

Within 20 minutes, the control tablets yielded 36% indomethacin dissolution while tablets containing physical mixtures yielded 61-68% and tablets containing coprecipitates yielded 73-95% dissolution.

b. Dextrose - SLS systems : The average disintegration times of tablets containing drug: (dextrose + SLS) were listed in Table 5. The increasing amount of SLS and decreasing amount of dextrose retarded tablet disintegration time. No difference in disintegration time between tablets containing coprecipitate and tablets containing corresponding physical mixture was observed (α = 0.05) except at 0.4:0.6 dextrose : SLS, the tablets containing coprecipitate gave faster disintegration time than tablets containing physical mixture. Nevertheless, the disintegration times of tablets containing carriers were slower or equal to those of control tablets.

Table 5 Average Disintegration Times of Tables Containing Various Systems of 1:1 Indomethacin: (dextrose + SLS)

Indomethacin tablets containing	**Average disintegration time* ± S.D. (min)**
1:0 drug : carrier coprecipitate	5.03 ± 0.93
1:(0.0+1.0) drug : (dextrose + SLS) coprecipitate	20.73 ± 2.34
1:(0.0+1.0) drug : (dextrose + SLS) physical mixture	22.02 ± 2.03
1:(0.2+0.8) drug : (dextrose + SLS) coprecipitate	20.51 ± 1.70
1:(0.2+0.8) drug : (dextrose + SLS) physical mixture	17.50 ± 2.54
1:(0.4+0.6) drug : (dextrose + SLS) coprecipitate	7.93 ± 1.25
1:(0.4+0.6) drug : (dextrose + SLS) physical mixture	14.92 ± 1.86
1:(0.6+0.4) drug : (dextrose + SLS) coprecipitate	7.82 ± 1.07
1:(0.6+0.4) drug : (dextrose + SLS) physical mixture	7.63 ± 0.86
1:(0.8+0.2) drug : (dextrose + SLS) coprecipitate	4.56 ± 0.58
1:(0.8+0.2) drug : (dextrose + SLS) physical mixture	5.03 ± 0.90
1:(1.0+0.0) drug : (dextrose + SLS) coprecipitate	1.96 ± 0.90
1:(1.0+0.0) drug : (dextrose + SLS) physical mixture	1.51 ± 0.73

* From 6 tablets

Dissolution studies : The dissolution parameters and dissolution profiles of tablets containing drug : dextrose + SLS were presented in Table 6 and Figure 3, 4. The presence of dextrose and SLS in tables clearly caused enhancement in drug dissolution. The tablets containing coprecipitate yielded faster dissolution rate than tablets containing corresponding physical mixture. All tablets containing dextrose + SLS exhibited faster dissolution rate than control tablets. However, tablets containing physical mixture showed slower dissolution rates during the first part of dissolution profile than control tablets except those containing dextrose alone.

By comparing T_{80} of these tablets, the best system for enhancement in indomethacin dissolution was 1 : (0.6 + 0.4) drug : (dextrose + SLS) coprecipitates. Within 20 minutes, the control tablets gave 36% drug dissolution while tablets containing physical mixtures produced 24-74% and tablets containing coprecipitates gave 91-96% dissolution.

Table 6 The Dissolution Parameters of Indomethacin Tablets Containing Various Systems of 1:1 Drug: (dextrose + SLS)

Indomethacin tablets containing	C^1_{20}	C^1_{60}	T^3_{80} (min)
1:0 drug : carrier coprecipitate	35.8 ± 21.3	70.2 ± 1.55	> 60
1:(0.0 + 1.0) drug : (dextrose + SLS) coprecipitate	42.4 ± 0.85	98.4 ± 0.42	37.0
1:(0.0 + 1.0) drug : (dextrose + SLS) physical mixture	24.4 ± 0.60	85.5 ± 0.06	55.5
1:(0.2 + 0.8) drug : (dextrose + SLS) coprecipitate	91.5 ± 3.08	100.7 ± 0.74	17.5
1:(0.2 + 0.8) drug : (dextrose + SLS) physical mixture	30.7 ± 0.24	87.4 ± 0.94	43.0
1:(0.4 + 0.6) drug : (dextrose + SLS) coprecipitate	93.2 ± 0.11	95.1 ± 0.26	24.0
1:(0.4 + 0.6) drug : (dextrose + SLS) physical mixture	38.7 ± 3.59	88.6 ± 0.21	42.0
1:(0.6 + 0.4) drug : (dextrose + SLS) coprecipitate	95.4 ± 1.70	101.0 ± 0.08	12.5
1:(0.6 + 0.4) drug : (dextrose + SLS) physical mixture	72.6 ± 4.96	89.6 ± 1.19	29.0
1:(0.8 + 0.2) drug : (dextrose + SLS) coprecipitate	95.0 ± 1.53	97.0 ± 0.48	10.0
1:(0.8 + 0.2) drug : (dextrose + SLS) physical mixture	65.2 ± 4.84	90.0 ± 1.65	33.5
1:(1.0 + 0.0) drug : (dextrose + SLS) coprecipitate	79.1 ± 0.45	93.5 ± 0.33	21.0
1:(1.0 + 0.0) drug : (dextrose + SLS) physical mixture	67.3 ± 0.00	86.3 ± 0.74	40.5

$^1C_{20}$ = % dissolved obtained at the time of 20 minutes.
$^2C_{60}$ = % dissolved obtained at the time of 60 minutes.
$^3T_{80}$ = The time required for 80% drug dissolution.

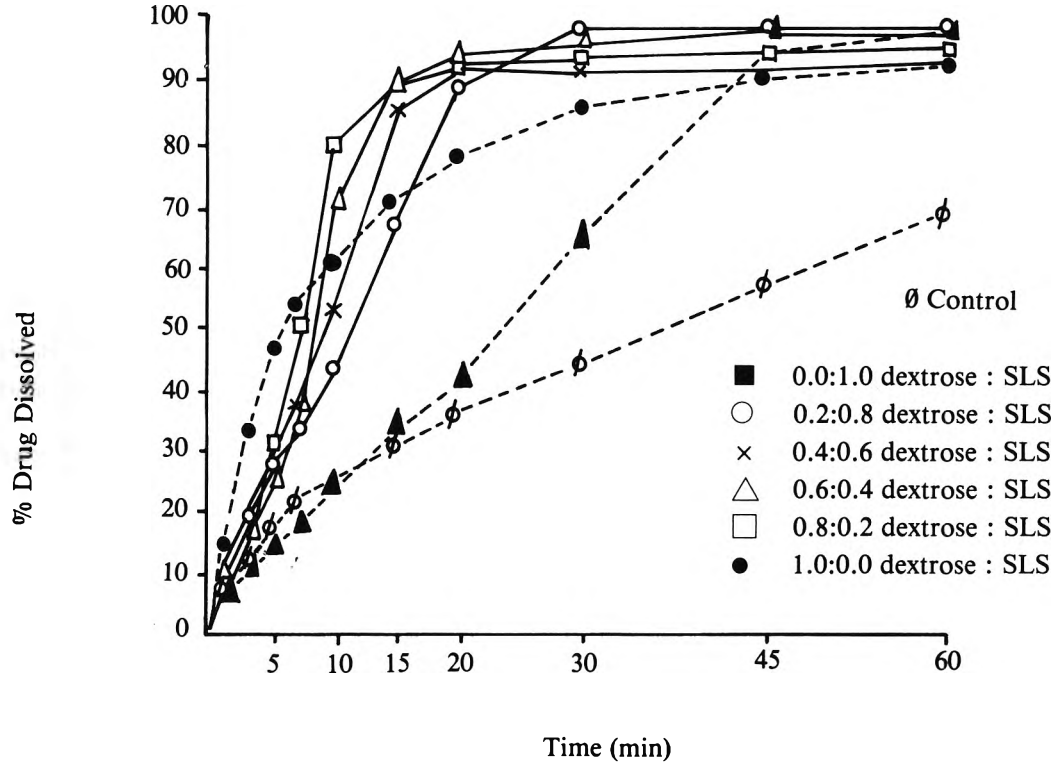

Figure 3 Dissolution profiles of tablets containing various system of 1:1 indomethacin: (dextrose + SLS) coprecipitates.

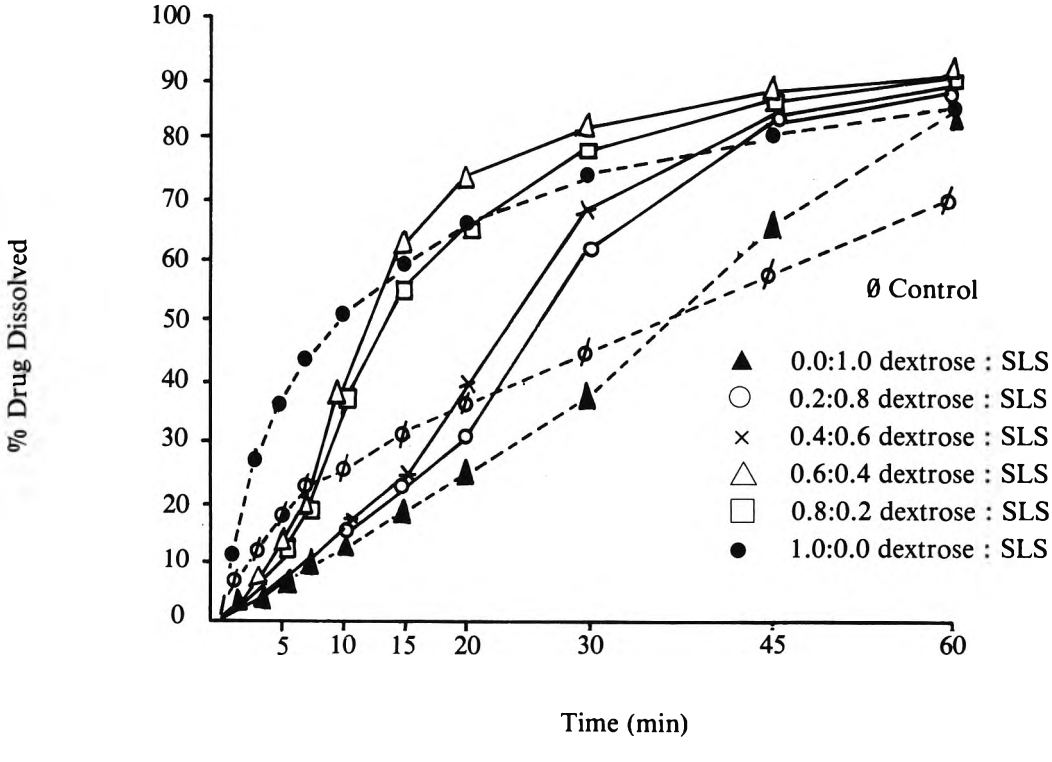

Figure 4 Dissolution profiles of tablets containing various systems of 1:1 indomethacin : (dextrose + SLS) physical mixtures.

DISCUSSION AND CONCLUSION

Indomethacin control tablets showed a poor dissolution rate in dissolution medium though their disintegration time was about 5 minutes. The percentage of the drug dissolved was only 36% in 20 minutes which did not meet the requirement of USP XXI and NF XIV that 80% of drug dissolved within 20 minutes for indomethacin solid dosage form. The presence of water-soluble carries, dextrose, PEG 4000 and SLS as individually or combined, increased the dissolution of the drug. The dissolution enhancement was markedly shown when coprecipitation technique was used. This is due to the reasons that solid dispersion systems were formed. Glass dispersion of drugs in dextrose was reported(2). The low density and lattice energy of the glass dispersion were expected. Each crystallite of drug surrounded by a water soluble crystal caused a better solubility, wettability and dispersibility effect of drug in the medium, thus, better dissolution rate. Solid solution of indomethacin was formed with polyethylene glycols (10). It was reported that drug could be trapped in their helical interstitial space. PEG's also provided solubilizing effect on hydrophobic drugs (11, 4) which would be greater when solid dispersion was formed. For drug-SLS coprecipitate, molecular or colloidal dispersion of drug in SLS was formed, thus more wetting effect of the surfactant was obtained (7). The other important reason for dissolution enhancement of solid dispersion systems was that the particle size of the drug in coprecipitate would be smaller causing an increase in surface area and hence dissolution rate.

However, the dissolution enhancement of solid dispersion systems was hindered by the disintegration retarding effect of PEG 4000 and SLS. This disintegration retarding effect was more prominent when coprecipitation technique was used. It could be explained that polyethylene glycols also act as binder in tabletting (12), and SLS is waxy in nature, thus the tablet disintegration might be retarded. However, after these tablets disintegrated, their dissolution markedly increased.

The combination of water soluble carriers, dextrose + PEG 4000 or dextrose + SLS, overcame this disintegration retarding effect especially when less amount of PEG 4000 or SLS was used. Thus dissolution enhancement was clearly exhibited. Also more reduction in drug particle size could be obtained which may result in higher amount of drug being dispersed at molecular or colloidal level. The ratio of 0.6 : 0.4 dextrose : PEG 4000 or dextrose : SLS precipitates seemed to be the optimum ratio for combined water soluble carriers. At this ratio of water soluble carriers, the binding or waxy effect of PEG 4000 or SLS was not great enough to retard tablet disintegration. Moreover, no lubricant was required because a small amount of PEG 4000 or SLS could be used as lubricant in tablet formulation.

Comparison between two water soluble carriers coprecipitates, dextrose : PEG 4000 or dextrose : SLS, dextrose : SLS seemed to be better combined carriers than dextrose : PEG 4000. Tablets containing four ratios of dextrose : SLS coprecipitates produced T_{80} within 20 minutes which met the USP XXI & NF XIV dissolution requirement. These tablets also completely dissolved within 60 minutes. For dextrose : PEG 4000 coprecipitates, only tablets containing 0.6 : 0.4 and 0.4 : 0.6 dextrose : PEG 4000 coprecipitates met the requirement. The more solubilizing and wetting effects of SLS were thought to make SLS better carrier for indomethacin coprecipitates than PEG 4000. Tablets containing other two ratios of dextrose : PEG 4000 0.2 : 0.8 and 0.8 : 0.2, which produced T_{80} of 24 and 25.5 minutes, could meet the USP requirement if the precipitates were filled into capsules. In this way the dissolution retarding effect produced by compaction process would be avoided.

It could be concluded that at the optimum ratio of dextrose : PEG 4000 or dextrose : SLS, indomethacin tablets prepared from drug-combined water soluble carrier coprecipitates produced better improvement in drug dissolution than those prepared from drug-combined water soluble carrier physical mixture and from drug-single carrier systems as well. Between these two combined carriers, dextrose-SLS offered faster disintegration and higher dissolution rate than dextrose-PEG 4000. Combined water soluble carriers markedly improved indomethacin dissolution. Optimum-ratio of dextrose : PEG 4000 or dextrose SLS coprecipitates produced indomethacin tablets of fast and complete dissolution.

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ผลของตัวพาชนิดละลายน้ำได้สองชนิดประกอบกันต่ออัตราการละลายของยาเม็ดอินโดเมธาซิน ที่เตรียมด้วยเทคนิคการตกตะกอนร่วม

*กาญจน์พิมล ฤทธิเดช, Ph.D.**
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บทคัดย่อ

ยาเม็ดอินโดเมธาซินตอกอัดโดยตรงจากตะกอนร่วมของยากับอัตราส่วนต่าง ๆ ของตัวพาชนิดละลายน้ำได้สองชนิดประกอบกัน dextrose : polyethylene glycol 4000 (PEG 4000) และ dextrose : sodium lauryl sulfate (SLS) จากการศึกษาการแตกตัวและการละลายของยาเม็ดเหล่านี้ และเปรียบเทียบกับยาเม็ดที่เตรียมจากส่วนผสมทางกายภาพ และยาเม็ดที่ปราศจากตัวพา ผลปรากฏว่ายาเม็ดที่มีตัวพาชนิดละลายน้ำได้สองชนิดประกอบกัน ซึ่งเตรียมจากการตกตะกอนร่วมให้การละลายดีกว่าที่เตรียมจากการผสมทางกายภาพ และตามด้วยยาเม็ดที่ปราศจากตัวพา จำนวน PEG 4000 หรือ SLS ที่มากขึ้นจะลดอัตราการละลาย เนื่องจากคุณสมบัติในการหน่วงการแตกตัวของสารทั้งสองนี้ ผลนี้ยิ่งเด่นชัดเมื่อใช้เทคนิคการตกตะกอนร่วม ตัวพาซึ่งละลายน้ำได้ทั้งสองคู่นี้ให้ตะกอนร่วมที่มีอัตราการละลายของตัวยาเร็วกว่าตัวพาเดี่ยวแต่ละตัว ระบบ dextrose : SLS ให้การละลายดีกว่าระบบ dextrose : PEG 4000 ที่อัตราส่วน 0.6 : 0.4 ยาเม็ดอินโดเมธาซินที่ประกอบด้วยตะกอนร่วมของ dextrose : PEG 4000 หรือ dextrose : SLS ให้อัตราการละลายสูงสุด
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