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IMPROVING DISSOLUTION AND ABSORPTION RATES OF NAPROXEN AND THIAMPHENICOL USING CO - EVAPORATION METHOD

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Thesis Title Improving Dissolution and Absorption Rates of Naproxen and Thiamphenicol Using Co-evaporation Method

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สิริรัศมี ปิ่นสุวรรณ : การเพิ่มอัตราการละลายและการดูดซึมของนาโพรเซนและไธแอมเฟนิคอล โดยวิธีการตกตะกอนร่วม (IMPROVING DISSOLUTION AND ABSORPTION RATES OF NAPROXEN AND THIAMPHENICOL USING CO-EVAPORATION METHOD) อ.ที่ปรึกษา : รศ.ดร.อุทัย สุวรรณกูฏ , ๒๐๕ หน้า

เพื่อเพิ่มอัตราการละลายและการดูดซึมของตัวยานาโพรเซนและไธแอมเฟนิคอล ซึ่งมีความแตกต่างกันของคุณสมบัติความเป็นกรดด่าง ได้มีการเตรียมสารตกตะกอนร่วมหรือโซลิดดีสเพอร์ชันของตัวยาแต่ละชนิด โดยใช้สารโพลีเมอร์ที่ละลายน้ำได้ คือ Polyvinylpyrrolidone (PVP) และ Polyethylene glycol (PEG) ที่มีน้ำหนักโมเลกุลต่าง ๆ กัน เป็นตัวพาโดยวิธีการตกตะกอนร่วม แล้วศึกษาการละลายของตัวยาจากสารตกตะกอนร่วมนี้ เปรียบเทียบกับสารผสมทางกายภาพและตัวยาเดี่ยว ๆ และศึกษาถึงผลของชนิดและปริมาณของตัวพาที่ใช้ นอกจากนี้ได้ศึกษาการดูดซึมของตัวยานอกร่างกายและลักษณะทางกายภาพของสารตกตะกอนร่วมที่ให้การละลายสูงสุด

จากการศึกษาการละลายของตัวยาในสารละลายบัฟเฟอร์ฟอสเฟต พี.เอช 1.5 , 4.5 และ 7.5 พบว่าการละลายของตัวยาทั้งสองชนิดจากสารตกตะกอนร่วมจะเร็วกว่าการละลายของตัวยาทั้งสองชนิดจากสารผสมทางกายภาพ และตัวยาเดี่ยว ๆ จากการเปรียบเทียบการละลายพบว่าสารตกตะกอนร่วมที่ใช้ PVP K-30 เป็นตัวพา จะให้อัตราและปริมาณที่ละลายของตัวยาสูงที่สุด ตามด้วยสารตกตะกอนร่วมที่ใช้ PVP K-90, PEG 4000, 6000 และ 20000 ตามลำดับ นอกจากนี้พบว่าเมื่อลดปริมาณของตัวพา คือ PVP K-30 จากอัตราส่วนของตัวยาต่อตัวพา 1:1 เป็น 1:0.75, 1:0.50 และ 1:0.25 จะทำให้การเพิ่มอัตราและปริมาณการละลายของตัวยานาโพรเซนลดลง แต่สำหรับไธแอมเฟนิคอล พบว่าการเพิ่มการละลายของตัวยาจากสารตกตะกอนร่วมในอัตราส่วน 1:1 และ 1:0.75 ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ($p > 0.10$) ดังนั้นในการทดลองนี้ ระบบที่ดีที่สุดในการเพิ่มการละลายของนาโพรเซนและไธแอมเฟนิคอล คือสารตกตะกอนร่วม กับ PVP K-30 ในอัตราส่วน 1:1 และ 1:0.75 ตามลำดับ

การศึกษาการดูดซึมของตัวยานอกร่างกายกระทำโดยใช้เครื่องมือ Sartorius absorption Simulator (SM 16750) พบว่าการดูดซึมของตัวยาจากสารตกตะกอนร่วมจะสูงกว่าการดูดซึมของตัวยาเดี่ยว ๆ อย่างมีนัยสำคัญทางสถิติ ($p < 0.05$) และเฉพาะไธแอมเฟนิคอลเท่านั้นที่พบว่ามีความสัมพันธ์กันอย่างมีนัยสำคัญ ($p < 0.05$) ระหว่างค่าคงที่ของอัตราการละลายและค่าคงที่ของอัตราการดูดซึมของตัวยา

จากการศึกษา X-ray diffraction และ differential thermal analysis ของตัวยาและสารตกตะกอนร่วม แสดงให้เห็นว่าตัวยานาโพรเซนและไธแอมเฟนิคอลกระจายตัวอยู่ในตัวพา คือ PVP K-30 ในรูปของผลึกและอสัณฐานตามลำดับ ซึ่งสามารถอธิบายปัจจัยที่มีผลต่อการเพิ่มขึ้นของอัตราการละลายและการดูดซึมของตัวยาทั้งสองจากสารตกตะกอนร่วมได้

ภาควิชา เภสัชกรรม ลายมือชื่อนิสิต .....

สาขาวิชา เภสัชกรรม

ปีการศึกษา 2530 ลายมือชื่ออาจารย์ที่ปรึกษา .....

SIRIRAT PINSUWAN : IMPROVING DISSOLUTION AND ABSORPTION RATES OF NAPROXEN AND THIAMPHENICOL USING CO-EVAPORATION METHOD.
THSIS ADVISOR : ASSO. PROF. UTHAI SUVANAKOOT, Ph.D. 205 PP.

In order to increase dissolution and absorption rates of naproxen and thiamphenicol which have the difference of acid-base properties, coevaporates or solid dispersions of the drugs with water- soluble polymers such as polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) with different molecular weights were prepared using co-evaporation method. Dissolution of the drugs from these preparations were studied compared to the corresponding physical mixtuers and pure drug alone. The influence of types and amount of carriers used on dissolution characteristic of both drugs were investigated. Furthermore, in vitro absorption and physical characterization of the co-evaporates with the best dissolution were evaluated.

From dissolution studies in phosphate buffer pHs 1.5, 4.5 and 7.5 similar results were observed for both naproxen and thiamphenicol that the coevaporates exhibited faster dissolution than the corresponding physical mixtures and pure drugs. The highest dissolution rate and extent of both drugs were obtained from PVP K-30 coevaporate followed by PVP K-90, PEGs 4000, 6000, and 20000 coevaporates, respectively. Moreover, decreasing the weight fraction of PVP K-30 in the coevaporates from the ratio 1:1 of drug:carrier to 1:0.25, decreased the dissolution rates of the drug from the preparations. However, there were no statistically significant difference of dissolution rates between 1:1 and 1:0.75 thiamphenicol-PVP K-30 coevaporates ($p > 0.10$). Hence, the best systems for enhancing the dissolution of naproxen and thiamphenicol were 1:1 naproxen-PVP K-30 and 1:0.75 thiamphenicol-PVP K-30 coevaporates, respectively.

The in vitro absorption studies using Sartorious absorption simulator (SM 16750) exhibited statistically significant higher absorption of the drugs from the coevaporates as compared to the pure drugs ($p < 0.05$). However, significant correlation between dissolution and absorption rates were observed in thiamphenicol system only ($p < 0.05$).

X-ray diffraction studies and differential thermal analysis of the drugs and the coevaporates showed evidences that naproxen and thiamphenicol dispersed in PVP K-30 matrix in crystalline and amorphous formes, respectively, which may explain the increasing factors of dissolution and absorption of the drugs from the coevaporates.

ภาควิชา เภสัชกรรม ลายมือชื่อนิสิต Siriarat Pinsuwan

สาขาวิชา เภสัชกรรม

ปีการศึกษา 2530 ลายมือชื่ออาจารย์ที่ปรึกษา

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ABBREVIATIONS

°C	degree celcius
conc	concentration
DTA	Differential Thermal Analysis
g	gram
Kd	dissolution rate constant
Kdf	diffusion rate constant
Ki	in vitro absorption rate contstant
mcg	microgram
mg	milligram
min	minute
ml	milliliter
nm	nanometer
No	number
NPX	Naproxen
PEG	Polyethylene glycol
PVP	Polyvinylpyrrolidone
pKa	the native logarithem of the dissocication contstant
r.p.m.	revolutions per minute
S.D.	Standard Deviation
S.E.	Standard Error
THI	Thiamphenicol
UV	Ultraviolet

CHAPTER I

INTRODUCTION

One of the techniques that can potentially enhance the dissolution rate of hydrophobic drugs is the formation of coevaporate or solid dispersion with pharmacologically inert,polymeric materials. A number of investigations demonstrated that this formation can significantly increase the dissolution and/or absorption rate of such drugs (1-3).

In this study, the model drugs, Naproxen and Thiamphenicol were chosen based on their low solubitities in water and their difference of acid - base properties. Polyethylene glycol (PEG) 4000, 6000 and 20000 and polyvinylpyrrolidone (PVP) K-30 and K-90, the popular inert carriers, were selected to be used as dispersion carriers because of their nontoxicities, physiologically acceptabilities and their high solubilities in a wide range of organic solvents.

Dispersion systems containing drug and carriers were prepared by coevaporation technique and physical mixing. The solidified masses were subjects to in vitro dissolution and absorption evaluation at pHs 1.5, 4.5, and 7.5

The objectives of the present study were to :

1. Obtain coevaporates of naproxen and thiamphenicol in various carriers using coevaporation technique.

2. Probe the coevaporation technique for preparing coevaporate system of poorly water soluble drugs with difference of acid - base properties.

3. Investigate the influence of types of carriers on the dissolution and absorption rate of naproxen and thiamphenicol from coevaporates compared to each physical mixture and pure drug.

4. Select the carrier of choice and its appropriate amount to increase the dissolution and absorption rate of each drug.

5. Demonstrate the correlation of in vitro absorption and dissolution rates of each pure drug and coevaporate using Sartorius Absorption Simulator (SM 16750) and correlation coefficient test.

6. Characterize some physical characteristics of naproxen and thiamphenicol coevaporates using X-ray diffractometry and Thermal Differential Analysis.

In addition to dissolution and absorption enhancement, the coevaporation technique may be attempted to present the dispersion in a more handable form that can

be formulated stable tablets or capsules. (1,3) Furthermore, it is possible that such a technique can be used to stabilize unstable drugs (1) and produce sustained release products by using poorly soluble carriers (2). It is hoped that this study would be valuable in drug products development and this useful technique could be applied to other poorly water soluble drugs as well.

CHAPTER II

EXPERIMENTAL SECTION

A. Materials

1. Drugs

-Naproxen BP 1980 (Lot no. 253/84, Agrar, Societa Industriale & Commerciale Ltd.)

-Thiamphenicol BP 1980 (Lot no. 43946700, Boehringer Mannheim GmbH, Mannhaeim 31)

2. Carriers

-PEG 4000 (BASF, West Germany)

-PEG 6000 (Batch no. 54-0197, BASF, West Germany)

-PEG 20000 (Batch no. 314522, Chemiche Werke Huls AG., West Germany)

-PVP K-30 (Lot no. 83-4515, BASF, West Germany)

-PVP K-90 (Lot no. D61231, GAF, U.S.A.)

3. Others

-Ethyl alcohol (Lot no. 3380, Liquor Distillery Organization, Excise Department)

-Methyl alcohol (Lot no. K2710909, Merck, Germany)

-Concentrated Hydrocholic acid (Lot no. K00188817, Merck, Germany)

-Sodium hydroxide (Lot no. C605098, Merck,Germany)

-Potassium dihydrogen phosphate (Lot no. A751273, Merck, Germany)

-Sodium chloride (Lot no.000630, Vidhyasom Co.Ltd.)

All materials were used without further purification. Water was deionized prior to use.

B. Apparatus

-Analytical balance (August Sauter KD D7470, West Germany and Mettler PC 440, Switzerland)

-UV-visible spectrophotometer (Spectronic 2000, Bausch & Lomb, U.S.A.)

-Dissolution apparatus (72 RL, Hanson Research Corp., U.S.P.)

-Sartorius Absorption Simulator SM 16750 (Sartorius GmbH, West Germany)

-X - ray Diffractometor (Philips, Type pw 1730/10, No. Dy 1023)

-Differential Thermal Analyzer (Shimadzu DT-30)

-US.Standard sieve no.40 mesh (W.S.Tyler Co,U.S.A)

-pH Meter (Model 7030, Electronic Instruments Ltd, England)

-Water bath (Memmert, West Garmany)

C. Methods

1. Preparation of Naproxen or Thiamphenicol Coevaporates

Naproxen or thiamphenicol coevaporates were prepared by dissolving weighed quantities of naproxen or thiamphenicol and carrier(s) as showed in Table 1 and 2 in sufficient volume of ethyl alcohol or methyl alcohol, respectively. The solution were mixed thoroughly and evaporated directly on water bath (37 - 40 °C) with constant stirring until obtaining the transparant viscous liquid which were allowed to solidify by pouring onto glass plates and then kept in a desicator in order to remove the last traces of solvents. The dry products were then scratched from the glass plates, powdered and passed through a 40 - mesh sieve. The productcs were kept in a desicator.

2. Preparation of Naproxen or Thiamphenicol Physical Mixtures.

Appropiate amount of naproxen or thiamphenicol and carrier(s) were accurately weighed and mixed by geometric dilution method using a mortar and a pestle. The mixtures were then passed through a 40 - mesh seive and stored in a desicator.

Table 1 The Amount of Naproxen and Carriers Used in Preparing Coevaporates and Physical Mixtures

Preparations	The Amount of Drug and Carriers Used (g)					
	NPX	PEGs			PVPs	
		4000	6000	20000	K-90	K-30
Coevaporates :						
1:1 NPX-PEG 4000	10	10	-	-	-	-
1:1 NPX-PEG 6000	10	-	10	-	-	-
1:1 NPX-PEG 20000	10	-	-	10	-	-
1:1 NPX-PVP K-90	10	-	-	-	10	-
1:1 NPX-PVP K-30	10	-	-	-	-	10
1:0.75 NPX-PVP K-30	10	-	-	-	-	7.5
1:0.50 NPX-PVP K-30	10	-	-	-	-	5.0
1:0.25 NPX-PVP K-30	10	-	-	-	-	2.5
Physical Mixtures :						
1:1 NPX-PEG 4000	10	10	-	-	-	-
1:1 NPX-PEG 6000	10	-	10	-	-	-
1:1 NPX-PEG 20000	10	-	-	10	-	-
1:1 NPX-PVP K-90	10	-	-	-	10	-
1:1 NPX-PVP K-30	10	-	-	-	-	10

Table 2 The Amount of Thiamphenicol and Carriers Used in Preparing Coevaporates and Physical Mixtures

Preparations	The Amount of Drug and Carriers Used (g)					
	THI	PEGs			PVPs	
		4000	6000	20000	K-90	K-30
Coevaporates :						
1:1 THI-PEG 4000	10	10	-	-	-	-
1:1 THI-PEG 6000	10	-	10	-	-	-
1:1 THI-PEG 20000	10	-	-	10	-	-
1:1 THI-PVP K-90	10	-	-	-	10	-
1:1 THI-PVP K-30	10	-	-	-	-	10
1:0.75 THI-PVP K-30	10	-	-	-	-	7.5
1:0.50 THI-PVP K-30	10	-	-	-	-	5.0
1:0.25 THI-PVP K-30	10	-	-	-	-	2.5
Physical Mixtures :						
1:1 THI-PEG 4000	10	10	-	-	-	-
1:1 THI-PEG 6000	10	-	10	-	-	-
1:1 THI-PEG 20000	10	-	-	10	-	-
1:1 THI-PVP K-90	10	-	-	-	10	-
1:1 THI-PVP K-30	10	-	-	-	-	10

3. Determination of Amount of Naproxen or Thiamphenicol in Coevaporates and Physical Mixtures.

The amount of naproxen or thiamphenicol in the preparations were determined according to B.P. 1980 (4) by spectrophotometry at 331 nm for naproxen and at 266 nm for thiamphenicol content.

4. In Vitro Dissolution Studies

4.1. Dissolution procedure: Dissolution rates of naproxen or thiamphenicol coevaporates and physical mixtures prepared were obtained using the U.S.P. XXI dissolution apparatus type II at 37±0.5 °C with rotating paddle speed of 50+4 rpm in phosphate buffer pHs 1.5, 4.5 and 7.5. Coevaporates or physical mixtures samples containing 250 mg naproxen or thiamphenicol were used in each study. Samples were collected at predetermined time intervals for 3 hours, and the volume removed was replaced by temperature equilibrated dissolution medium. In addition, dissolution rates of naproxen and thiamphenicol powders were determined in order to serve as a basis of comparison.

4.2. Analytical procedure: Samples at each time interval were assayed spectrophotometrically for naproxen at 331 nm and for thiamphenicol at 266 nm. The presence of the carriers in this study did not affect the assays. Each point reported is the average of six

determinations and good agreement existed among the datas.

4.3. Standard curves: Known amount of each drug were dissolved in each pH of dissolution medium. and the UV absorbance at each concentration was determined using spectrophotometer. Absorbances obtained versus known concentrations of each drug were fitted to a straight line using linear regression (5).

5. In vitro Absorption Studies

Naproxen and thiamphenicol coevaporates with the best dissolution were selected to study for their in vitro absorption compare to the drugs alone using Sartorius Absorption Simulator (SM 16750).

5.1. The substances under test : The powder form of drugs and the coevaporates selected were evaluated. The amounts used were chosen base on their abilities to dissolve in phase I solutions, that were 5,10 and 100 mg for naproxen and 100 mg for thiamphenicol.

5.2. The lipid barriers : Two different lipid barriers used were the artificial gastric barrier (SM 15701) and the artificial intestinal barrier (SM 15702) Both barriers were prepared shortly before the start of the experiment. The effective area of the barrier was 80 cm^2. The pores of the barriers were filled with the liquid lipid-phase mixture of the following components :

Type	components (unit by weight)		
	N	S1	S2
Lipid mixture for SM 15701	4.20	0.10	-
SM 15702	0.92	-	4.00

The barriers should have a weight increase of 85 to 105 % for SM 15701, and 90 to 110 % for SM 15702.

5.3. **The aqueous phases**

Conditions	Phase I	Phase II
Volume initial	100 ml	100 ml
Artificial gastric fluid	pH 1.5	pH 7.5
	pH 4.5	
Artificial intestinal fluid	pH 7.5	pH 8.0
Temperature	39 ± 1 °C	39 ± 1 °C

5.4. **Sample collection** : Samples were collected from phase I and phase II at predetermined time interval for 3 hours, with no replacing of the volume removed.

5.5. **Analytical procedure**: Samples at each time interval were determined spectrophotometrically at 331 and 266 nm for naproxen and thiamphenicol, repectively. Each point reported was the average of duplicate determinations.

5.6. **Standard Curve** : Stand curves for each drug in solutions of phase I and phase II were obtained in the same way as in dissolution test, as mentioned previously.

6. Statistical Evaluation.

Significantly differences of percentage drugs dissolved and dissolution rate contants (Kd) of the coevaporates of each drug were determined using one - way ANOVA and t - test. Correlation coefficient tests were used to evaluated the correlation between the dissolution rate contstants (Kd) and absorption rate contstants (Ka) of the coevaporates and the drugs alone.

7. Characterization of Coevaporates.

7.1. X - ray diffraction studies

Samples for x - ray diffraction studies were firmly packed into the cavity of a thin recticular metal plate using two glass slides which were fastend to metal plated with adhensive tape. The first glass slide was then removed before taken the prepared sample to expose the x - ray in the x - ray diffraction chamber. The x - ray diffraction patterned were recorded at the rate of 1 e/min from 4 to 40 angle for naproxen and 4 to 46 angle for thiamphenicol in term of the 2 e.

7.2. Differential Thermal Analysis.

A shimadzu DT-30 Differential Thermal Analyzer was used. Samples were placed and crimped in aluminium pans. Temperature range was from 40 to 300 °C and the empty pan was used as reference. Other conditions for the instrument were :

-for naproxen studies : sample size 10-11 mg, heat range 10 °C/min. and nitrogen effluent flow rate of 50 ml/min.

-for thiamphenicol studies : sample size 9 - 10 mg, heat range 20 °C/min. and nitrogen effluent flow rate of 30 ml/min.

Schematic outline of this investigation was shown in Figure 1.

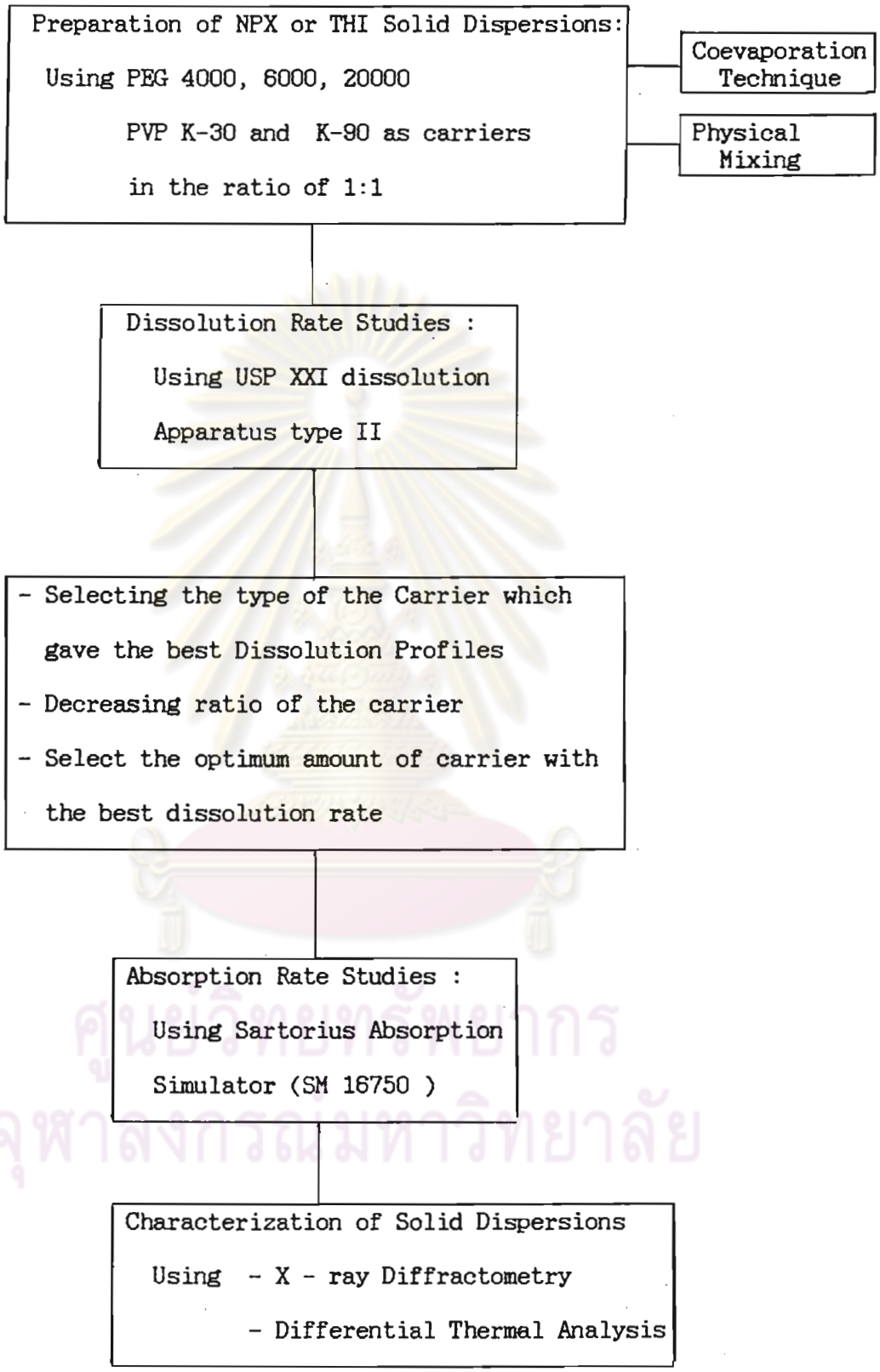


Figure 1. Schematic Outline of The Investigation

CHAPTER III

RESULTS

I. NAPROXEN (NPX)

Dispersion systems of NPX and various types of water-soluble carriers, i.e. PEGs 4000, 6000, 20000, PVPs K-30 and K-90 were prepared using coevaporation technique and physical mixing. All preparations were relatively easy to be prepared. The coevaporates from PEG 4000, 6000 and PVP K-30 were nonsticky and easy to manipulate to powder forms. In PEG 20000 and PVP K-90 systems, the products were somewhat sticky but when dried they were white stable masses which could be pulverized to yield dry nonsticky white powders.

The percentage content of NPX and NPX in each dispersion systems prepared were shown in Table 3. The NPX content was between 99.06 and 100.92 %

1.1. In Vitro Dissolution Studies

Typical standard curves of NPX at pHs 1.5, 4.5 and 7.5 were presented in Figures 2 - 4 and Tables 4 - 6, respectively. Dissolution profiles and data of pure NPX powders were shown in Figure 5 and Table 7. Dissolution rates of the drug were greater at pH 7.5 than pH 4.5 and 1.5, respectively. Dissolution of powder drug alone was

Table 3 Percentage Contents of NPX and NPX in Coevaporates and Physical Mixtures

Preparations	Percent NPX Content			
	1	2	3	Average + S.D.
Pure NPX	99.78	99.60	99.53	99.64 ± 0.13
Coevaporates :				
1:1 NPX-PEG 4000	99.48	99.44	99.55	99.50 ± 0.07
1:1 NPX-PEG 6000	99.76	99.58	100.14	99.82 ± 0.29
1:1 NPX-PEG 20000	99.31	99.82	98.96	99.36 ± 0.43
1:1 NPX-PVP K-90	100.25	99.98	100.15	100.12 ± 0.13
1:1 NPX-PVP K-30	99.83	100.05	99.98	99.95 ± 0.11
1:0.75 NPX-PVP K-30	100.83	101.01	100.92	100.92 ± 0.09
1:0.50 NPX-PVP K-30	99.96	99.91	100.12	99.99 ± 0.11
1:0.25 NPX-PVP K-30	98.96	99.92	99.84	99.57 ± 0.53
Physical Mixtures :				
1:1 NPX-PEG 4000	99.84	98.99	99.35	99.39 ± 0.43
1:1 NPX-PEG 6000	98.95	99.24	99.02	99.07 ± 0.15
1:1 NPX-PEG 20000	100.20	101.08	100.17	100.48 ± 0.52
1:1 NPX-PVP K-90	98.82	99.46	98.90	99.06 ± 0.35
1:1 NPX-PVP K-30	100.90	101.02	100.46	100.73 ± 0.29

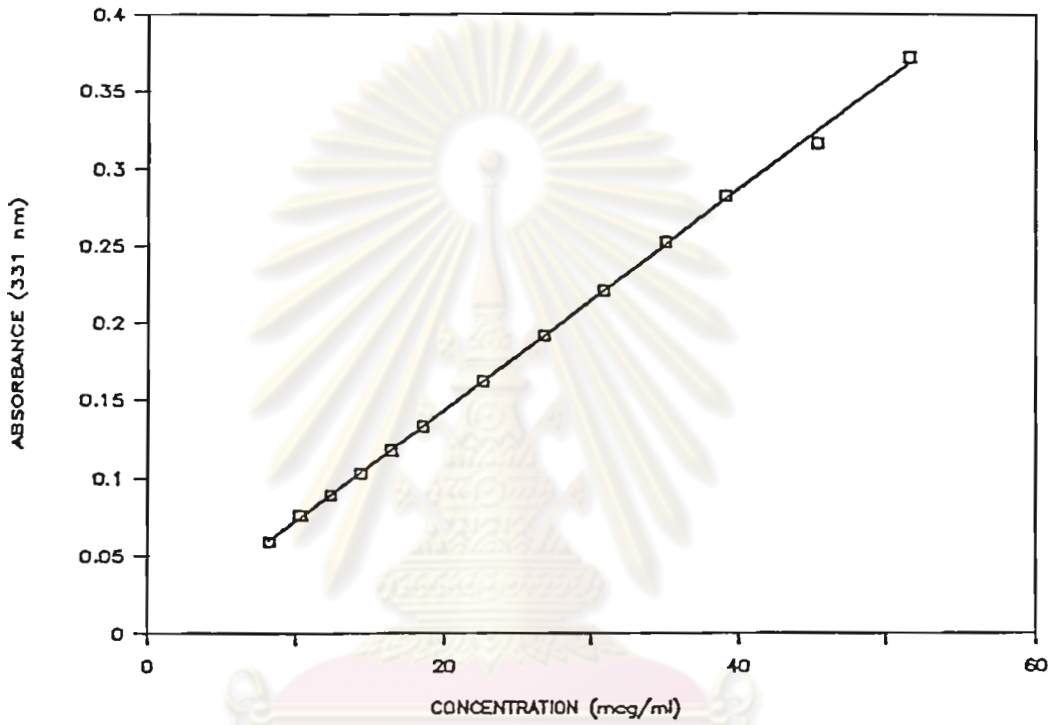


Figure 2 Typical Standard curve for Naproxen concentration vs. absorbance at pH 1.5 estimated using linear regression

Table 4 Typical Standard Curve Data for Naproxen Concentrations at pH 1.5 Estimated Using Linear Regression[1]

Standard No.	Conc. (mcg/ml)	Absorbance at 331 nm	Inversely estimated[2] Conc.(mcg/ml)	%Theory[3]
1	8.24	0.059	8.14	98.76
2	14.41	0.103	14.31	99.32
3	16.47	0.118	16.42	99.67
4	18.53	0.133	18.52	99.95
5	22.65	0.162	22.59	99.73
6	26.76	0.192	26.80	100.15
7	30.80	0.221	30.87	100.22
8	35.00	0.252	35.22	100.62
9	39.12	0.282	39.43	100.78
10	45.30	0.316	44.20	97.57
11	51.48	0.372	52.05	101.12
			Mean	100.00
			S.D.	0.90
			C.V.[4]	0.90 %

1. $r^2 = 0.9992$

2. Inversely estimated concentration $= \frac{\text{Absorbance} - 0.0010}{0.0071}$

3 %Theory $= \frac{\text{Inversely estimated concentration}}{\text{known concentration}} \times 100$

4. C.V. $= \frac{\text{S.D.}}{\text{Mean}} \times 100$

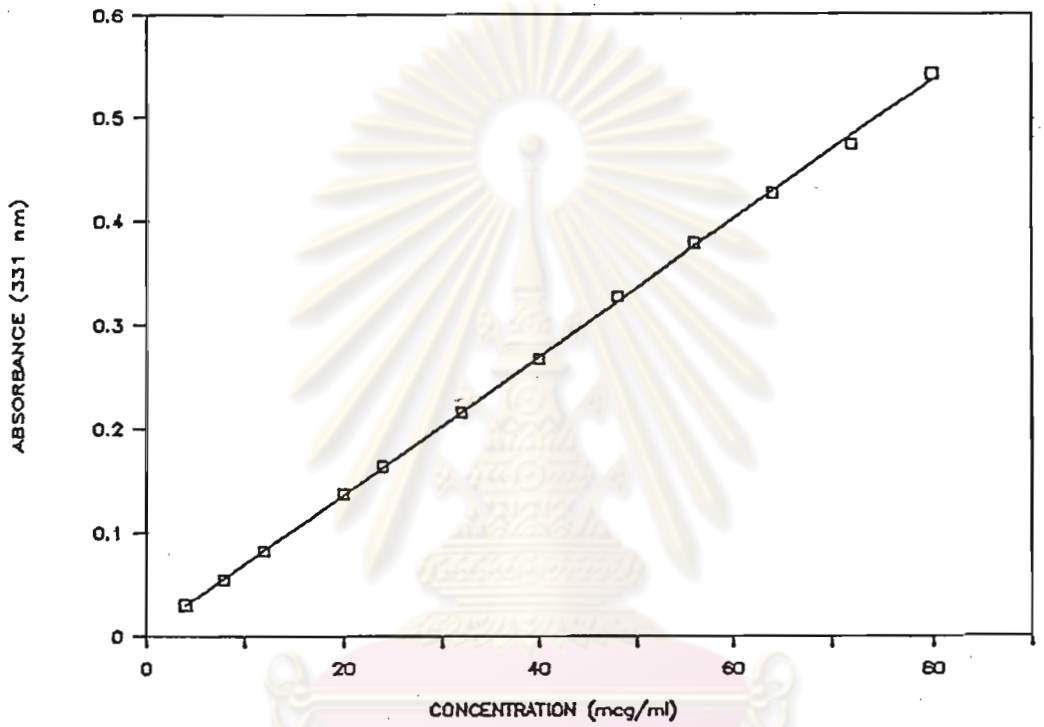


Figure 3 Typical Standard curve for Naproxen concentration vs. absorbance at pH 4.5 estimated using linear regression

Table 5 Typical Standard Curve Data for Naproxen Concentrations at pH 4.5 Estimated Using Linear Regression[1]

Standard No.	Conc. (mcg/ml)	Absorbance at 331 nm	Inversely estimated[2] Conc.(mcg/ml)	%Theory[3]
1	7.99	0.055	7.70	96.38
2	11.99	0.083	11.92	99.39
3	19.98	0.138	20.20	101.09
4	23.98	0.164	24.11	100.56
5	31.98	0.216	31.94	99.88
6	39.97	0.267	39.62	99.13
7	47.97	0.327	48.66	101.43
8	55.96	0.378	56.34	100.67
9	63.95	0.426	63.56	99.40
10	71.95	0.473	70.64	98.18
11	79.94	0.541	80.88	101.18
			Mean	99.95
			S.D.	1.61
			C.V.[4]	1.61 %

1. $r^2 = 0.9995$

2. Inversely estimated concentration $= \frac{\text{Absorbance} - 0.0039}{0.0066}$

3. $\%\text{Theory} = \frac{\text{Inversely estimated concentration}}{\text{known concentration}} \times 100$

4. $\text{C.V.} = \frac{\text{S.D.}}{\text{Mean}} \times 100$

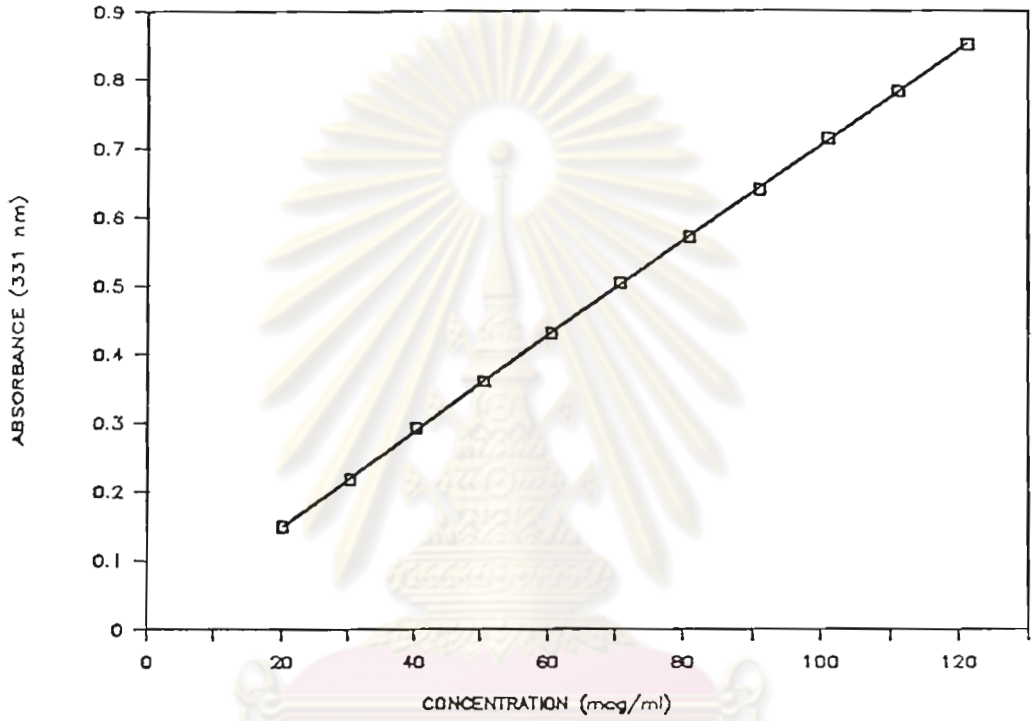


Figure 4 Typical Standard curve for Naproxen concentration vs. absorbance at pH 7.5 estimated using linear regression

Table 6 Typical Standard Curve Data for Naproxen Concentrations at pH 7.5 Estimated Using Linear Regression[1]

Standard No.	Conc. (mcg/ml)	Absorbance at 331 nm	Inversely estimated[2] Conc.(mcg/ml)	%Theory[3]
1	20.19	0.149	20.04	99.29
2	30.30	0.219	30.11	99.39
3	40.40	0.292	40.61	100.53
4	50.49	0.361	50.53	100.08
5	60.59	0.431	60.60	100.02
6	70.69	0.503	70.95	100.37
7	80.79	0.571	80.73	99.93
8	90.89	0.640	90.66	99.74
9	100.99	0.714	101.30	100.30
10	111.09	0.783	111.22	100.12
11	121.19	0.850	120.86	99.72
			Mean	99.95
			S.D.	0.39
			C.V.[4]	0.39 %

1. $r^2 = 0.9999$

2. Inversely estimated concentration $= \frac{\text{Absorbance} - 0.0099}{0.0069}$

3. %Theory $= \frac{\text{Inversely estimated concentration}}{\text{known concentration}} \times 100$

4. C.V. $= \frac{\text{S.D.}}{\text{Mean}} \times 100$

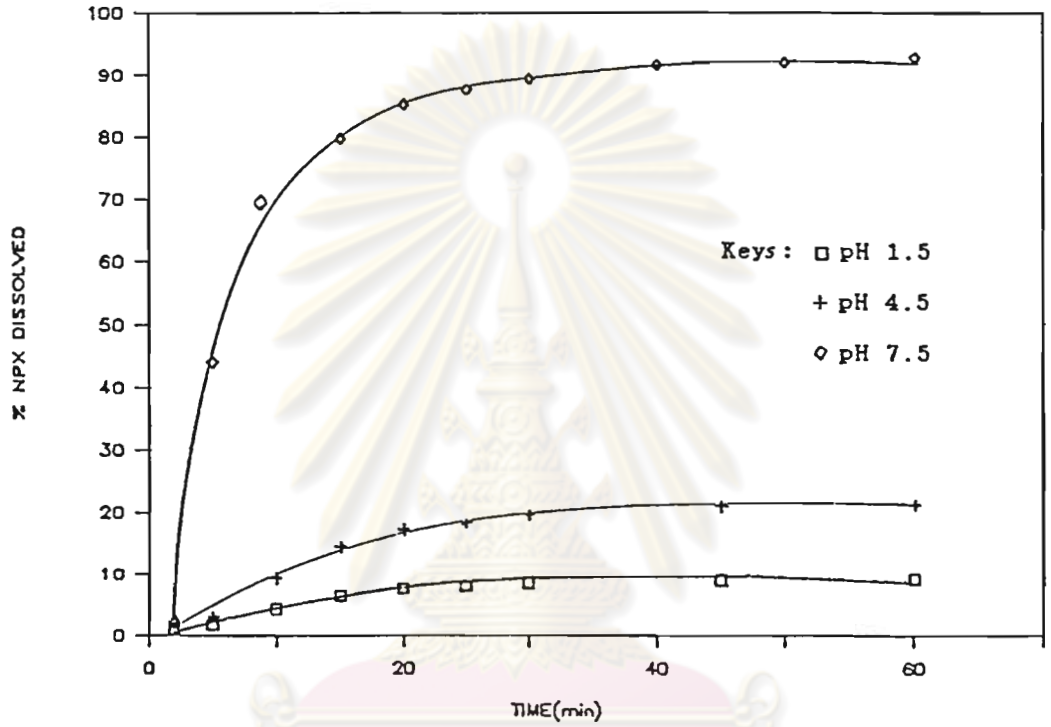


Figure 5 Dissolution Profiles of Naproxen from It's Powder at pHs 1.5, 4.5 and 7.5

Table 7 In Vitro Dissolution of Naproxen from 250 mg Naproxen Powders at pHs 1.5, 4.5 and 7.5

Time (min)	Percent Naproxen Dissolved		
	pH 1.5	pH 4.5	pH 7.5
5	1.76[a] (0.34)[b]	3.05 (0.13)	44.03 (0.69)
10	4.32 (0.50)	9.39 (0.55)	72.68 (0.59)
15	6.45 (0.50)	14.55 (0.49)	79.82 (1.14)
30	8.55 (0.23)	19.69 (0.13)	89.53 (0.89)
45	9.02 (0.69)	20.82 (0.13)	91.68 (0.92)
60	9.24 (0.65)	21.13 (0.61)	92.74 (0.64)
120	9.40 (0.60)	21.32 (0.49)	
180	9.53 (0.38)	21.51 (0.40)	
Kd^{c} (hr^{-1})	2.06 (0.13)	2.44 (0.42)	6.67 (0.87)

[a] The mean of six determinations

[b] Standard error

[c] Dissolution rate contstant

slow.

In the first step, the dissolution of coevaporates with various types of carrier fixed at the ratio 1:1 of drug:carrier were studied compared to the same ratio of physical mixtures and pure NPX. The codes used for all preparations prepared in this step and NPX were as follows :

Code	Preparation / NPX
NC1	1:1 NPX-PEG 4000 Coevaporate
NC2	1:1 NPX-PEG 6000 Coevaporate
NC3	1:1 NPX-PEG 20000 Coevaporate
NC4	1:1 NPX-PVP K-90 Coevaporate
NC5	1:1 NPX-PVP K-30 Coevaporate
NP1	1:1 NPX-PEG 4000 Physical mixture
NP2	1:1 NPX-PEG 6000 Physical mixture
NP3	1:1 NPX-PEG 20000 Physical mixture
NP4	1:1 NPX-PVP K-90 Physical mixture
NP5	1:1 NPX-PVP K-30 Physical mixture
NO	Pure NPX

The dissolution profiles of the coevaporates and physical mixtures with the same type of carrier used in all dissolution mediums were displayed in Figures 6 - 20 and Tables 8 - 17 which pure NPX was included as a control. The statistical comparisons for average percent NPX dissolved at various times and dissolution rate constants (Kd) using one - way ANOVA and t - test were

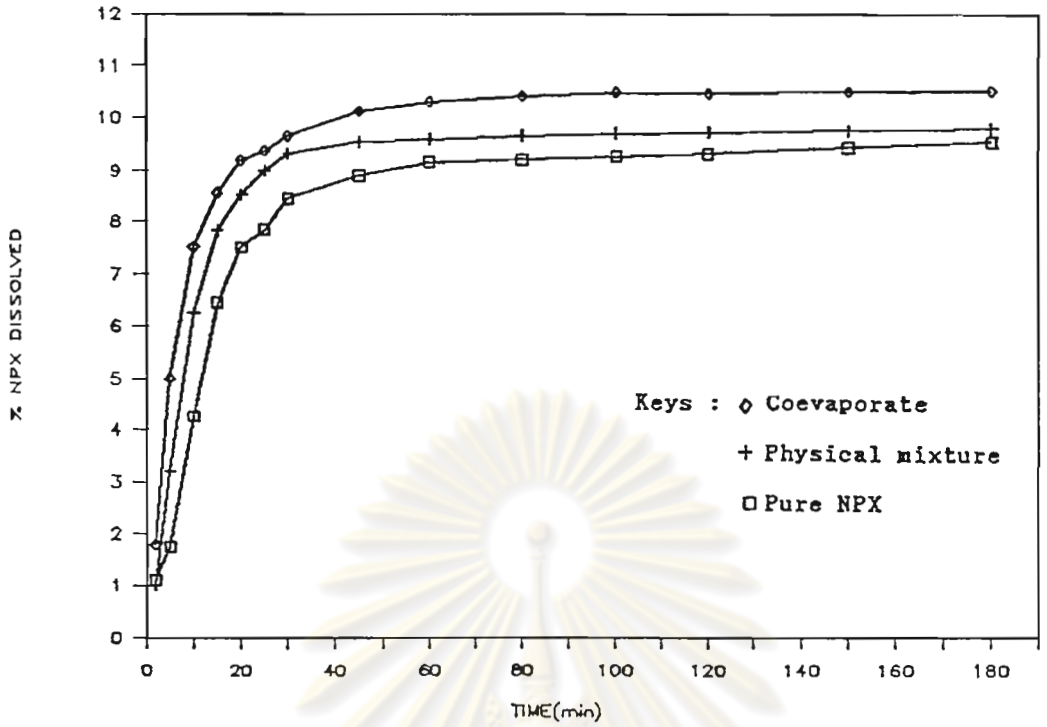


Figure 6 Dissolution Profiles of Naproxen from 1:1 NPX-PEG 4000 System at pH 1.5

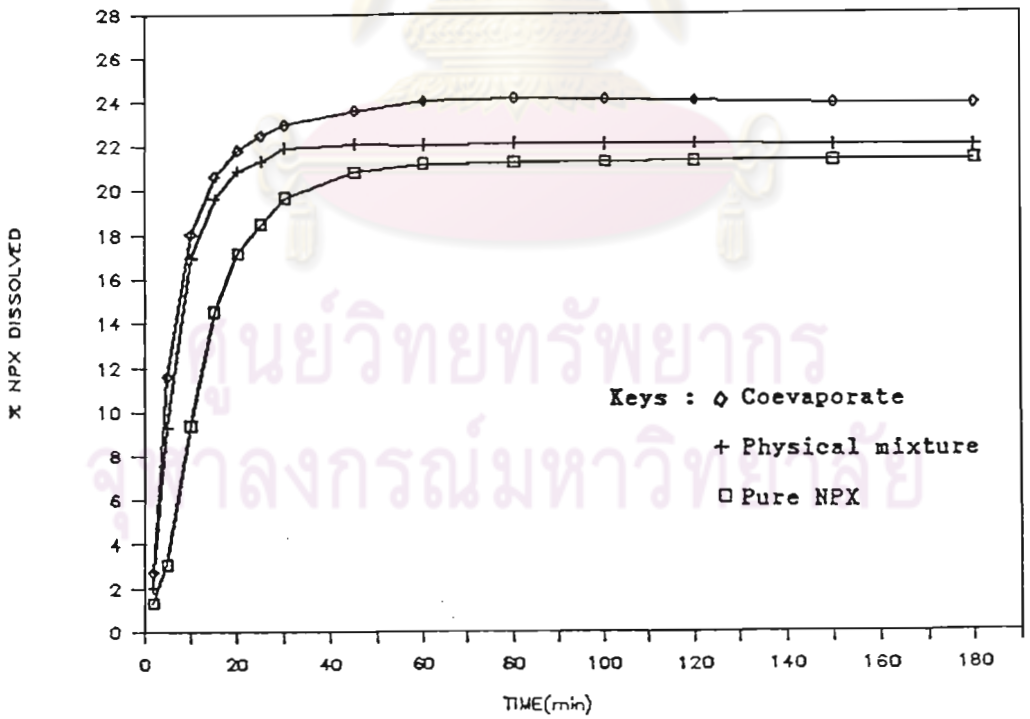


Figure 7 Dissolution Profiles of Naproxen from 1:1 NPX-PEG 4000 System at pH 4.5

Table 8 In Vitro Dissolution of Naproxen from 1:1 NPX-PEG 4000 Coevaporate, Physical Mixture and Pure Drug at pHs 1.5 and 4.5

Time (min)	Percent Naproxen Dissolved					
	pH 1.5			pH 4.5		
	1[a]	2[b]	3[c]	1	2	3
5	5.01[d] (0.10)[e]	3.21 (0.08)	1.76 (0.34)	11.72 (0.20)	9.29 (0.13)	3.05 (0.13)
10	7.52 (0.06)	6.26 (0.14)	4.32 (0.50)	18.24 (0.14)	13.79 (0.15)	9.32 (0.55)
15	8.57 (0.05)	7.84 (0.11)	6.45 (0.50)	20.77 (0.10)	17.18 (0.13)	14.55 (0.49)
30	9.66 (0.69)	9.33 (0.04)	8.55 (0.23)	23.09 (0.08)	19.82 (0.12)	19.69 (0.13)
45	10.16 (0.05)	9.54 (0.02)	9.02 (0.69)	23.68 (0.06)	20.93 (0.05)	20.82 (0.13)
60	10.29 (0.06)	9.58 (0.01)	9.24 (0.65)	24.14 (0.04)	21.71 (0.05)	21.13 (0.61)
120	10.47 (0.06)	9.72 (0.15)	9.40 (0.60)	24.18 (0.05)	22.01 (0.05)	21.32 (0.49)
180	10.53 (0.07)	9.82 (0.02)	9.53 (0.38)	24.07 (0.08)	22.01 (0.07)	21.51 (0.41)
Kd[f] (hr^{-1})	2.85 (0.32)	2.79 (0.20)	2.06 (0.13)	3.53 (0.50)	3.58 (0.41)	2.44 (0.42)

[a] Coevaporate

[b] Physical mixture

[c] Pure drug

[d] The mean of six determinations

[e] Stantdard error

[f] Dissolution rate contstant

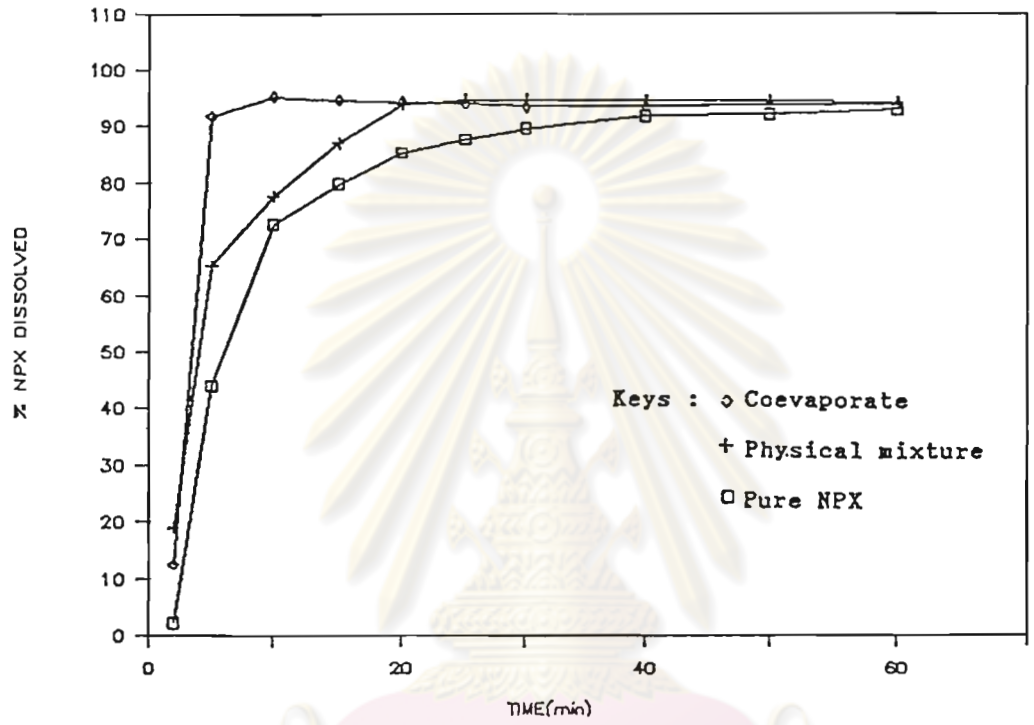


Figure 8 Dissolution Profiles of Naproxen from 1:1 NPX-PEG 4000 System at pH 7.5

Table 9 In Vitro Dissolution of Naproxen from 1:1 NPX-PEG 4000 Coevaporate, Physical Mixture and Prue Drug at pH 7.5.

Time (min)	Percent Naproxen Dissolved		
	1[a]	2[b]	3[c]
5	91.76[d] (0.71)[e]	65.34 (0.22)	44.03 (0.69)
10	95.24 (0.21)	77.69 (0.25)	72.68 (0.59)
15	94.60 (0.35)	87.06 (0.44)	79.82 (1.14)
30	93.38 (0.41)	94.58 (0.26)	89.53 (0.89)
40	93.45 (0.39)	94.51 (0.23)	91.68 (0.92)
60	93.62 (0.29)	94.06 (0.29)	92.74 (0.64)
Kd[f] (hr^{-1})	59.53 (5.78)	13.67 (1.18)	6.67 (0.87)

[a] Coevaporate

[b] Physical mixture

[c] Pure drug

[d] The mean of six determinations

[e] Standard error

[f] Dissolution rate constant

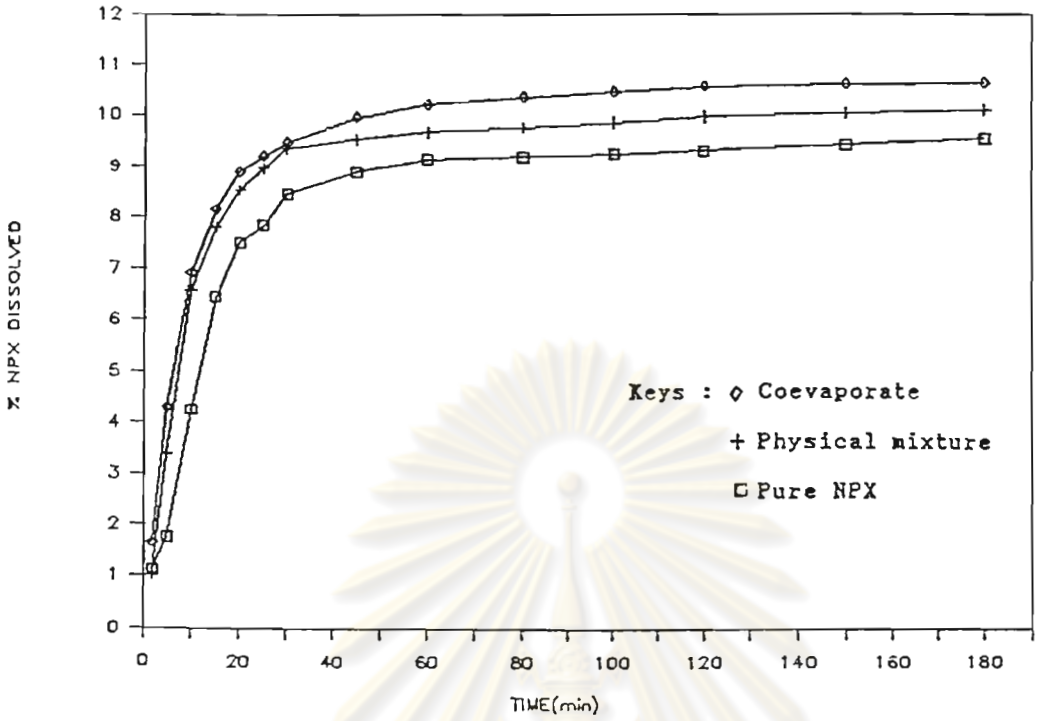


Figure 9 Dissolution Profiles of Naproxen from 1:1 NPX-PEG 6000 System at pH 1.5

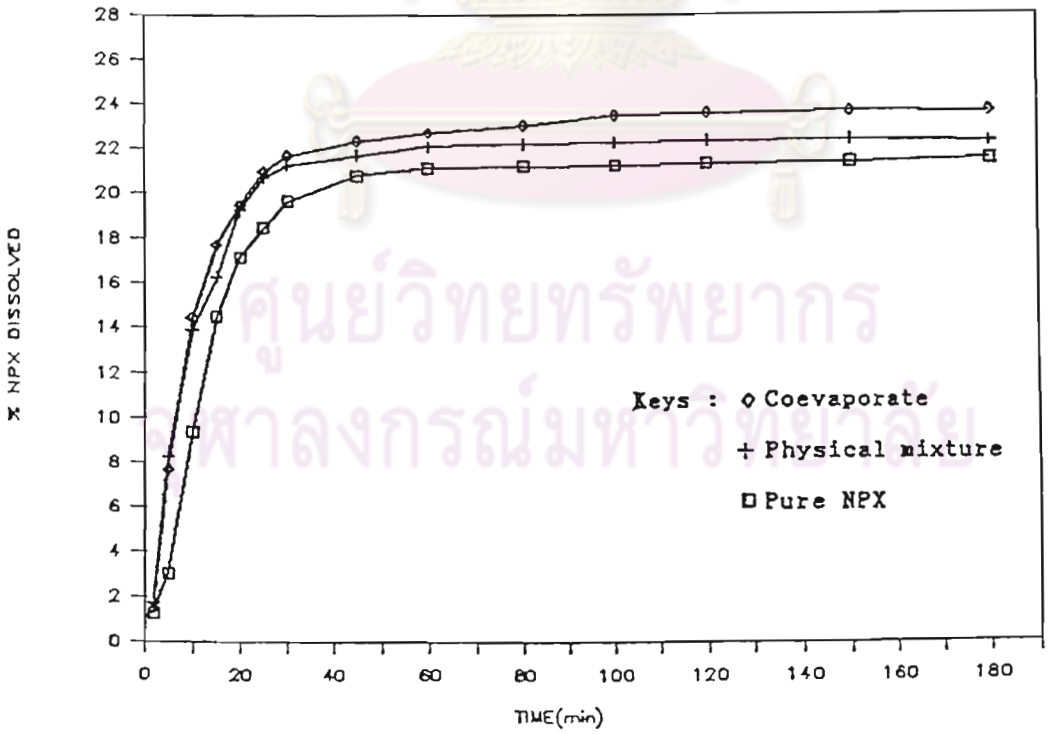


Figure 10 Dissolution Profiles of Naproxen from 1:1 NPX-PEG 6000 System at pH 4.5

Table 10 In Vitro Dissolution of Naproxen from 1:1 NPX-PEG 6000 Coevaporate, Physical Mixture and Pure Drug at pHs 1.5 and 4.5

Time (min)	Percent Naproxen Dissolved					
	pH 1.5			pH 4.5		
	1[a]	2[b]	3[c]	1	2	3
5	4.23[d] (0.10)[e]	3.39 (0.09)	1.76 (0.34)	8.27 (0.09)	7.14 (0.22)	3.05 (0.13)
10	6.93 (0.04)	6.57 (0.15)	4.32 (0.50)	13.91 (0.09)	13.77 (0.11)	9.32 (0.55)
15	8.17 (0.05)	7.82 (0.12)	6.45 (0.50)	16.28 (0.05)	16.91 (0.77)	14.55 (0.49)
30	9.49 (0.02)	9.36 (0.04)	8.55 (0.23)	21.26 (0.05)	20.11 (0.12)	19.69 (0.13)
45	9.97 (0.02)	9.54 (0.08)	9.02 (0.69)	21.73 (0.04)	20.87 (0.08)	20.82 (0.13)
60	10.22 (0.06)	9.68 (0.05)	9.24 (0.65)	22.11 (0.07)	21.41 (0.05)	21.13 (0.61)
120	10.57 (0.09)	9.99 (0.07)	9.40 (0.60)	22.36 (0.03)	22.30 (0.04)	21.32 (0.49)
180	10.63 (0.09)	10.11 (0.02)	9.53 (0.38)	22.30 (0.03)	22.56 (0.06)	21.51 (0.41)
Kd^{f} (hr^{-1})	1.94 (0.23)	1.93 (0.22)	2.06 (0.13)	3.04 (0.22)	2.93 (0.49)	2.44 (0.42)

[a] Coevaporate

[b] Physical mixture

[c] Pure drug

[d] The mean of six determinations

[e] Stantdard error

[f] Dissolution rate contstant

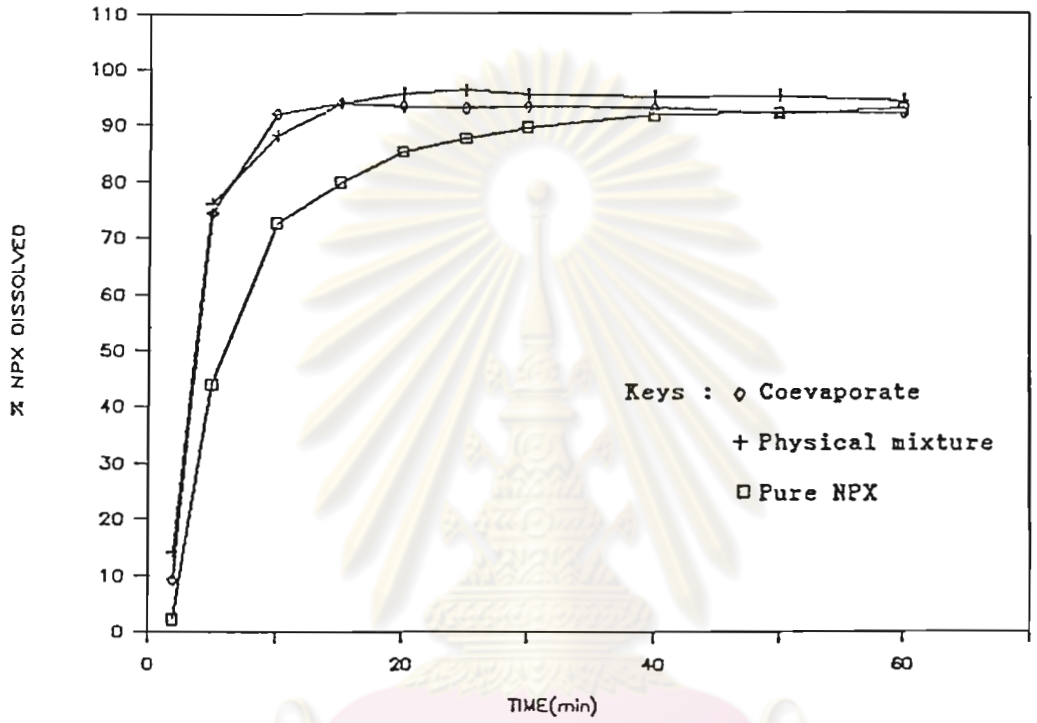


Figure 11 Dissolution Profiles of Naproxen from 1:1 NPX-PEG 6000 System at pH 7.5

Table 11 In Vitro Dissolution of Naproxen from 1:1 NPX-PEG 6000 Coevaporate, Physical Mixture and Prue Drug at pH 7.5.

Time (min)	Percent Naproxen Dissolved		
	1[a]	2[b]	3[c]
5	74.48[d] (3.52)[e]	76.08 (3.05)	44.03 (0.69)
10	92.12 (1.14)	88.32 (1.39)	72.68 (0.59)
15	93.99 (0.47)	93.90 (0.69)	79.82 (1.14)
30	93.99 (0.47)	95.36 (0.41)	89.53 (0.89)
40	93.00 (0.45)	95.05 (0.33)	91.68 (0.92)
60	91.88 (0.37)	94.20 (0.42)	92.74 (0.64)
Kd[f] (hr^{-1})	17.04 (1.21)	15.49 (2.79)	6.67 (0.87)

[a] Coevaporate

[b] Physical mixture

[c] Pure drug

[d] The mean of six determinations

[e] Standard error

[f] Dissolution rate constant

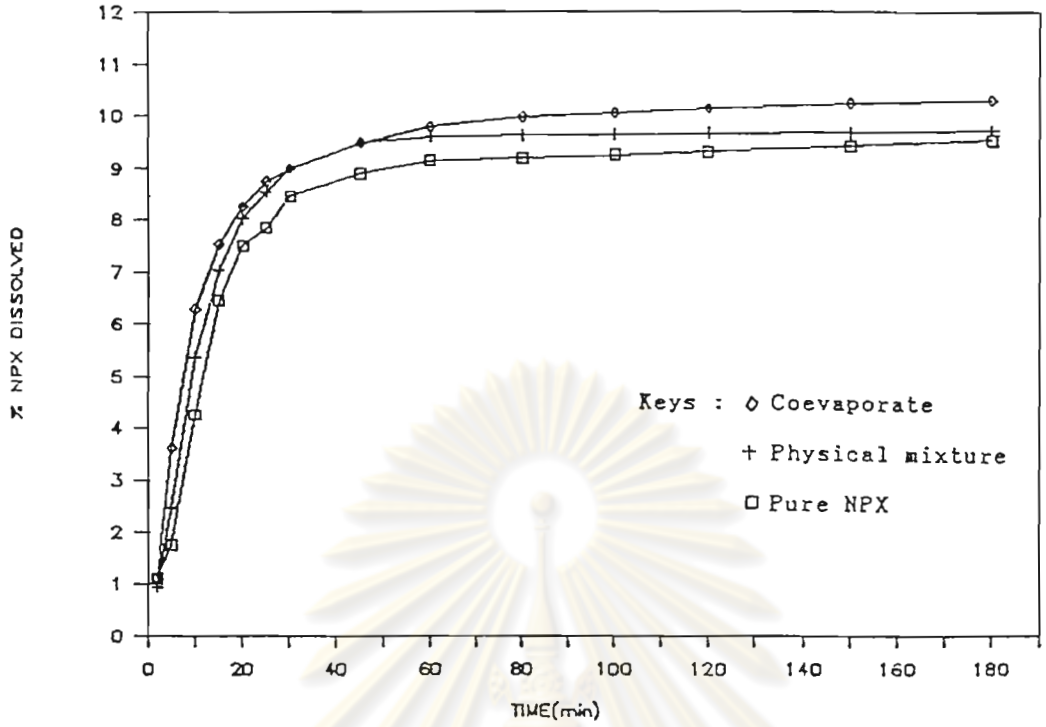


Figure 12 Dissolution Profiles of Naproxen from 1:1 NPX-PEG 20000 System at pH 1.5

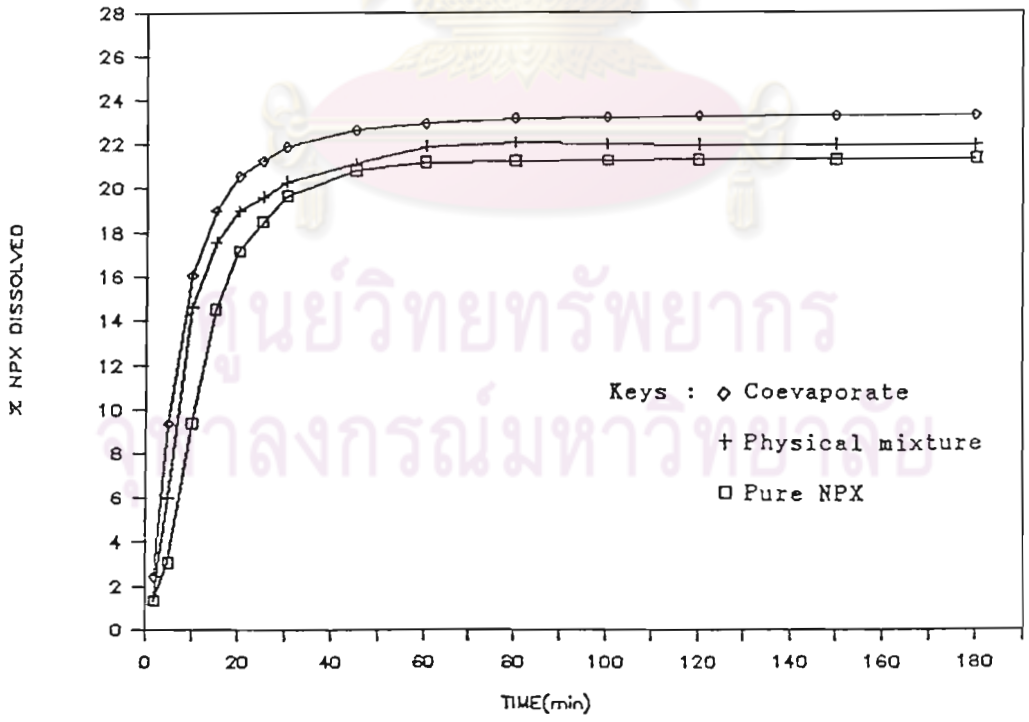


Figure 13 Dissolution Profiles of Naproxen from 1:1 NPX-PEG 20000 System at pH 4.5

Table 12 In Vitro Dissolution of Naproxen from 1:1 NPX-PEG 20000 Coevaporate, Physical Mixture and Pure Drug at pHs 1.5 and 4.5

Time (min)	Percent Naproxen Dissolved					
	pH 1.5			pH 4.5		
	1[a]	2[b]	3[c]	1	2	3
5	3.38[d] (0.29)[e]	2.45 (0.05)	1.76 (0.34)	9.34 (0.16)	6.03 (0.16)	3.05 (0.13)
10	6.30 (0.35)	5.37 (0.11)	4.32 (0.50)	16.07 (0.10)	14.60 (0.14)	9.32 (0.55)
15	7.60 (0.30)	7.05 (0.08)	6.45 (0.50)	19.20 (0.09)	17.59 (0.15)	14.55 (0.49)
30	9.10 (0.19)	9.00 (0.25)	8.55 (0.23)	21.90 (0.04)	20.31 (0.96)	19.69 (0.13)
45	9.60 (0.13)	9.49 (0.03)	9.02 (0.69)	22.65 (0.04)	21.15 (0.09)	20.82 (0.13)
60	9.90 (0.14)	9.60 (0.02)	9.24 (0.65)	22.92 (0.03)	21.89 (0.13)	21.13 (0.61)
120	10.20 (0.90)	9.68 (0.16)	9.40 (0.60)	23.27 (0.05)	22.19 (0.09)	21.32 (0.49)
180	10.44 (0.12)	9.74 (0.02)	9.53 (0.38)	23.30 (0.05)	22.12 (0.08)	21.51 (0.41)
Kd[f] (hr^{-1})	2.06 (0.47)	2.04 (0.37)	2.06 (0.13)	3.05 (0.35)	3.08 (0.35)	2.44 (0.42)

[a] Coevaporate

[b] Physical mixture

[c] Pure drug

[d] The mean of six determinations

[e] Stantdard error

[f] Dissolution rate contstant

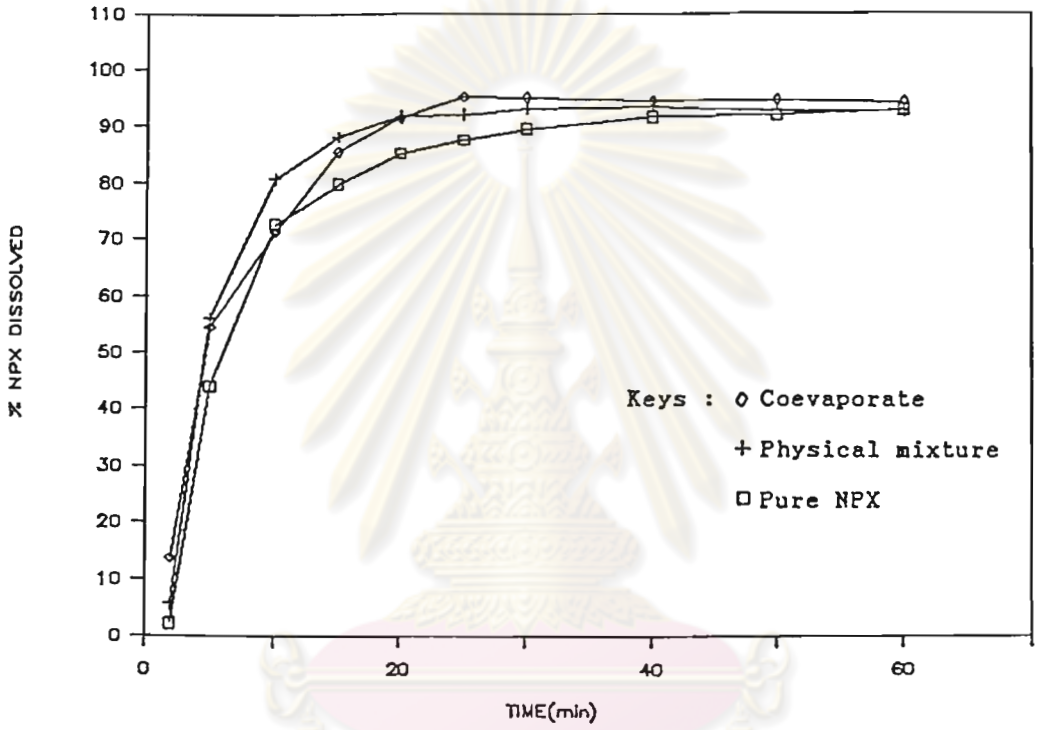


Figure 14 Dissolution Profiles of Naproxen from 1:1 NPX-PEG 20000 System at pH 7.5

Table 13 In Vitro Dissolution of Naproxen from 1:1 NPX-PEG 20000 Coevaporate, Physical Mixture and Prue Drug at pH 7.5.

Time (min)	Percent Naproxen Dissolved		
	1[a]	2[b]	3[c]
5	56.02[d] (2.63)[e]	54.44 (0.63)	44.03 (0.69)
10	80.72 (1.69)	71.35 (0.26)	72.68 (0.59)
15	88.17 (1.29)	85.56 (0.25)	79.82 (1.14)
30	93.09 (0.43)	94.99 (0.21)	89.53 (0.89)
40	93.46 (0.47)	94.40 (0.31)	91.68 (0.92)
60	92.58 (0.23)	94.16 (0.33)	92.74 (0.64)
Kd[f] (hr^{-1})	12.61 (4.05)	10.06 (0.89)	6.67 (0.87)

[a] Coevaporate

[b] Physical mixture

[c] Pure drug

[d] The mean of six determinations

[e] Standard error

[f] Dissolution rate constant

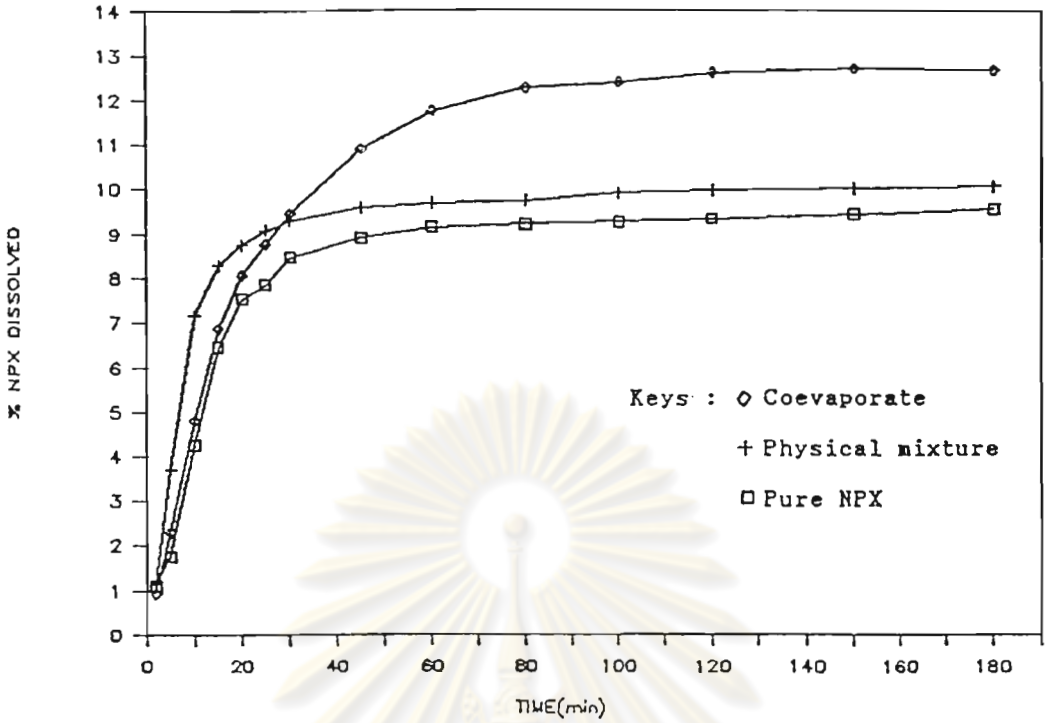


Figure 15 Dissolution Profiles of Naproxen from 1:1 NPX-PVP K-90 System at pH 1.5

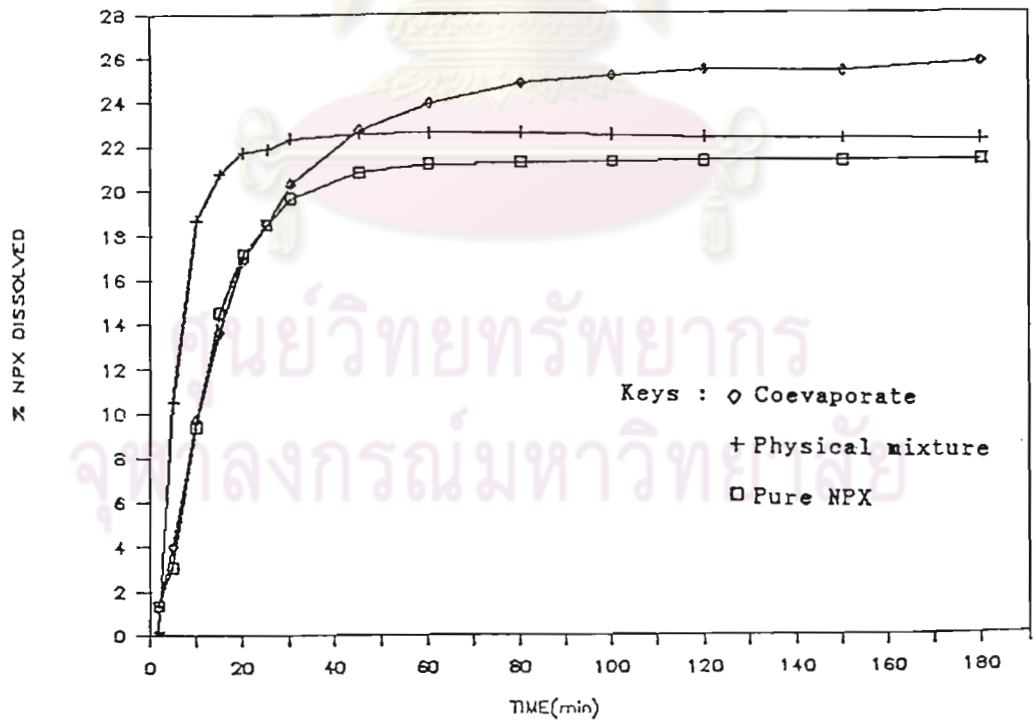


Figure 16 Dissolution Profiles of Naproxen from 1:1 NPX-PVP K-90 System at pH 4.5

Table 14 In Vitro Dissolution of Naproxen from 1:1 NPX-PVP K-90 Coevaporate, Physical Mixture and Pure Drug at pHs 1.5 and 4.5

Time (min)	Percent Naproxen Dissolved					
	pH 1.5			pH 4.5		
	1[a]	2[b]	3[c]	1	2	3
5	2.30[d] (0.06)[e]	3.71 (0.09)	1.76 (0.34)	4.03 (0.15)	10.47 (0.11)	3.05 (0.13)
10	4.80 (0.09)	7.16 (0.09)	4.32 (0.50)	9.69 (0.24)	18.70 (0.92)	9.32 (0.55)
15	6.87 (0.15)	8.28 (0.45)	6.45 (0.50)	13.62 (0.26)	20.77 (0.26)	14.55 (0.49)
30	9.45 (0.51)	9.30 (0.45)	8.55 (0.23)	20.33 (0.15)	21.86 (0.26)	19.69 (0.13)
45	10.90 (0.51)	9.58 (0.11)	9.02 (0.69)	22.73 (0.13)	22.07 (0.24)	20.82 (0.13)
60	11.74 (0.08)	9.67 (0.11)	9.24 (0.65)	23.93 (0.10)	22.16 (0.18)	21.13 (0.61)
120	12.55 (0.42)	9.96 (0.11)	9.40 (0.60)	25.41 (0.72)	22.54 (0.18)	21.32 (0.49)
180	12.67 (0.38)	10.06 (0.12)	9.53 (0.38)	25.72 (0.63)	22.39 (0.75)	21.51 (0.41)
Kd^{f} (hr^{-1})	2.26 (0.23)	2.36 (0.32)	2.06 (0.13)	2.50 (0.56)	2.90 (0.23)	2.44 (0.42)

[a] Coevaporate

[b] Physical mixture

[c] Pure drug

[d] The mean of six determinations

[e] Stantdard error

[f] Dissolution rate contstant

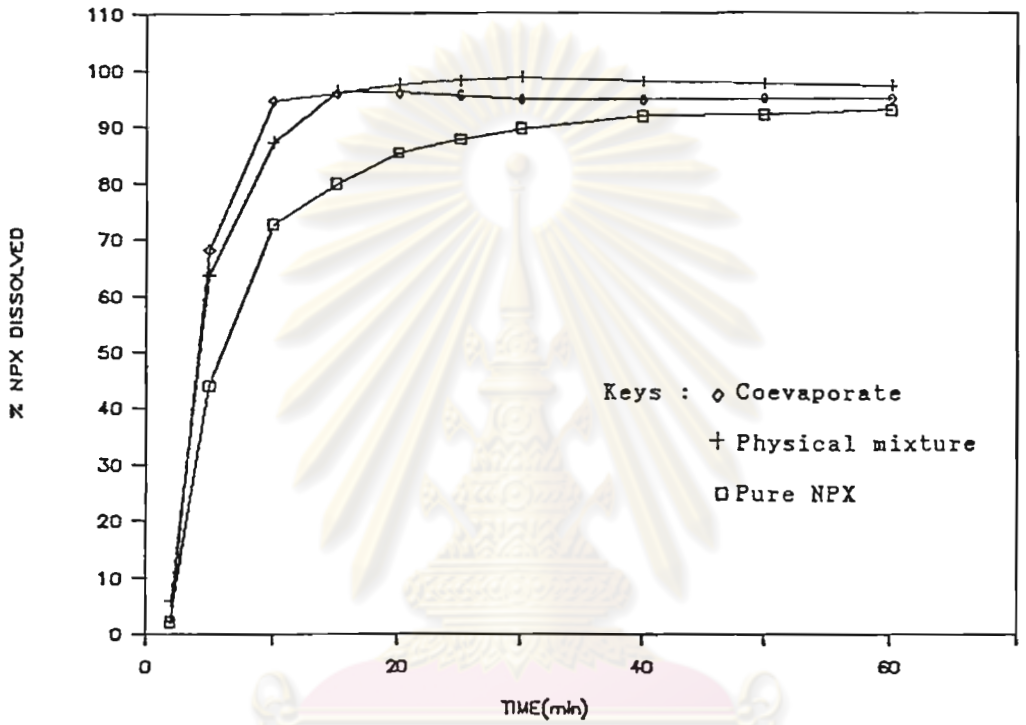


Figure 17 Dissolution Profiles of Naproxen from 1:1 NPX-PVP K-90 System at pH 7.5

Table 15 In Vitro Dissolution of Naproxen from 1:1 NPX-PVP K-90 Coevaporate, Physical Mixture and Prue Drug at pH 7.5.

Time (min)	Percent Naproxen Dissolved		
	1[a]	2[b]	3[c]
5	68.25[d] (2.68)[e]	63.73 (1.48)	44.03 (0.69)
10	94.72 (1.34)	87.42 (1.55)	72.68 (0.59)
15	95.98 (0.34)	96.30 (1.70)	79.82 (1.14)
30	94.72 (0.31)	98.65 (0.16)	89.53 (0.89)
40	94.65 (0.42)	97.87 (0.51)	91.68 (0.92)
60	94.89 (0.32)	97.05 (0.56)	92.74 (0.64)
Kd^{f} (hr^{-1})	28.79 (3.91)	13.13 (0.61)	6.67 (0.87)

[a] Coevaporate

[b] Physical mixture

[c] Pure drug

[d] The mean of six determinations

[e] Standard error

[f] Dissolution rate constant

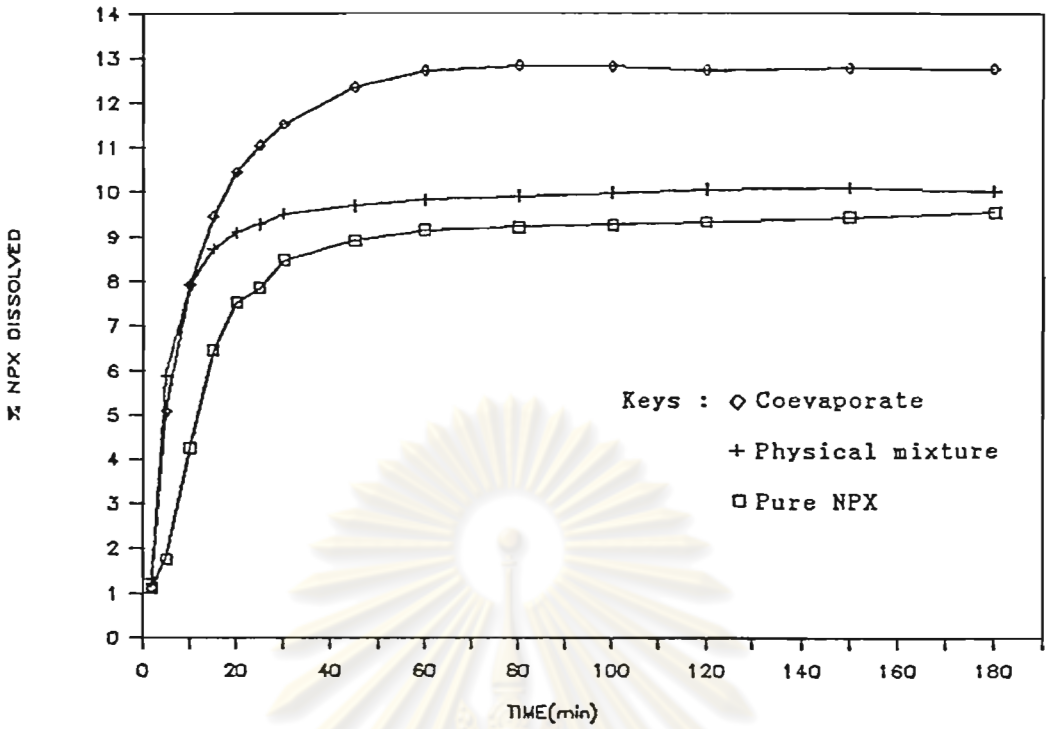


Figure 18 Dissolution Profiles of Naproxen from 1:1 NPX-PVP K-30 System at pH 1.5

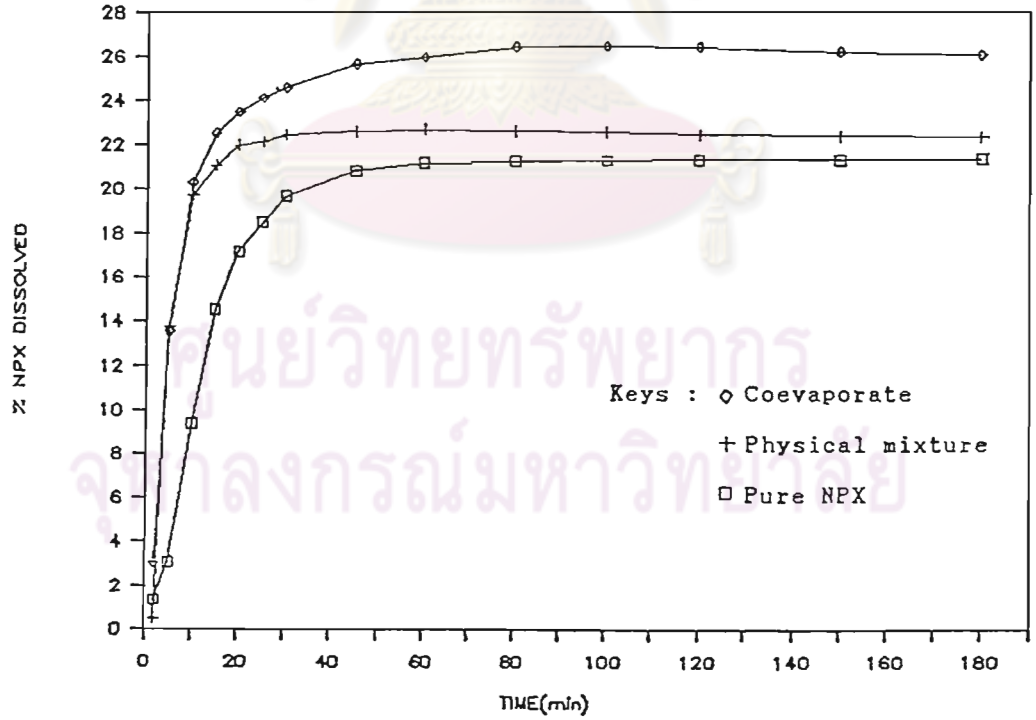


Figure 19 Dissolution Profiles of Naproxen from 1:1 NPX-PVP K-30 System at pH 4.5.

Table 16 In Vitro Dissolution of Naproxen from 1:1 NPX-PVP K-30 Coevaporate, Physical Mixture and Pure Drug at pHs 1.5 and 4.5

Time (min)	Percent Naproxen Dissolved					
	pH 1.5			pH 4.5		
	1[a]	2[b]	3[c]	1	2	3
5	5.06[d] (0.14)[e]	5.89 (0.13)	1.76 (0.34)	13.52 (0.69)	10.44 (0.06)	3.05 (0.13)
10	7.92 (0.05)	7.94 (0.15)	4.32 (0.50)	20.28 (0.42)	15.80 (0.09)	9.32 (0.55)
15	9.46 (0.10)	8.73 (0.05)	6.45 (0.50)	22.51 (0.32)	16.49 (0.11)	14.55 (0.48)
30	11.52 (0.09)	9.51 (0.28)	8.55 (0.23)	24.57 (0.19)	22.02 (0.03)	19.69 (0.13)
45	12.34 (0.07)	9.68 (0.03)	9.02 (0.69)	25.63 (0.15)	22.15 (0.03)	20.82 (0.13)
60	12.68 (0.06)	9.81 (0.02)	9.24 (0.65)	25.95 (0.11)	22.30 (0.02)	21.13 (0.61)
120	12.71 (0.07)	10.05 (0.04)	9.40 (0.60)	26.37 (0.10)	22.54 (0.02)	21.32 (0.49)
180	12.76 (0.05)	10.02 (0.02)	9.53 (0.38)	26.03 (0.03)	22.54 (0.05)	21.51 (0.41)
Kd[f] (hr^{-1})	3.92 (0.44)	2.83 (0.43)	2.06 (0.13)	4.21 (0.77)	3.19 (0.44)	2.44 (0.42)

[a] Coevaporate

[b] Physical mixture

[c] Pure drug

[d] The mean of six determinations

[e] Stantdard error

[f] Dissolution rate contstant

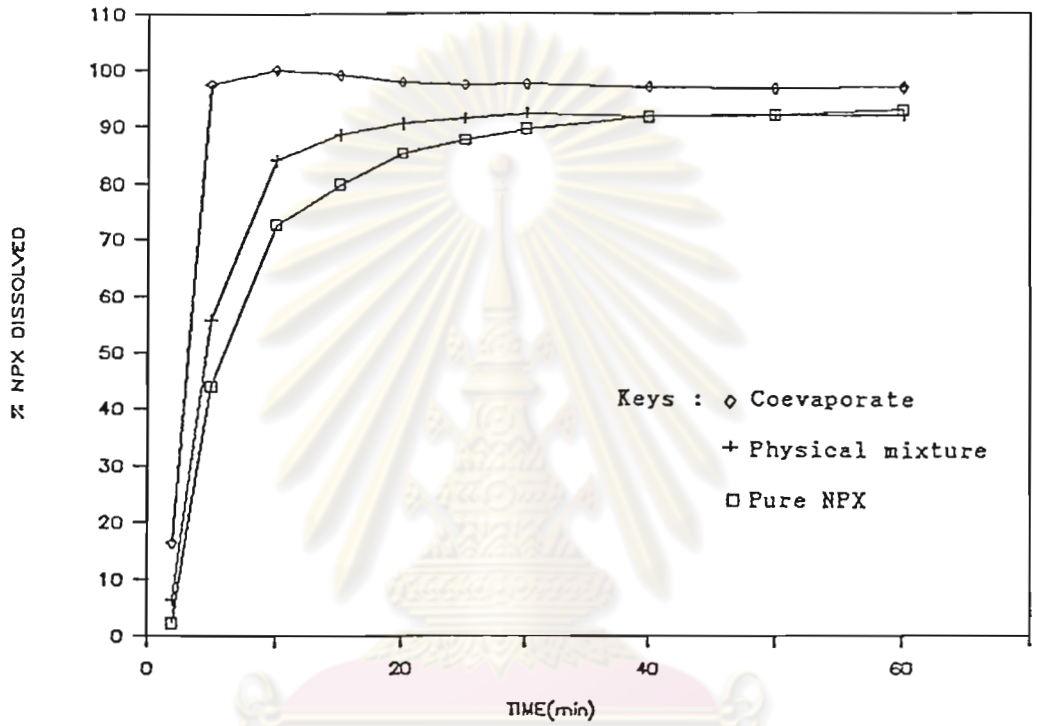


Figure 20 Dissolution Profiles of Naproxen from 1:1 NPX-PVP K-30 System at pH 7.5

Table 17 In Vitro Dissolution of Naproxen from 1:1 NPX-PVP K-30 Coevaporate, Physical Mixture and Prue Drug at pH 7.5.

Time (min)	Percent Naproxen Dissolved		
	1[a]	2[b]	3[c]
5	97.45[d] (0.54)[e]	55.73 (0.95)	44.03 (0.69)
10	100.00 (0.34)	84.11 (0.62)	72.68 (0.58)
15	98.03 (0.60)	88.57 (0.64)	79.82 (1.14)
30	97.41 (0.52)	92.26 (0.38)	89.53 (0.89)
40	96.93 (0.30)	91.78 (0.39)	91.68 (0.92)
60	96.79 (0.19)	91.81 (0.41)	92.74 (0.64)
Kd[f] (hr^{-1})	63.68 (7.50)	17.96 (1.22)	6.67 (0.87)

[a] Coevaporate

[b] Physical mixture

[c] Pure drug

[d] The mean of six determinations

[e] Standard error

[f] Dissolution rate constant

presented in Tables 18 - 23.

The results revealed that in all carrier systems the coevaporates gave statistically significant higher dissolution than the corresponding physical mixtures and pure NPX ($p < 0.05$) except in PEG 6000 and PEG 20000 systems that there were no statistically significant of dissolution rate between the coevaporates and the physical mixture ($p > 0.10$).

NPX-PEG 4000 coevaporate (NC1) showed statistically significant higher percent NPX dissolved at each time interval than the physical mixture (NP1) in dissolution mediums pHs 1.5 and 4.5 and during the first 30 minutes at pH 7.5 ($p < 0.05$). (Figures 6 - 8)

Although there were no statistically significant difference of dissolution rate between the coevaporate and the corresponding physical mixture at all pHs of dissolution medium in PEG 6000 and 20000 systems ($p > 0.10$), but the percent NPX dissolved from the coevaporates (NC2 or NC3) were significantly higher than the corresponding physical mixtures (NP2 or NP3) at pHs 1.5 and 4.5 ($p < 0.10$). (Figures 9 -14)

In NPX-PVP K-90 system (Figures 15 - 17), at pHs 1.5 and 4.5, the physical mixture (NP4) exhibited higher dissolution than the coevaporate (NC4) during the first 30 minutes, but after that, NC4 then markedly greater dissolved than NP4. However, at pH 7.5 NC4

Table 18 The Statistical Comparisons of Percent NPX Dissolved at Various Times and Dissoltion Rate Constants (Kd) from Various NPX Dispersion Systems and Pure NPX (NC1-NC5, NP1-NP5, NO) at pH 1.5 Using one - way ANOVA.

Time (min)	Source of Variation	d.f[a]	SS[b]	MS[c]	F[d]
5	Treatment	10	97.60	9.76	151.61
	Error	55	3.54	0.06	
	Total	65	101.14		
15	Treatment	10	46.91	4.69	61.86
	Error	55	4.02	0.08	
	Total	65	51.70		
30	Treatment	10	33.80	3.38	96.54
	Error	55	1.93	0.04	
	Total	65	35.72		
60	Treatment	10	66.08	6.61	455.16
	Error	55	0.79	0.01	
	Total	65	66.88		
120	Treatment	10	76.01	7.60	510.65
	Error	55	0.81	0.01	
	Total	65	76.83		
Kd (hr^{-1})	Treatment	10	0.36	0.04	10.61
	Error	55	0.19	0.03	
	Total	65	0.55		

[e] $F_{0.05\ (10,\ 55)} = 2.01$

[f] $F_{0.10\ (10,\ 55)} = 1.72$

[a] Degree of freedom

[b] Sum of square error

[c] Mean square error

[d] Variance ratio

[e,f] F obtained from the table

Table 19 The Statistical Comparisons of Percent NPX Dissolved at Various Times and Dissoltion Rate Constants (Kd) from Various NPX Dispersion Systems and Pure NPX (NC1-NC5, NP1-NP5, NO) at pH 4.5 Using one - way ANOVA.

Time (min)	Source of Variation	d.f[a]	SS[b]	MS[c]	F[d]
5	Treatment	10	558.86	55.88	52.73
	Error	55	58.29	1.06	
	Total	65	617.15		
15	Treatment	10	449.82	44.98	181.84
	Error	55	13.61	0.25	
	Total	65	463.43		
30	Treatment	10	139.18	13.92	135.20
	Error	55	5.66	0.10	
	Total	65	144.84		
60	Treatment	10	117.59	11.76	53.71
	Error	55	12.04	0.22	
	Total	65	129.64		
120	Treatment	10	103.74	10.37	22.72
	Error	55	25.11	0.46	
	Total	65	128.85		
Kd (hr^{-1})	Treatment	10	0.25	0.02	7.21
	Error	55	0.19	0.03	
	Total	65	0.44		

[e] $F_{0.05\ (10,\ 55)} = 2.01$

[f] $F_{0.10\ (10,\ 55)} = 1.72$

[a] Degree of freedom

[b] Sum of square error

[c] Mean square error

[d] Variance ratio

[e,f] F obtained from the table

Table 20 The Statistical Comparisons of Percent NPX Dissolved at Various Times and Dissoltion Rate Constants (Kd) from Various NPX Dispersion Systems and Pure NPX (NC1-NC5, NP1-NP5, NO) at pH 7.5 Using one - way ANOVA.

Time (min)	Source of Variation	d.f[a]	SS[b]	MS[c]	F[d]
5	Treatment	10	15751.00	1575.10	76.70
	Error	55	1129.49	20.54	
	Total	65	16880.50		
15	Treatment	10	1659.78	165.98	12.29
	Error	55	742.68	13.50	
	Total	65	2402.47		
30	Treatment	10	413.94	41.69	24.89
	Error	55	92.12	1.67	
	Total	65	509.06		
60	Treatment	10	189.83	18.98	29.06
	Error	55	35.92	0.65	
	Total	65	225.75		
Kd (hr^{-1})	Treatment	10	394.80	39.60	58.43
	Error	55	36.00	0.60	
	Total	65	432.60		

[e] $F_{0.05\ (10,\ 55)} = 2.01$

[f] $F_{0.10\ (10,\ 55)} = 1.72$

[a] Degree of freedom

[b] Sum of square error

[c] Mean square error

[d] Variance ratio

[e,f] F obtained from the table

Table 21 The Statistical Comparisons of Percent NPX Dissolved at Various Times and Dissoltion Rate Constants(Kd) from Various NPX Dispersion Systems and Pure NPX (NC1-NC5, NP1-NP5, NO) at pH 1.5 Using T-test.

	Comparative Percent NPX Dissolved at time (min)										Kd (hr^{-1})	
	5		15		30		60		120			
Prep.	NP1	NC1	NP1	NC1	NP1	NC1	NP1	NC1	NP1	NC1	NP1	NC1
NO	++	++	++	++	++	++	++	++	++	++	++	++
NP1		++		++		++		++		++		+
	NP2	NC2	NP2	NC2	NP2	NC2	NP2	NC2	NP2	NC2	NP2	NC2
NO	++	++	++	++	++	++	++	++	++	++	+	+
NP2		+		+		+		+		+		-
	NP3	NC3	NP3	NC3	NP3	NC3	NP3	NC3	NP3	NC3	NP3	NC3
NO	++	++	++	++	++	++	+	++	++	++	+	+
NP3		+		+		-		+		+		-
	NP4	NC4	NP4	NC4	NP4	NC4	NP4	NC4	NP4	NC4	NP4	NC4
NO	++	-	++	-	++	-	++	++	++	++	+	-
NP4		++		++		-		++		++		-
	NP5	NC5	NP5	NC5	NP5	NC5	NP5	NC5	NP5	NC5	NP5	NC5
NO	++	++	++	++	++	++	++	++	++	++	++	++
NP5		++		++		++		++		++		++
	NC2	NC3	NC2	NC3	NC2	NC3	NC2	NC3	NC2	NC3	NC2	NC3
NC1	++	++	++	++	+	++	-	++	-	++	+	+
NC2		++		++		++		++		++		-
	NC4	NC5	NC4	NC5	NC4	NC5	NC4	NC5	NC4	NC5	NC4	NC5
NC1	++	-	++	++	-	++	++	++	++	++	+	++
NC2	++	++	++	++	-	++	++	++	++	++	-	++
	NC4	NC5	NC4	NC5	NC4	NC5	NC4	NC5	NC4	NC5	NC4	NC5
NC3	++	++	+	++	+	++	++	++	++	++	-	++
NC4		++		++		++		++		-		++

+ = Significant difference ($p < 0.10$)
++ = Significant difference ($p < 0.05$)
- = Not Significant difference ($p > 0.10$)

Table 22 The Statistical Comparisons of Percent NPX Dissolved at Various Times and Dissoltion Rate Constants (Kd) from Various NPX Dispersion Systems and Pure NPX (NC1-NC5, NP1-NP5, NO) at pH 4.5 Using T-test.

	Comparative Percent NPX Dissolved at time (min)										Kd (hr^{-1})	
	5		15		30		60		120			
Prep.	NP1	NC1	NP1	NC1	NP1	NC1	NP1	NC1	NP1	NC1	NP1	NC1
NO	++	++	++	++	++	++	++	++	++	++	++	++
NP1		++		+		+		++		++		+
	NP2	NC2	NP2	NC2	NP2	NC2	NP2	NC2	NP2	NC2	NP2	NC2
NO	++	++	++	++	++	++	++	++	++	++	+	+
NP2		+		+		-		+		+		-
	NP3	NC3	NP3	NC3	NP3	NC3	NP3	NC3	NP3	NC3	NP3	NC3
NO	++	++	++	++	+	++	+	++	+	++	+	+
NP3		++		+		++		++		++		-
	NP4	NC4	NP4	NC4	NP4	NC4	NP4	NC4	NP4	NC4	NP4	NC4
NO	++	-	++	-	++	-	++	++	++	++	+	-
NP4		++		++		++		++		++		-
	NP5	NC5	NP5	NC5	NP5	NC5	NP5	NC5	NP5	NC5	NP5	NC5
NO	++	++	++	++	++	++	++	++	++	++	++	++
NP5		-		++		++		++		++		++
	NC2	NC3	NC2	NC3	NC2	NC3	NC2	NC3	NC2	NC3	NC2	NC3
NC1	++	++	++	++	++	++	-	+	++	++	+	+
NC2		++		++		-		-		-		-
	NC4	NC5	NC4	NC5	NC4	NC5	NC4	NC5	NC4	NC5	NC4	NC5
NC1	++	++	++	++	++	++	-	++	-	-	+	+
NC2	+	++	++	++	++	++	+	++	++	++	-	++
	NC4	NC5	NC4	NC5	NC4	NC5	NC4	NC5	NC4	NC5	NC4	NC5
NC3	++	++	++	++	++	++	++	++	+	++	-	++
NC4		++		++		++		++		-		++

+ = Significant difference ($p < 0.10$)
++ = Significant difference ($p < 0.05$)
- = Not Significant difference ($p > 0.10$)

Table 23 The Statistical Comparisons of Percent NPX Dissolved at Various Times and Dissolution Rate Contants (Kd) from Various NPX Dispersion Systems and Pure NPX (NC1-NC5, NP1-NP5, NO) at pH 7.5 Using T-test.

	Comparative % NPX Dissolved at time (min)								Kd (hr^{-1})	
	5		15		30		60			
Prep.	NP1	NC1	NP1	NC1	NP1	NC1	NP1	NC1	NP1	NC1
NO	++	++	++	++	++	++	-	-	++	++
NP1		++		++		+		-		++
	NP2	NC2	NP2	NC2	NP2	NC2	NP2	NC2	NP2	NC2
NO	++	++	++	++	++	++	-	-	++	++
NP2		-		+		-		-		-
	NP3	NC3	NP3	NC3	NP3	NC3	NP3	NC3	NP3	NC3
NO	++	++	++	+	+	+	-	-	++	+
NP3		-		+		-		-		-
	NP4	NC4	NP4	NC4	NP4	NC4	NP4	NC4	NP4	NC4
NO	++	++	++	++	++	++	++	++	++	++
NP4		+		-		+		+		++
	NP5	NC5	NP5	NC5	NP5	NC5	NP5	NC5	NP5	NC5
NO	++	++	++	++	-	++	-	++	++	++
NP5		++		++		++		++		++
	NC2	NC3	NC2	NC3	NC2	NC3	NC2	NC3	NC2	NC3
NC1	++	++	-	+	-	-	++	++	++	++
NC2		++		++		-		-		-
	NC4	NC5	NC4	NC5	NC4	NC5	NC4	NC5	NC4	NC5
NC1	++	++	-	-	+	++	+	++	++	-
NC2	-	++	++	-	+	++	++	++	-	++
	NC4	NC5	NC4	NC5	NC4	NC5	NC4	NC5	NC4	NC5
NC3	+	++	+	+	+	++	++	++	++	++
NC4		++		-		++		++		++

+ = Significant difference ($p < 0.10$)
++ = Significant difference ($p < 0.05$)
- = Not Significant difference ($p > 0.10$)

showed statistically significant faster dissolution rate than NP4 ($p < 0.05$).

Initially, there was no statistically significant difference of dissolution between NPX-PVP K-30 coevaporate (NC5) and the physical mixture (NP5) at pHs 1.5 and 4.5 ($p > 0.10$) but after 15 minutes NC5 gave markedly higher dissolution than NP5 and also yield significant faster dissolution rate ($p < 0.05$). Moreover, at pH 7.5, NC5 exhibited the fastest dissolution rate which gave 100% NPX dissolved within 10 minutes whereas NP5 and NO gave 84 and 73%, respectively. (Figures 18 - 20)

By comparing among the coevaporates, the dissolution profiles of the coevaporates with various types of carrier were illustrated in Figures 21 - 23 and the statistical comparisons of the dissolution parameters for each coevaporate using t - test were also presented in Tables 21 - 23. NC5 produced the quickest dissolution rate and the highest amount of NPX dissolved. The maximum average percent NPX dissolved from NC5 were 12.76, 26.37 and 100.00 % whereas NO gave 9.53, 12.51 and 92.74% at pHs 1.5, 4.5 and 7.5, respectively. However in PEGs system, NC1 gave statistically significant higher dissolution than NC2 and NC3 ($p < 0.05$). Finally, NC4 showed slower dissolution rate than the others in the initial part of dissolution profile, followed by subsequent faster dissolution rate in the latter part of the dissolution profile.

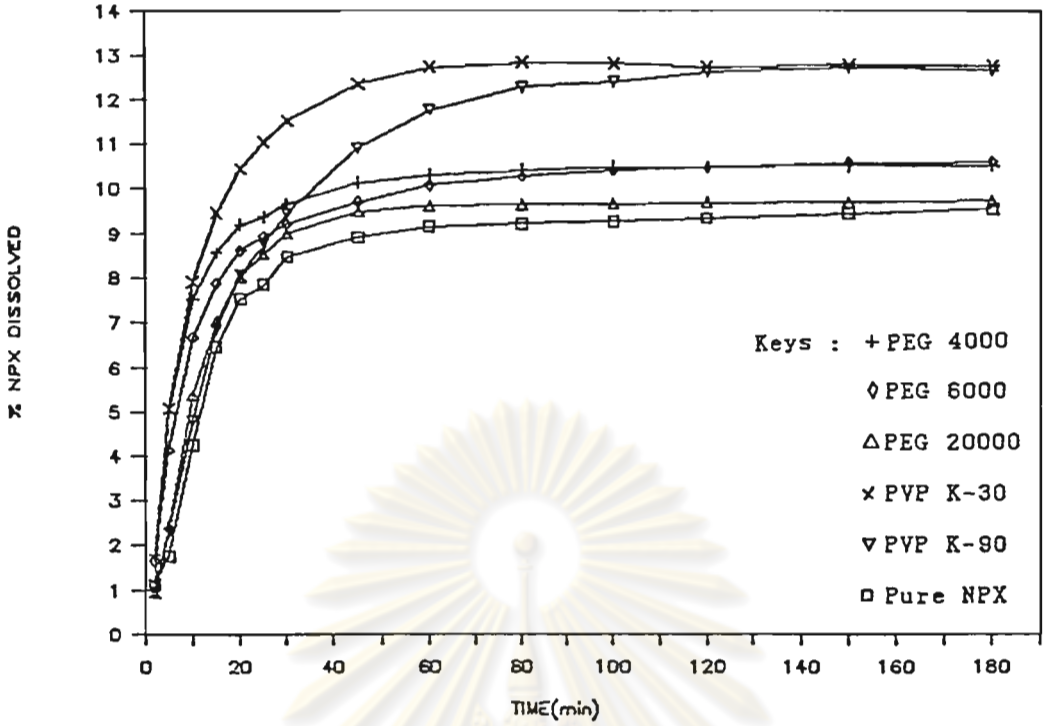


Figure 21 Dissolution Profiles of Naproxen from 1:1 NPX Coevaporates with various types of carrier at pH 1.5

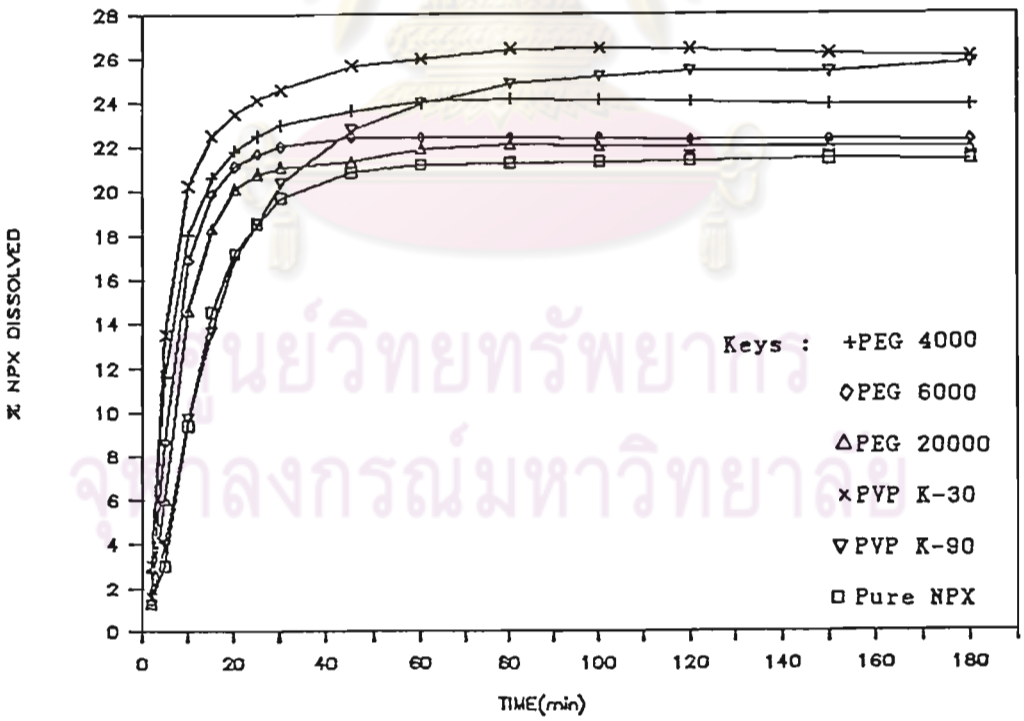


Figure 22 Dissolution Profiles of Naproxen from 1:1 NPX Coevaporates with various types of carrier at pH 4.5

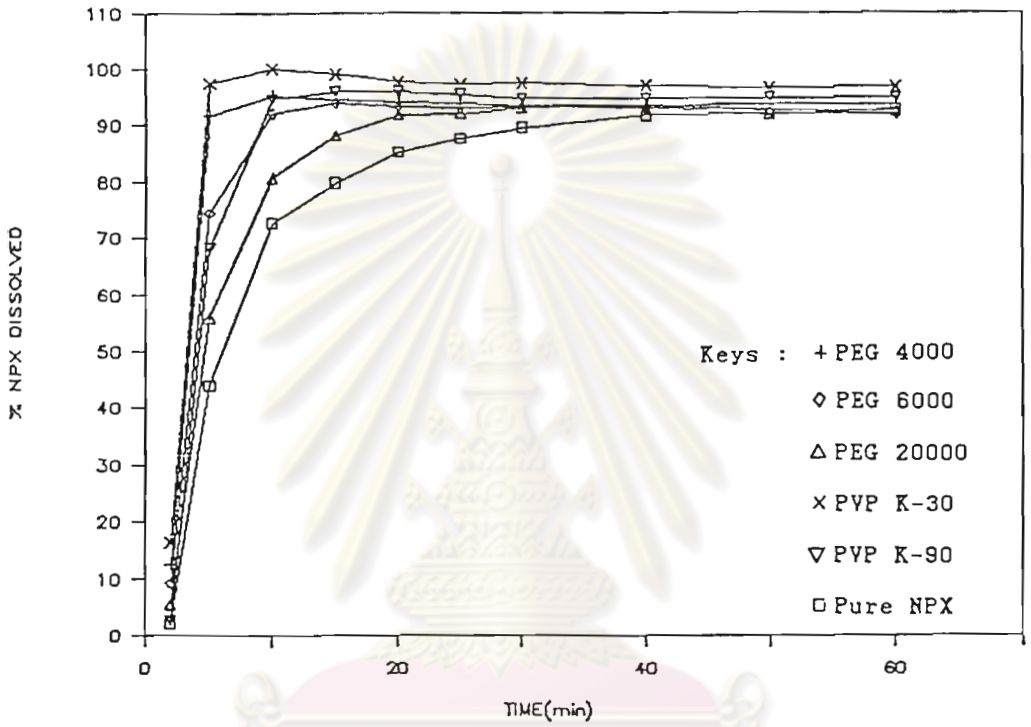


Figure 23 Dissolution Profiles of Naproxen from 1:1 NPX Coevaporates with various types of carrier at pH 7.5

Due to the above dissolution results the PVP K-30 system was chosen for further studies by means of decreasing amount of the carrier for the preparation of coevaporates in order to find the coevaporate which produces the greatest dissolution while using the less amount of carrier. The three newly NPX-PVP K-30 coevaporates were prepared by varying the ratio of drug:carrier to 1:0.75, 1:0.50 and 1:0.25. The codes used for these preparations were as follows :

Code	Preparation
NC6	1:0.75 NPX-PVP K-30 Coevaporate
NC7	1:0.50 NPX-PVP K-30 Coevaporate
NC8	1:0.25 NPX-PVP K-30 Coevaporate

Figures 24 - 26 and Tables 24 - 26 presented the dissolution profiles of NPX-PVP K-30 with various ratios of drug:carrier by comparing with 1:1 ratio of physical mixture and pure NPX. The statistical comparisons of the dissolution parameters among these preparation at all pH of dissolution mediums using one - way ANOVA and T -test were shown in Tables 27 - 30.

The results showed that the average percent dissolved of NPX decreased with decreasing amount of the carrier. NC5 gave the highest dissolution rate and extent followed by NC6, NC7 and NC8, respectively, at pH 7.5. Unless there were no statistically significant difference of dissolution rates between NC5 and NC6 at pHs 1.5 and

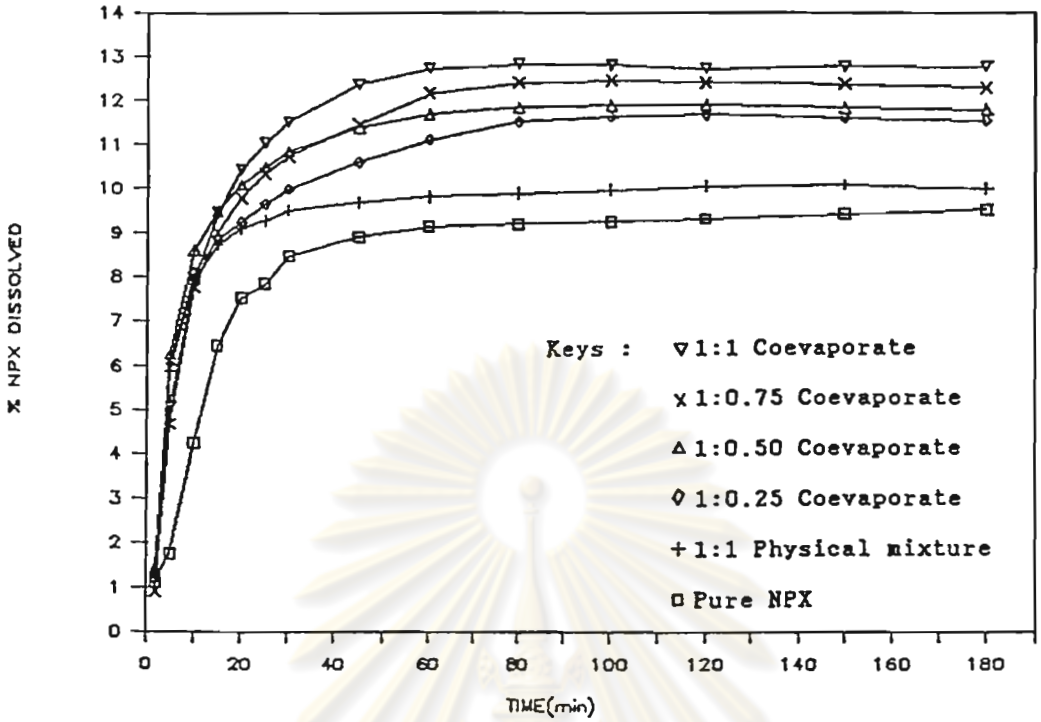


Figure 24 Dissolution Profiles of Naproxen from NPX-PVP K-30 Coevaporates with various ratios of Drug:Carrier at pH 1.5

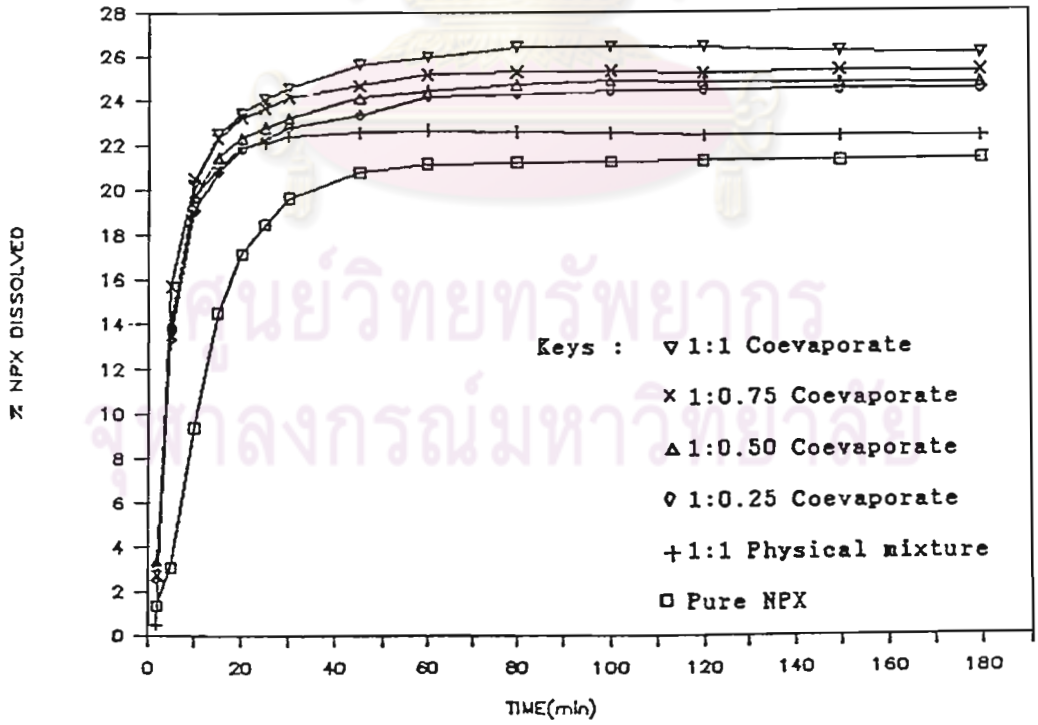


Figure 25 Dissolution Profiles of Naproxen from NPX-PVP K-30 Coevaporates with various ratios of Drug:Carrier at pH 4.5

Table 24 In Vitro Dissolution of Naproxen from NPX-PVP K-30 Coevaporates with Various Ratios of Drug:Carrier at pH 1.5

Time (min)	Percent Naproxen Dissolved			
	Ratios of Drug:Carrier			
	1:1	1:0.75	1:0.50	1:0.25
5	5.06[a] (0.14)[b]	4.06 (0.15)	6.34 (0.08)	6.05 (0.10)
10	7.92 (0.05)	7.61 (0.08)	8.66 (0.12)	8.11 (0.08)
15	9.46 (0.10)	8.90 (0.09)	9.60 (0.05)	8.86 (0.12)
30	11.52 (0.09)	10.74 (0.12)	10.89 (0.06)	9.99 (0.10)
45	12.34 (0.07)	11.41 (0.04)	11.48 (0.04)	10.59 (0.14)
60	12.68 (0.06)	11.68 (0.06)	11.77 (0.04)	10.59 (0.09)
120	12.71 (0.07)	12.41 (0.09)	11.94 (0.04)	11.67 (0.05)
180	12.76 (0.05)	12.29 (0.05)	11.86 (0.04)	11.55 (0.07)
Kd[c] (hr^{-1})	3.92 (0.45)	3.85 (0.24)	3.29 (0.19)	3.09 (0.25)

[a] The mean of six determinations

[b] Standard error

[c] Dissolution rate constant

Table 25 In Vitro Dissolution of Naproxen from NPX-PVP K-30 Coevaporates with Various Ratios of Drug : Carrier at pH 4.5

Time (min)	Percent Naproxen Dissolved			
	Ratios of Drug:Carrier			
	1:1	1:0.75	1:0.50	1:0.25
5	13.52[a] (0.69)[b]	15.72 (0.13)	14.11 (0.20)	13.33 (0.20)
10	20.28 (0.42)	20.57 (0.06)	19.76 (0.08)	19.09 (0.16)
15	22.51 (0.32)	22.34 (0.05)	21.52 (0.05)	20.84 (0.11)
30	24.57 (0.19)	24.19 (0.13)	23.24 (0.03)	22.83 (0.14)
45	25.63 (0.15)	24.69 (0.11)	24.14 (0.03)	23.36 (0.17)
60	25.95 (0.11)	25.17 (0.06)	24.42 (0.13)	24.18 (0.17)
120	26.37 (0.10)	25.24 (0.06)	24.80 (0.01)	24.45 (0.20)
180	26.03 (0.03)	25.25 (0.06)	25.73 (0.02)	24.46 (0.21)
Kd^{c} (hr^{-1})	4.21 (0.77)	4.10 (0.25)	3.26 (0.08)	2.91 (0.12)

[a] The mean of six determinations

[b] Standard error

[c] Dissolution rate constant

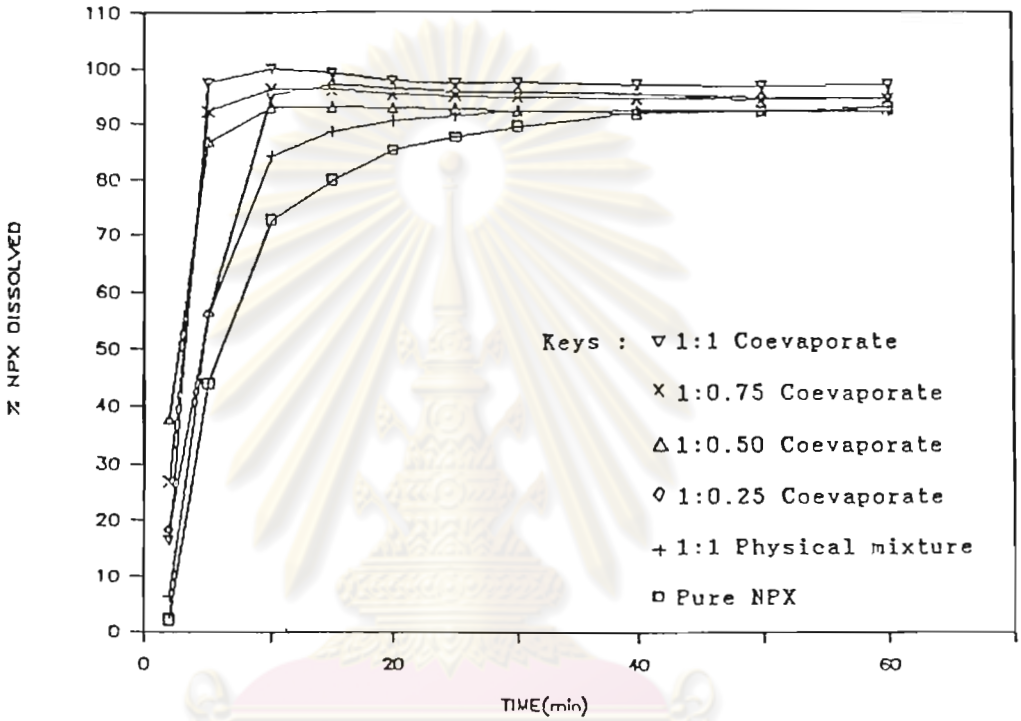


Figure 26 Dissolution Profiles of Naproxen from NPX-PVP K-30 Coevaporates with various ratios of Drug:Carrier at pH 7.5

Table 26 In Vitro Dissolution of Naproxen from NPX-PVP K-30 Coevaporates with Various Ratios of Drug : Carrier at pH 7.5

Time (min)	Percent Naproxen Dissolved			
	Ratios of Drug:Carrier			
	1:1	1:0.75	1:0.50	1:0.25
5	97.45[a] (0.54)[b]	92.31 (0.24)	86.76 (0.44)	56.15 (0.96)
10	100.00 (0.34)	96.36 (0.46)	93.02 (0.32)	95.32 (0.28)
15	99.03 (0.60)	96.15 (0.55)	93.95 (0.33)	96.93 (0.31)
30	97.41 (0.52)	94.73 (0.56)	92.40 (0.15)	95.74 (0.36)
40	96.93 (0.30)	94.42 (0.52)	92.37 (0.25)	95.40 (0.49)
60	96.79 (0.19)	94.25 (0.48)	92.26 (0.51)	94.44 (0.22)
Kd[c] (hr^{-1})	63.68 (7.50)	56.59 (7.03)	43.54 (0.86)	30.40 (0.92)

[a] The mean of six determinations

[b] Standard error

[c] Dissolution rate constant

Table 27 The Statistical Comparisons of Percent NPX Dissolved at Various Times and Dissoltion Rate Constants (Kd) from NPX-PVP K-30 Coevaporates with Various Ratios of Drug: Carrier, 1:1 Physical Mixture and Pure NPX (NC5-NC8, NP5, NO) at pH 1.5 Using one - way ANOVA.

Time (min)	Source of Variation	d.f[a]	SS[b]	MS[c]	F[d]
5	Treatment	5	84.51	16.90	173.98
	Error	30	2.91	0.09	
	Total	35	87.42		
15	Treatment	5	38.38	7.67	95.40
	Error	30	2.41	0.05	
	Total	35	40.79		
30	Treatment	5	33.56	6.71	142.15
	Error	30	1.42	0.04	
	Total	35	34.98		
60	Treatment	5	54.05	10.81	425.31
	Error	30	0.76	0.02	
	Total	35	54.81		
120	Treatment	5	52.82	10.56	536.07
	Error	30	0.59	0.02	
	Total	35	53.41		
Kd (hr^{-1})	Treatment	5	0.22	0.04	23.16
	Error	30	0.05	0.02	
	Total	35	0.28		

[e] $F_{0.05\ (\ 5,30\ )} = 2.53$

[f] $F_{0.10\ (\ 5,30\ )} = 2.05$

[a] Degree of freedom

[b] Sum of square error

[c] Mean square error

[d] Variance ratio

[e,f] F obtained from the table

Table 28 The Statistical Comparisons of Percent NPX Dissolved at Various Times and Dissoltion Rate Constants (Kd) from NPX-PVP K-30 Coevaporates with Various Ratios of Drug: Carrier, 1:1 Physical Mixture and Pure NPX (NC5-NC8, NP5, NO) at pH 4.5 Using one - way ANOVA.

Time (min)	Source of Variation	d.f[a]	SS[b]	MS[c]	F[d]
5	Treatment	5	626.30	125.26	212.81
	Error	30	17.65	0.58	
	Total	35	643.96		
15	Treatment	5	266.82	53.36	157.04
	Error	30	10.19	0.34	
	Total	35	277.02		
30	Treatment	5	93.25	18.65	119.97
	Error	30	4.66	0.16	
	Total	35	97.91		
60	Treatment	5	77.69	15.54	41.11
	Error	30	11.34	0.37	
	Total	35	89.03		
120	Treatment	5	82.20	16.44	33.26
	Error	30	14.83	0.49	
	Total	35	97.03		
Kd (hr^{-1})	Treatment	5	0.18	0.04	11.77
	Error	30	0.09	0.03	
	Total	35	0.42		

[e] $F_{0.05\ (\ 5,30\ )} = 2.53$

[f] $F_{0.10\ (\ 5,30\ )} = 2.05$

[a] Degree of freedom

[b] Sum of square error

[c] Mean square error

[d] Variance ratio

[e,f] F obtained from the table

Table 29 The Statistical Comparisons of Percent NPX Dissolved at Various Times and Dissoltion Rate Contants (Kd) from NPX-PVP K-30 Coevaporates with Various Ratios of Drug: Carrier, 1:1 Physical Mixture and Pure NPX (NC5-NC8, NP5, NO) at pH 7.5 Using one - way ANOVA.

Time (min)	Source of Variation	d.f[a]	SS[b]	MS[c]	F[d]
5	Treatment	5	14627.00	2925.40	89.66
	Error	30	978.80	32.63	
	Total	35	15605.80		
15	Treatment	5	1321.74	264.23	15.39
	Error	30	515.03	17.17	
	Total	35	1836.19		
30	Treatment	5	295.19	59.04	23.52
	Error	30	75.29	2.51	
	Total	35	370.48		
60	Treatment	5	101.72	20.34	38.15
	Error	30	15.99	0.53	
	Total	35	117.72		
Kd (hr^{-1})	Treatment	5	273.07	54.15	269.45
	Error	30	6.08	0.21	
	Total	35	279.14		

[e] $F_{0.05\ (\ 5,30\ )} = 2.53$

[f] $F_{0.10\ (\ 5,30\ )} = 2.05$

[a] Degree of freedom

[b] Sum of square error

[c] Mean square error

[d] Variance ratio

[e,f] F obtained from the table

Table 30 The Statistical Comparisons of Percent NPX Dissolved at Various Times and Dissoltion Rate Constants (Kd) from NPX-PVP K-30 Coevaporates with Various Ratios of Drug : Carrier, and Pure NPX (NC5-NC8, NO) Using T-test

A. at pH 1.5

	Comparative Percent NPX Dissolved at time (min)										Kd (hr^{-1})	
	5		15		30		60		120			
Prep.	NO	NC5	NO	NC5	NO	NC5	NO	NC5	NO	NC5	NO	NC5
NC6	++	-	++	-	++	++	++	++	++	+	+	-
NC7	++	++	++	-	++	++	++	++	++	++	+	+
NC8	++	++	++	++	++	++	++	++	++	++	-	++
	NC7	NC8	NC7	NC8	NC7	NC8	NC7	NC8	NC7	NC8	NC7	NC8
NC6	++	++	++	-	-	++	++	++	++	++	-	-
NC7		-		++		++		-		++		-

B. at pH 4.5

Prep.	NO	NC5	NO	NC5	NO	NC5	NO	NC5	NO	NC5	NO	NC5
NC6	++	+	++	-	++	-	++	+	++	+	++	-
NC7	++	-	++	+	++	++	++	++	++	++	++	+
NC8	++	-	++	++	++	++	++	++	++	++	++	++
	NC7	NC8	NC7	NC8	NC7	NC8	NC7	NC8	NC7	NC8	NC7	NC8
NC6	++	++	++	++	++	++	-	-	++	++	-	++
NC7		+		++		+		-		-		++

C. at pH 7.5

Prep.	NO	NC5	NO	NC5	NO	NC5	NO	NC5			NO	NC5
NC6	++	++	++	-	++	-	+	-			++	++
NC7	++	++	++	-	++	-	-	-			++	++
NC8	++	++	++	+	++	-	-	-			++	++
	NC7	NC8	NC7	NC8	NC7	NC8	NC7	NC8			NC7	NC8
NC6	++	++	++	-	++	-	++	++			++	++
NC7		++		++		++		-				++

+ = Significant difference ($p < 0.10$)
++ = Significant difference ($p < 0.05$)
- = Not Significant difference ($p > 0.10$)

4.5 (p > 0.10) but NC5 showed higher percent NPX dissolved than NC6 after 30 minutes of dissolution profiles.

From the above results NPX-PVP K-30 coevaporate in the ratio of 1:1 (NC5) was seleced to use for further studies.

1.2. In Vitro Absorption Studies

Typical standard curves of NPX in artificial plasma fluids pHs 7.5 and 9.0 were presented in Figures 27 -28 and Tables 31 -32. The representative increasing of NPX in phase II (artificial plasma fluid) absorbed from the test preparations in phase I (artificial gastric or intestinal fluids) were illustrated in Figures 29 - 31 and Table 33. The absorption of NPX from NC5 through the artificial membranes were statistically significant faster than from NO in artificial gastric fluids pHs 1.5 and 4.5, especially after 60 minutes, hence, NC5 exhibited higher apparent absorption rate constants than NO ($p < 0.05$). However, there were no statistically significant of absorption of NPX from NC5 and NO in artificial intestinal fluid pH 7.5 ($p > 0.10$).

The correlation between the apparent absorption and dissolution rate constants of NPX from the test preparations were shown in Figure 32. From the statitical test found that there were no significant correlation between the two parameters ($p > 0.10$).

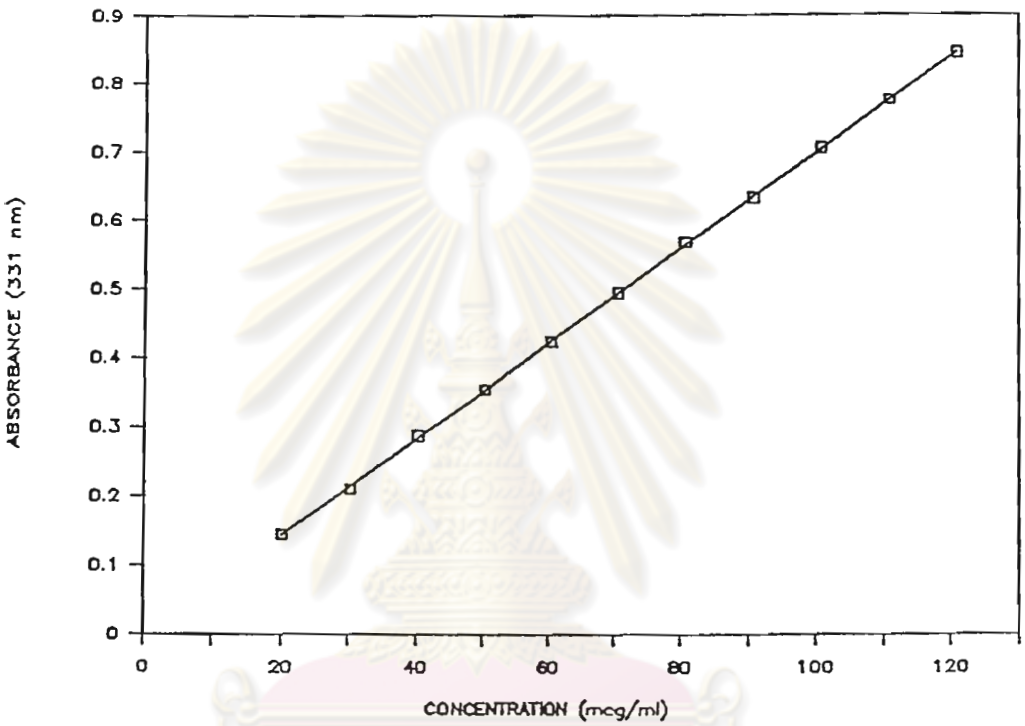


Figure 27 Typical Standard curve for Naproxen concentration vs. absorbance in Artificial Plasma Fluid pH 7.5 estimated using linear regression

Table 31 Typical Standard Curve Data for Naproxen Concentrations in Atrificial Plasma Fluid pH 7.5 Estimated Using Linear Regression[1]

Standard No.	Conc. (mcg/ml)	Absorbance at 331 nm	Inversely estimated[2] Conc.(mcg/ml)	%Theory[3]
1	20.14	0.145	20.22	100.40
2	30.21	0.211	29.71	98.35
3	40.28	0.288	40.78	101.25
4	50.35	0.354	50.28	99.85
5	60.42	0.424	60.34	99.87
6	70.49	0.494	70.41	99.88
7	80.56	0.568	81.05	100.60
8	90.63	0.633	90.40	99.74
9	100.70	0.705	100.75	100.05
10	110.77	0.775	110.82	100.04
11	120.84	0.844	120.74	99.91
			Mean	99.99
			S.D.	0.71
			C.V.[4]	0.71 %

1. $r^2 = 0.9999$

2. Inversely estimated concentration $= \frac{\text{Absorbance} - 0.0044}{0.0069}$

3. %Theory $= \frac{\text{Inversely estimated concentration}}{\text{known concentration}} \times 100$

4. C.V. $= \frac{\text{S.D.}}{\text{Mean}} \times 100$

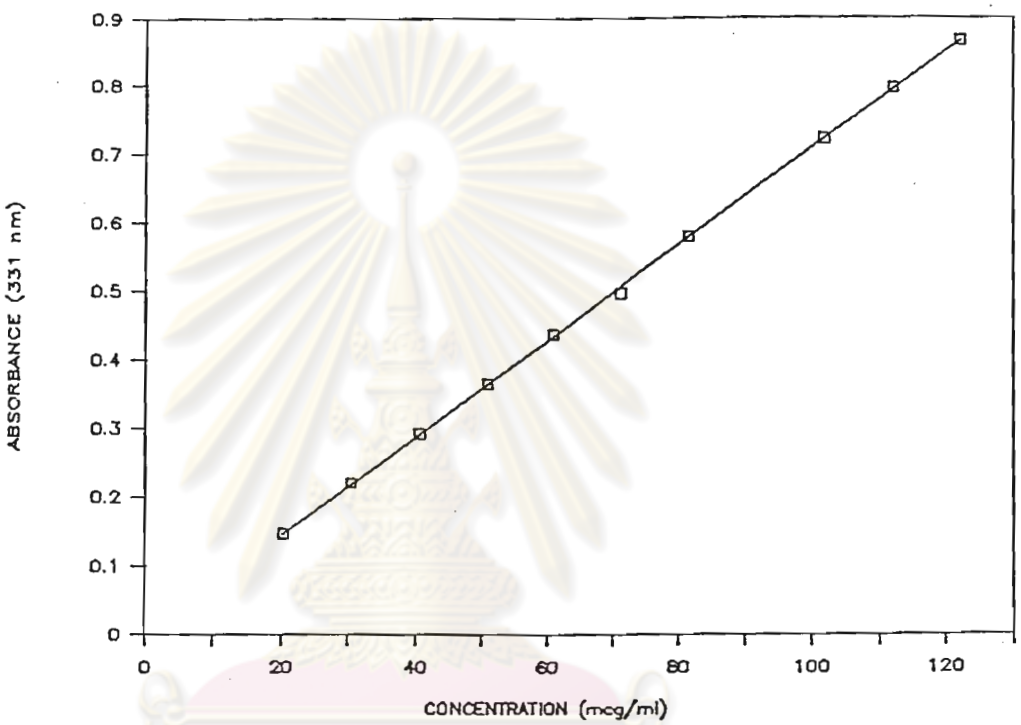


Figure 28 Typical Standard curve for Naproxen concentration vs. absorbance in Artificial Plasma Fluid pH 9.0 estimated using linear regression

Table 32 Typical Standard Curve Data for Naproxen Concentrations in Artificial Plasma Fluid pH 8.0 Estimated Using Linear Regression[1]

Standard No.	Conc. (mcg/ml)	Absorbance at 331 nm	Inversely estimated[2] Conc.(mcg/ml)	%Theory[3]
1	20.36	0.147	20.24	99.41
2	30.53	0.221	30.73	100.64
3	40.71	0.293	40.93	100.54
4	50.89	0.365	51.13	100.47
5	61.07	0.438	61.48	100.66
6	71.25	0.497	69.84	98.02
7	81.43	0.579	81.46	100.03
8	101.78	0.723	101.86	100.08
9	111.96	0.797	112.35	100.34
10	122.14	0.866	122.12	99.99
			Mean	100.02
			S.D.	0.80
			C.V.[4]	0.80 %

1. $r^2 = 0.9997$

2. Inversely estimated concentration $= \frac{\text{Absorbance} - 0.0042}{0.0071}$

3. $\%\text{Theory} = \frac{\text{Inversely estimated concentration}}{\text{known concentration}} \times 100$

4. $\text{C.V.} = \frac{\text{S.D.}}{\text{Mean}} \times 100$

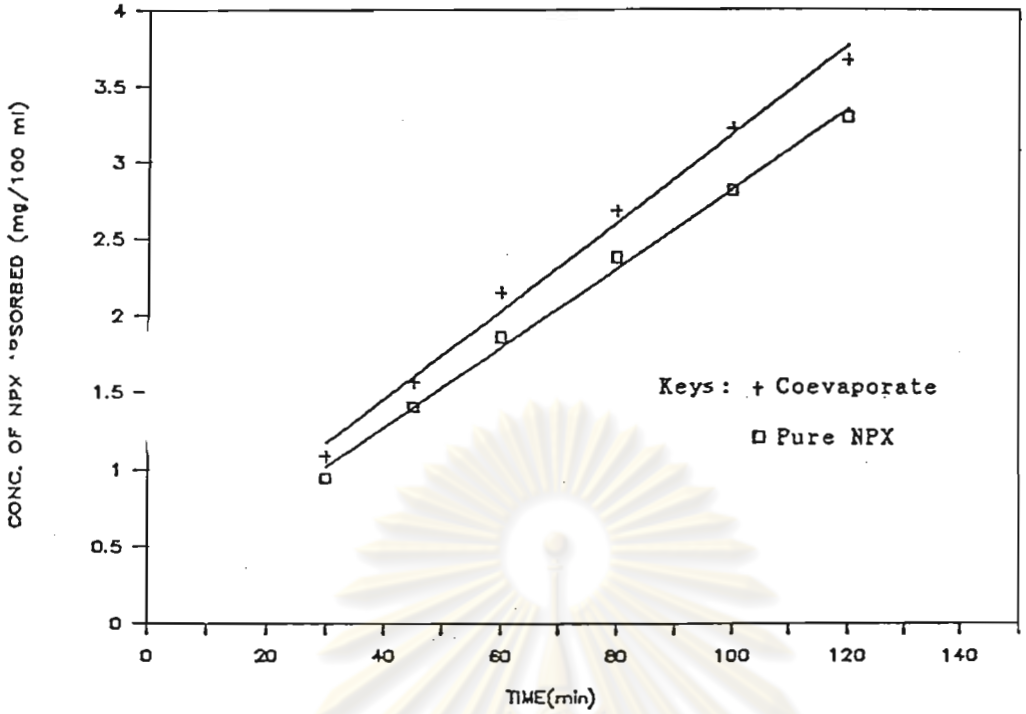


Figure 29 In Vitro Representative Increasing of Mean NPX Concentration (in Phase II) Absorbed from 1:1 NPX-PVP K-30 Coevaporate and Pure NPX in Artificial Gastric Fluid pH 1.5

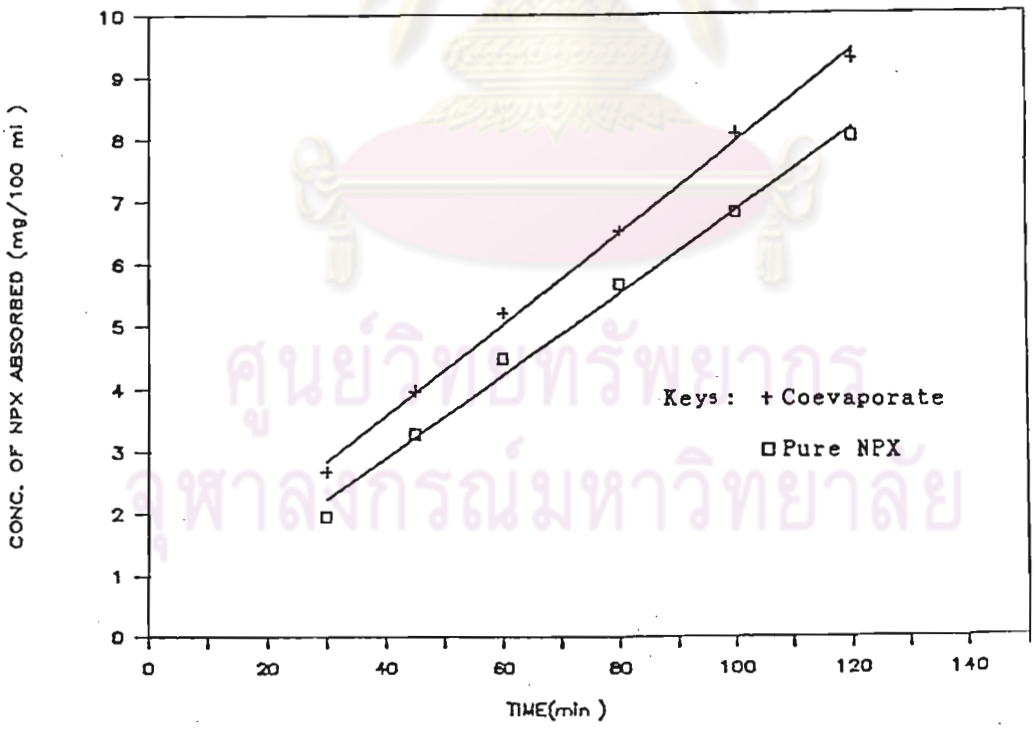


Figure 30 In Vitro Representative Increasing of Mean NPX Concentration (in Phase II) Absorbed from 1:1 NPX-PVP K-30 Coevaporate and Pure NPX in Artificial Gastric Fluid pH 4.5

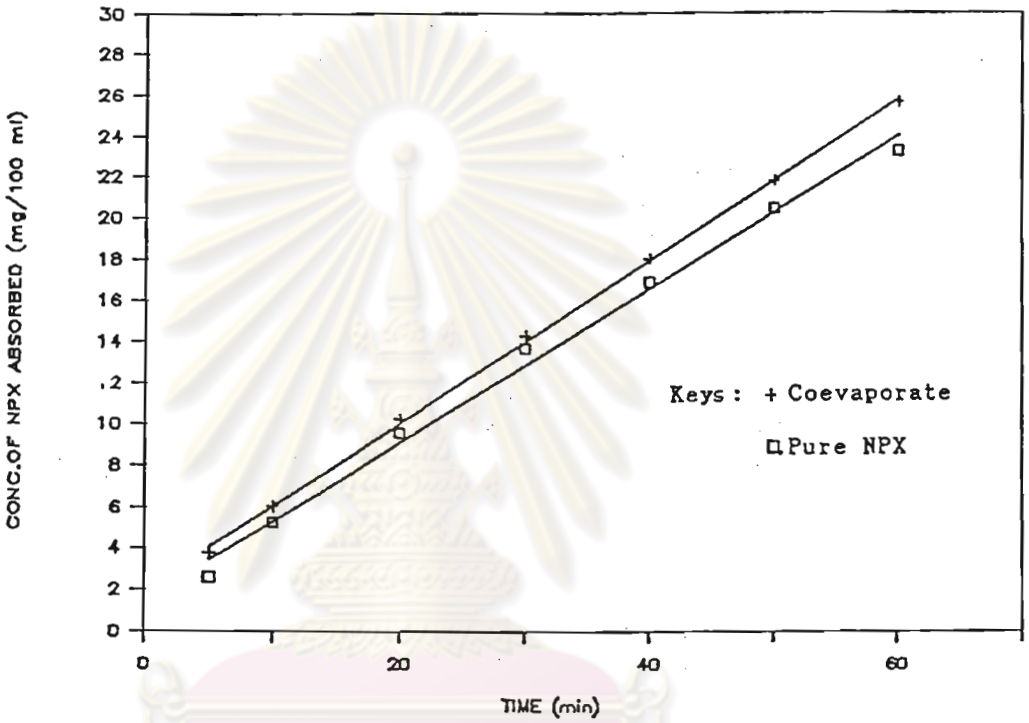


Figure 31 In Vitro Representative Increasing of Mean NPX Concentration (in Phase II) Absorbed from 1:1 NPX-PVP K-30 Coevaporate and Pure NPX in Artificial Intestinal Fluiid pH 7.5

Table 33 In Vitro Absorption Data of Naproxen from 1:1 NPX-PVP K-30 Coevaporate and Pure NPX in Artificial Gastro-intestinal Fluids pHs 1.5, 4.5 and 7.5

Time (min)	Concentration of Naproxen Absorbed in Phase II (mg/100ml)					
	pH 1.5		pH 4.5		pH 7.5	
	1[a]	2[b]	1	2	1	2
5	-	-	-	-	3.52[c] (0.37)[d]	2.88 (0.37)
10	-	-	-	-	6.52 (0.69)	5.29 (0.07)
15	-	-	-	-	10.37 (0.18)	9.54 (0.03)
30	1.09 (0.02)	0.94 (0.09)	2.63* (0.05)	1.88 (0.09)	14.43 (0.23)	13.71 (0.10)
45	1.56 (0.08)	1.46 (0.05)	3.82 (0.19)	3.27 (0.07)	-	-
60	2.17* (0.03)	1.82 (0.18)	5.20* (0.01)	4.63 (0.21)	-	-
80	2.69** (0.02)	2.37 (0.06)	6.32** (0.28)	5.56 (0.16)	-	-
100	3.22** (0.02)	2.79 (0.02)	8.08** (0.06)	6.86 (0.04)	-	-
120	3.66** (0.03)	3.27 (0.02)	9.26** (0.02)	8.07 (0.04)	-	-
Ci_o[e] (mg%)	3.49 (0.46)	3.30 (0.54)	9.03 (0.72)	8.02 (0.38)	100.07 (0.26)	99.71 (0.85)
Ki[f] (hr^{-1})	2.10** (0.02)	2.00 (0.01)	2.26** (0.01)	2.17 (0.02)	2.78 (0.04)	2.69 (0.03)

[a] Coevaporate

[b] Pure drug

[c] The mean of two determinations

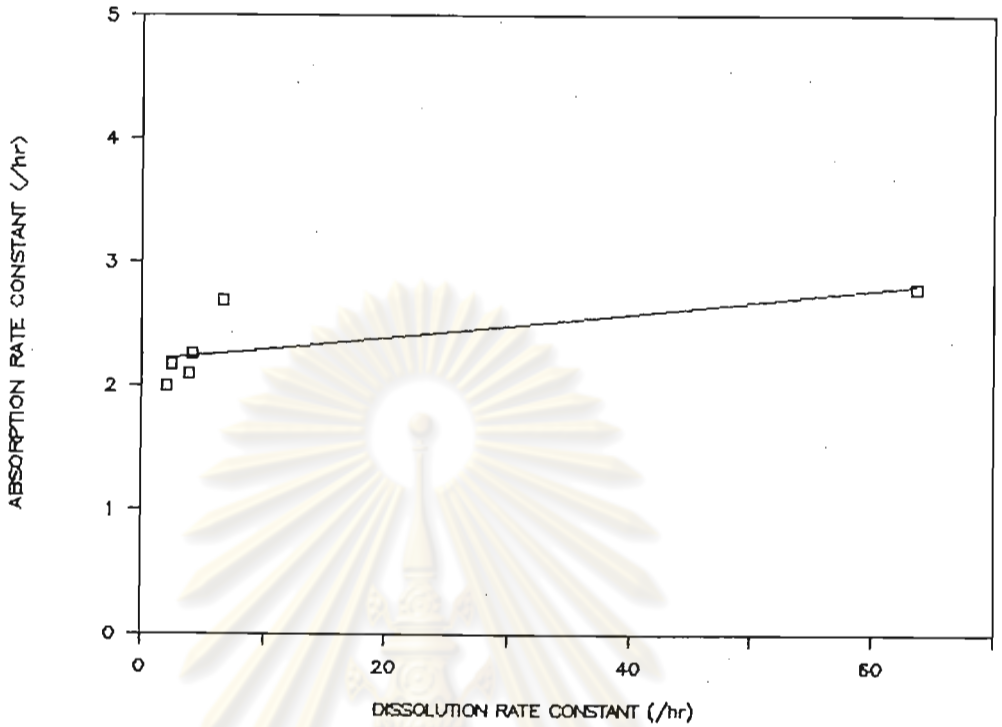
[d] Standard error

[e] Starting concentration

[f] In vitro absorption rate constant

* Significant higher than pure NPX's ($p < 0.10$)

** Significant higher than pure NPX's ($p < 0.05$)



Samples		Kd (hr^{-1})	Ki (hr^{-1})
Pure drug	at pH 1.5	2.06	2.00
	4.5	2.44	2.17
	7.5	6.67	2.67
Coevaporate	at pH 1.5	3.92	2.10
	4.5	4.21	2.26
	7.5	63.68	2.78
Correlation coefficient		0.73	
Degree of freedom		4	
t-value		2.08	
p-value		NS* ($p > 0.10$)	

* Not significant

Figure 32 Correlation between In Vitro Absorption Rate Constant (Ki) and Dissolution Rate Constant (Kd) of Naproxen

1.3. Physical Characteristic Studies

1.3.1. X-ray Diffraction Studies

X-ray diffraction patterns of pure NPX, PVP K-30, their 1:1 physical mixture (NP5) and their coevaporates with various ratio of drug:carrier (NC5-NC7) were demonstrated in Figure 33. Pure NPX showed diffraction peaks that indicated the presence of crystallinity. On the contrary, PVP K-30 exhibited no diffraction peak that proved to have amorphous form. The similar patterns were obtained in all the coevaporates and physical mixture. These patterns were due to the combination of the drug and the carrier. However, minor changes in the intensity of the diffraction peaks were seen as compared among the patterns of each preparation. The appearance of diffraction peaks of the drug in the coevaporates indicated that the crystalline drug dispersed in amorphous form of the carrier.

1.3.2. Differential Thermal Analysis

Only NC5 which gave the fastest dissolution was studied compared to NP5 and NO. Figure 34 showed the thermograms of pure NPX, PVP K-30 ,NP5 and NC5. The thermograms of pure drug and PVP K-30 had the characteristic melting endotherm at about 155 °C and 73°C, respectively. The thermogram of NC5 showed a couple endotherm due to the drug and carrier that similar to the NP5. However, there were small shift of endotherm peaks

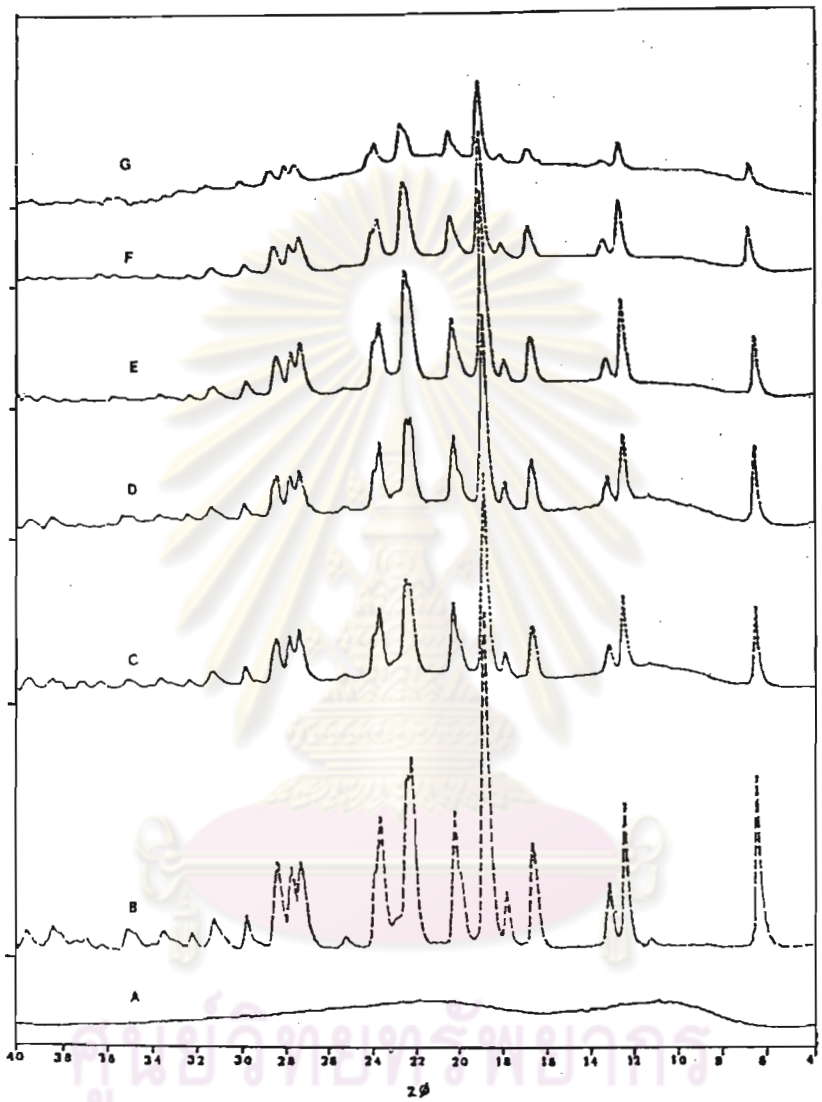


Figure 33 X-Ray Diffraction Patterns of NPX-PVP K-30 System

(A) PVP K-30

(B) Pure NPX

(C) 1:1 Physical Mixture

(D) 1:0.25 Coevaporate

(E) 1:0.50 Coevaporate

(F) 1:0.75 Coevaporate

(G) 1:1 Coevaporate

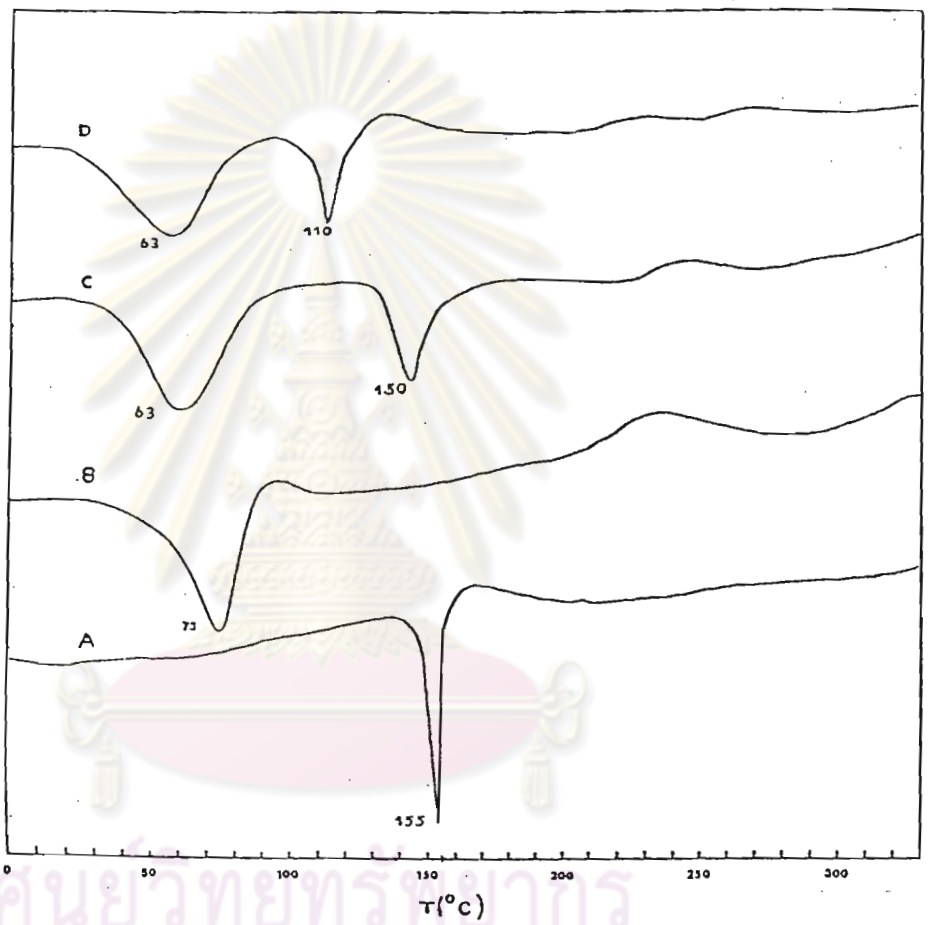


Figure 34 Differential Thermograms of 1:1 NPX-PVP K30 System

(A) Pure NPX

(B) PVP K-30

(C) Physical Mixture

(D) Coevaporate

because of the eutectic properties of the drug and the carrier. From this DTA result indicated that NPX is probably present in the crystalline form in PVP matrix.

II. THIAMPHENICOL (THI)

The coevaporates and physical mixtures of thiamphenicol and various type of carriers were prepared in the same way as the previously naproxen studies. The coevaporates obtained from THI and PEGs carriers were nonsticky white stable masses and easy to manipulate to powder form. On the other hand, the coevaporates obtained from PVP carriers were rather transparent and glassy masses that could be easily pulverized.

The percentage content of THI and THI in each preparation were between 99.58 to 100.76 % (Table 34)

2.1. In Vitro Dissolution Studies

Typical standard curves of thiamphenicol at pHs 1.5, 4.5 and 7.5 were presented in Figures 35 -37 and Tables 35 - 37. Dissolution profiles of pure thiamphenicol powders were shown in Figure 38 and Table 38. Dissolution of the drug was slightly higher at pH 1.5 than pHs 4.5 and 7.5, respectively.

Table 34 Percentage Contents of THI and THI in Coevaporates and Physical Mixtures

Preparations	Percent THI Content			
	1	2	3	Average + S.D.
Pure THI	100.16	100.09	100.19	100.14 ± 0.05
Coevaporates :				
1:1 THI-PEG 4000	100.61	100.85	100.75	100.73 ± 0.12
1:1 THI-PEG 6000	99.95	100.01	100.01	99.99 ± 0.03
1:1 THI-PEG 20000	100.27	99.91	99.98	100.05 ± 0.19
1:1 THI-PVP K-90	100.49	100.49	100.58	100.52 ± 0.05
1:1 THI-PVP K-30	100.01	99.98	100.18	100.06 ± 0.10
1:0.75 THI-PVP K-30	100.87	100.85	100.56	100.76 ± 0.17
1:0.50 THI-PVP K-30	100.70	100.81	100.36	100.62 ± 0.23
1:0.25 THI-PVP K-30	99.89	99.85	100.11	99.95 ± 0.14
Physical Mixtures :				
1:1 THI-PEG 4000	100.25	100.55	99.96	100.25 ± 0.29
1:1 THI-PEG 6000	100.35	100.50	100.39	100.41 ± 0.08
1:1 THI-PEG 20000	99.58	99.69	99.31	99.58 ± 0.11
1:1 THI-PVP K-90	100.15	100.51	100.40	100.35 ± 0.18
1:1 THI-PVP K-30	99.96	100.25	100.15	100.12 ± 0.15

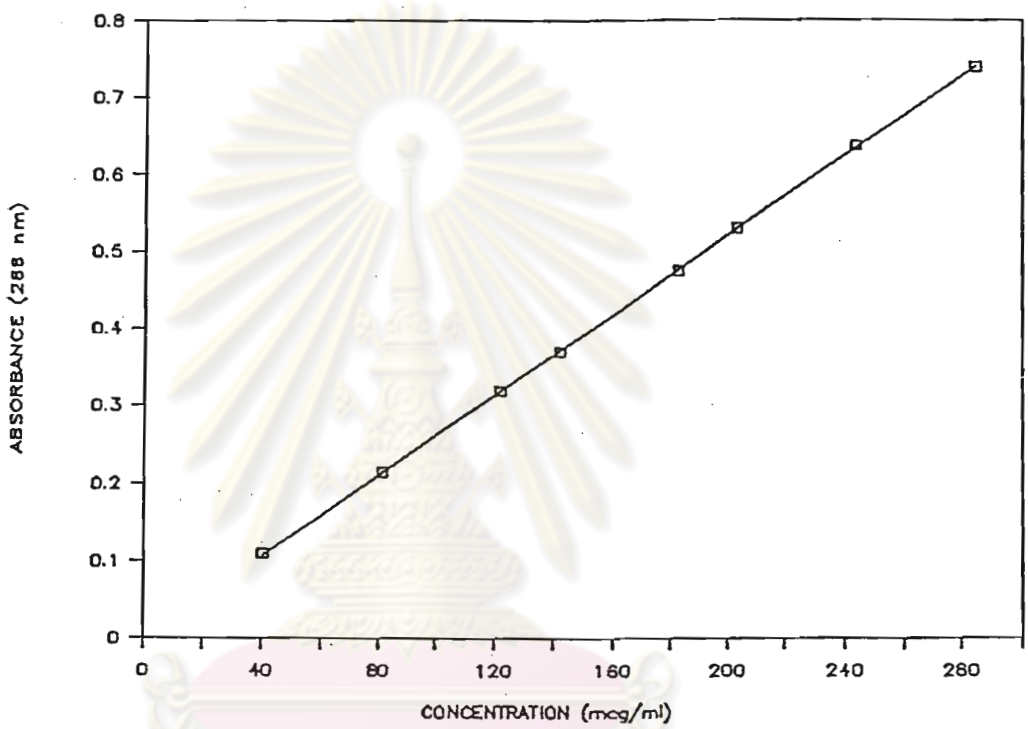


Figure 35 Typical Standard curve for Thiamphenicol concentration vs. absorbance at pH 1.5 estimated using linear regression

Table 35 Typical Standard Curve Data for Thiamphenicol Concentrations at pH 1.5 Estimated Using Linear Regression[1]

Standard No.	Conc. (mcg/ml)	Absorbance at 266 nm	Inversely estimated[2] Conc.(mcg/ml)	%Theory[3]
1	40.64	0.109	40.87	100.56
2	81.28	0.214	81.40	100.15
3	121.92	0.319	121.93	99.56
4	142.24	0.370	141.62	99.56
5	182.88	0.475	182.15	99.60
6	203.20	0.531	203.77	100.28
7	243.84	0.637	244.68	100.35
8	284.48	0.739	284.06	99.85
			Mean	100.05
			S.D.	0.35
			C.V.[4]	0.35 %

1. $r^2 = 0.9999$

2. Inversely estimated concentration $= \frac{\text{Absorbance} - 0.0031}{0.0026}$

3. %Theory $= \frac{\text{Inversely estimated concentration}}{\text{known concentration}} \times 100$

4. C.V. $= \frac{\text{S.D.}}{\text{Mean}} \times 100$

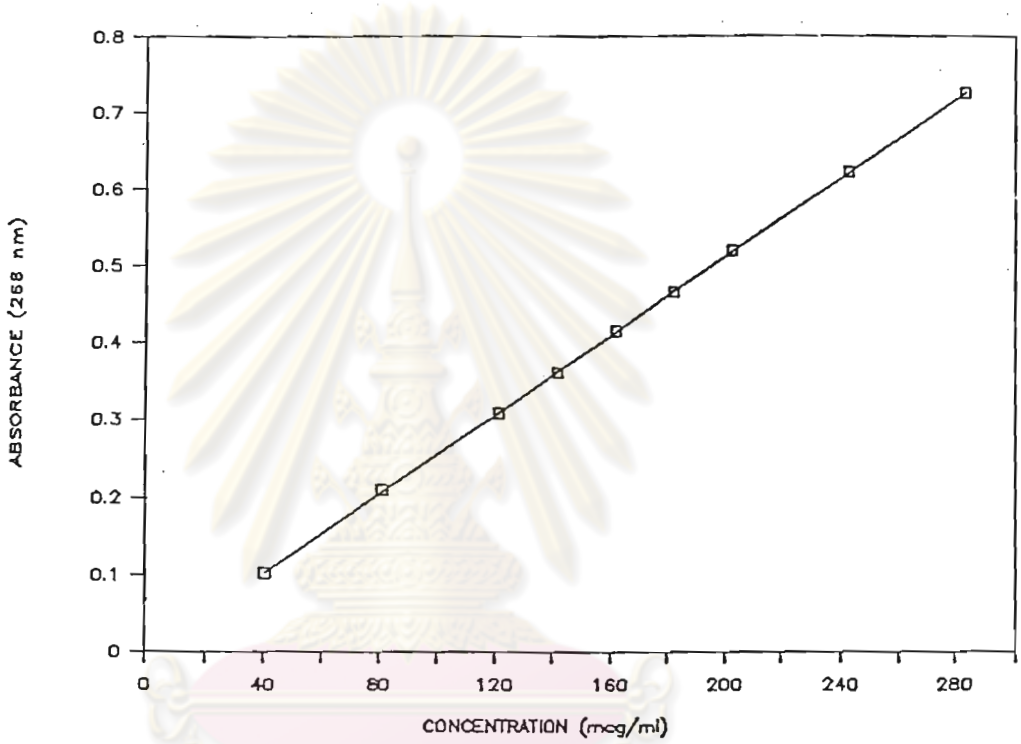


Figure 36 Typical Standard curve for Thiamphenicol concentration vs. absorbance at pH 4.5 estimated using linear regression

Table 36 Typical Standard Curve Data for Thiamphenicol Concentrations at pH 4.5 Estimated Using Linear Regression[1]

Standard No.	Conc. (mcg/ml)	Absorbance at 331 nm	Inversely estimated[2] Conc.(mcg/ml)	%Theory[3]
1	40.48	0.102	40.06	98.96
2	80.96	0.209	81.79	101.03
3	121.44	0.309	120.79	99.47
4	141.68	0.362	141.47	99.85
5	161.92	0.415	162.14	100.13
6	182.16	0.466	182.03	99.93
7	202.40	0.520	203.09	100.34
8	242.88	0.622	242.87	100.00
9	283.36	0.725	283.04	99.89
			Mean	99.95
			S.D.	0.56
			C.V.[4]	0.56 %

1. $r^2 = 0.9998$

2. Inversely estimated concentration $= \frac{\text{Absorbance} + 0.0007}{0.0026}$

3. $\%\text{Theory} = \frac{\text{Inversely estimated concentration}}{\text{known concentration}} \times 100$

4. $\text{C.V.} = \frac{\text{S.D.}}{\text{Mean}} \times 100$

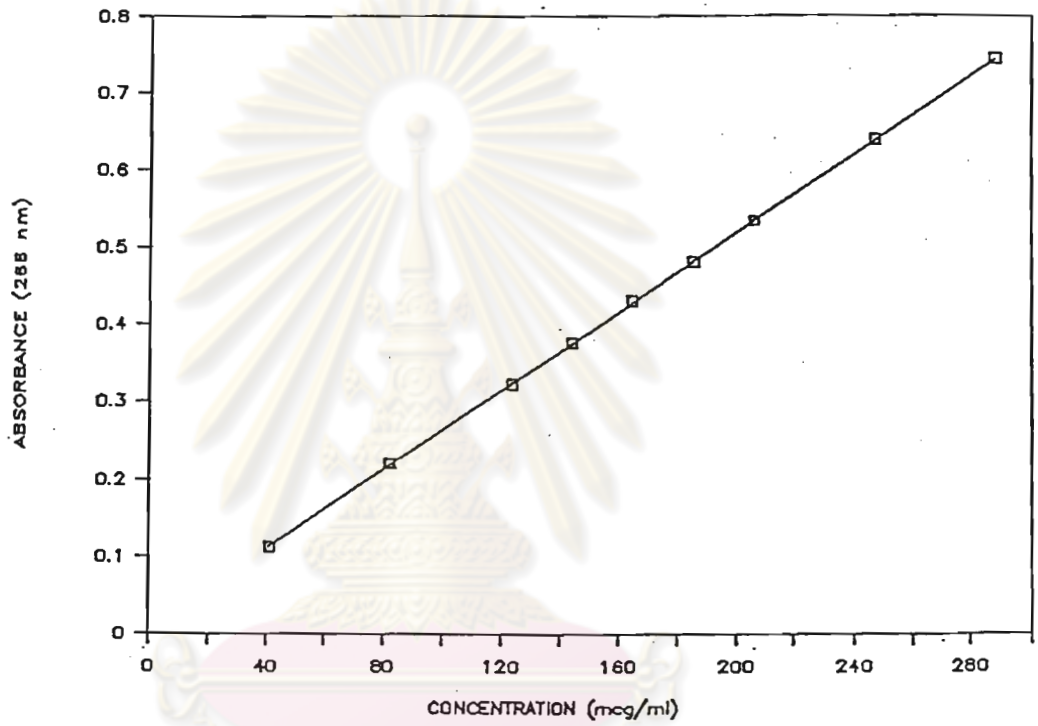


Figure 37 Typical Standard curve for Thiamphenicol concentration vs. absorbance at pH 7.5 estimated using linear regression

Table 37 Typical Standard Curve Data for Thiamphenicol Concentrations at pH 7.5 Estimated Using Linear Regression[1]

Standard No.	Conc. (mcg/ml)	Absorbance at 266 nm	Inversely estimated[2] Conc.(mcg/ml)	%Theory[3]
1	41.20	0.113	40.73	98.85
2	82.40	0.221	83.15	100.91
3	123.60	0.323	123.21	99.68
4	144.20	0.376	144.03	99.88
5	164.80	0.430	165.24	100.26
6	185.40	0.481	185.27	99.93
7	206.00	0.534	206.08	100.04
8	247.20	0.639	247.33	100.05
9	288.40	0.743	288.18	99.92
			Mean	99.95
			S.D.	0.53
			C.V.[4]	0.53 %

1. $r^2 = 0.9999$

2. Inversely estimated concentration $= \frac{\text{Absorbance} - 0.0093}{0.0025}$

3. $\%\text{Theory} = \frac{\text{Inversely estimated concentration}}{\text{known concentration}} \times 100$

4. $\text{C.V.} = \frac{\text{S.D.}}{\text{Mean}} \times 100$

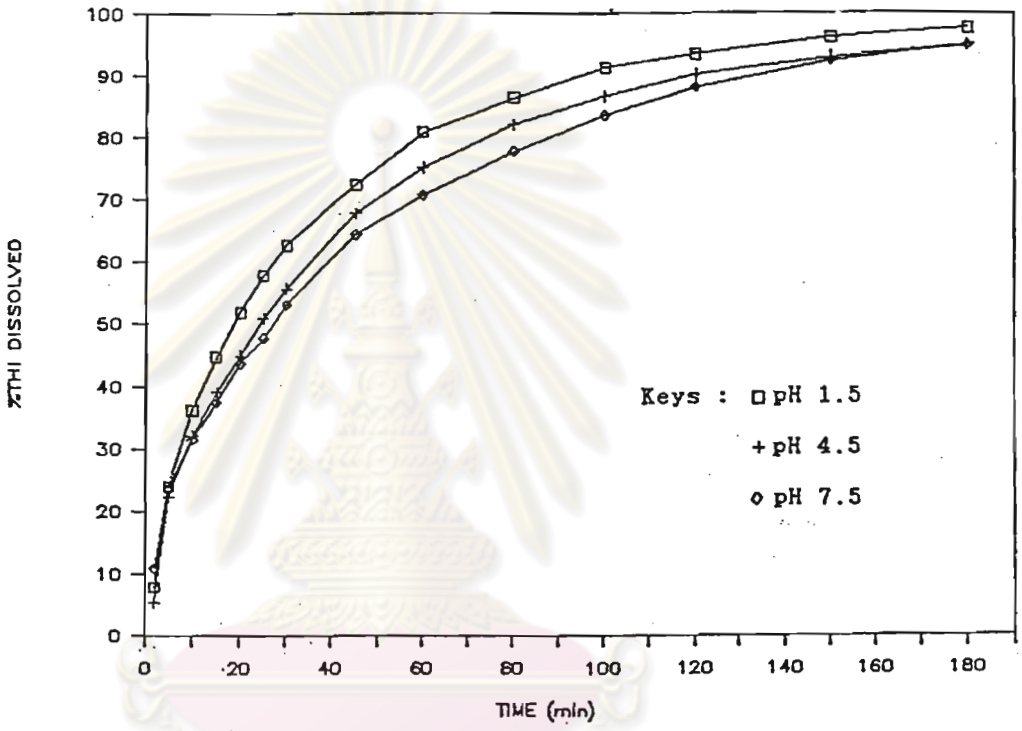


Figure 38 Dissolution Profiles of Thiamphenicol from It's Powder at pH 1.5, 4.5 and 7.5

Table 38 In Vitro Dissolution of Thiamphenicol from 250 mg Thiamphenicol Powders at pHs 1.5, 4.5 and 7.5

Time (min)	Percent Thiamphenicol Dissolved		
	pH 1.5	pH 4.5	pH 7.5
5	23.97[a] (0.57)[b]	2.25 (0.45)	23.46 (0.61)
10	36.16 (0.78)	32.10 (0.70)	31.45 (0.65)
15	44.75 (1.33)	39.05 (0.83)	37.39 (0.81)
30	62.47 (2.01)	55.68 (1.16)	53.14 (1.34)
45	72.40 (2.09)	67.88 (1.88)	64.36 (1.91)
60	80.80 (1.89)	75.10 (1.06)	70.75 (2.04)
120	93.30 (1.26)	90.04 (0.63)	88.03 (1.59)
180	97.59 (0.52)	94.92 (0.55)	94.81 (0.71)
Kd[c] (hr^{-1})	1.66 (0.16)	1.48 (0.17)	1.23 (0.11)

[a] The mean of six determinations

[b] Standard error

[c] Dissolution rate constant

The codes used for the preparation prepared were as follows :

Code	Preparation / THI
TC1	1:1 THI-PEG 4000 Coevaporate
TC2	1:1 THI-PEG 6000 Coevaporate
TC3	1:1 THI-PEG 20000 Coevaporate
TC4	1:1 THI-PVP K-90 Coevaporate
TC5	1:1 THI-PVP K-30 Coevaporate
TP1	1:1 THI-PEG 4000 Physical mixture
TP2	1:1 THI-PEG 6000 Physical mixture
TP3	1:1 THI-PEG 20000 Physical mixture
TP4	1:1 THI-PVP K-90 Physical mixture
TP5	1:1 THI-PVP K-30 Physical mixture
TO	Pure THI

Figures 39 - 53 and Tables 39 - 48 demonstrated the dissolution profiles of the coevaporates and the physical mixtures in each type of carrier used including pure THI as a control. The statistical comparisons of the dissolution parameters of these preparations in all dissolution mediums using one - way ANOVA and t -test were presented in Tables 49 - 54.

The results of each carrier system showed that TP3, TP4 and TP5 gave statistically significant slower dissolution rate than TO ($p < 0.05$) whereas TP1 and TP2 showed no statistically significant higher dissolution rate than TO ($p > 0.10$). However, all the coevaporates

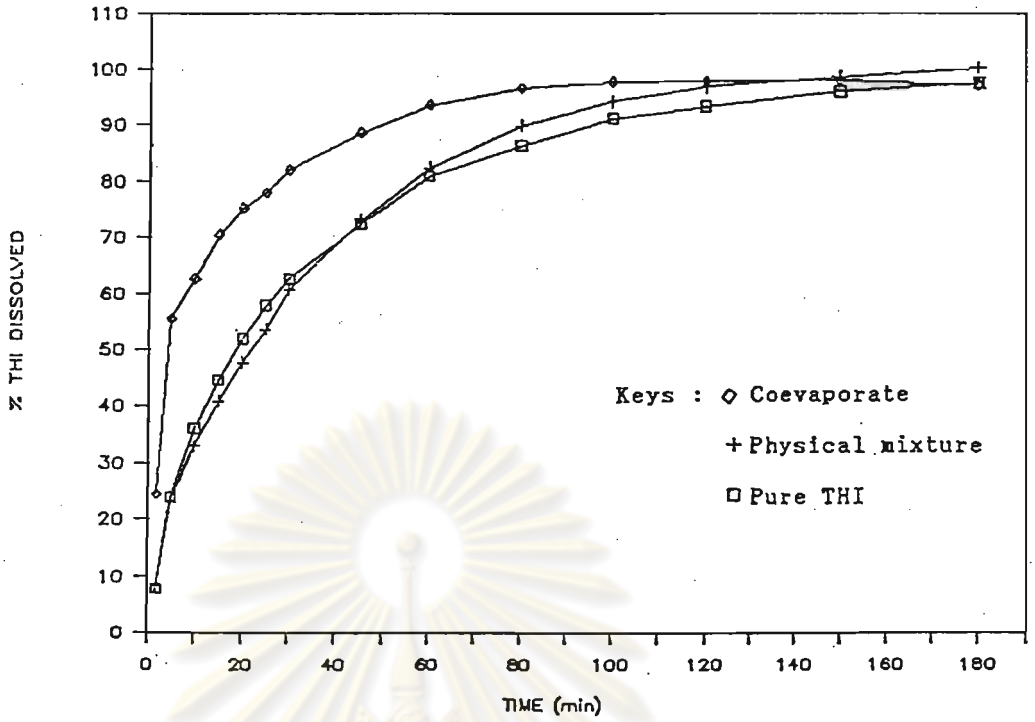


Figure 39 Dissolution Profiles of Thiamphenicol from 1:1 THI-PEG 4000 System at pH 1.5

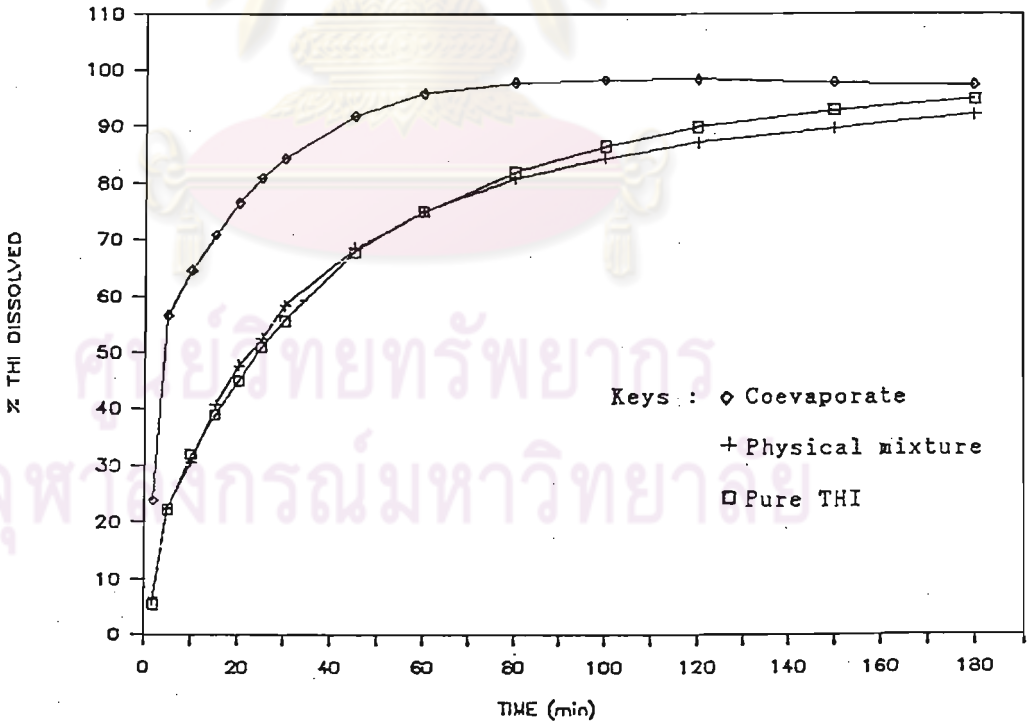


Figure 40 Dissolution Profiles of Thiamphenicol from 1:1 THI-PEG 4000 System at pH 4.5

Table 39 In Vitro Dissolution of Thiamphenicol from 1:1 THI-PEG 4000 Coevaporate, Physical Mixture and Pure Drug at pHs 1.5 and 4.5

Time (min)	Percent Thiamphenicol Dissolved					
	pH 1.5			pH 4.5		
	1[a]	2[b]	3[c]	1	2	3
5	55.47[d] (3.75)[e]	23.22 (1.88)	23.97 (0.57)	56.60 (1.97)	22.41 (0.51)	23.25 (0.45)
10	62.75 (4.52)	33.06 (1.35)	36.16 (0.78)	64.62 (3.63)	30.59 (1.44)	32.10 (0.70)
15	70.54 (4.52)	40.94 (1.61)	44.75 (1.33)	70.89 (3.63)	40.85 (2.55)	39.05 (0.83)
30	82.01 (4.03)	60.55 (2.25)	62.47 (2.01)	84.37 (4.07)	58.42 (1.67)	55.68 (1.16)
45	88.71 (3.11)	73.12 (2.91)	72.40 (2.09)	91.91 (3.41)	68.67 (1.53)	67.88 (1.88)
60	93.49 (2.13)	82.39 (1.21)	80.80 (1.89)	95.90 (2.43)	75.21 (2.75)	75.10 (1.06)
120	97.85 (0.25)	96.77 (1.21)	93.30 (1.26)	98.49 (0.39)	87.28 (1.65)	90.04 (0.63)
180	97.19 (0.54)	100.25 (0.71)	97.59 (0.52)	97.52 (0.32)	92.11 (1.52)	94.92 (0.55)
Kd[f] (hr^{-1})	3.91 (0.63)	1.63 (0.11)	1.66 (0.16)	3.74 (0.59)	1.40 (0.05)	1.48 (0.17)

[a] Coevaporate

[b] Physical mixture

[c] Pure drug

[d] The mean of six determinations

[e] Stantdard error

[f] Dissolution rate contstant

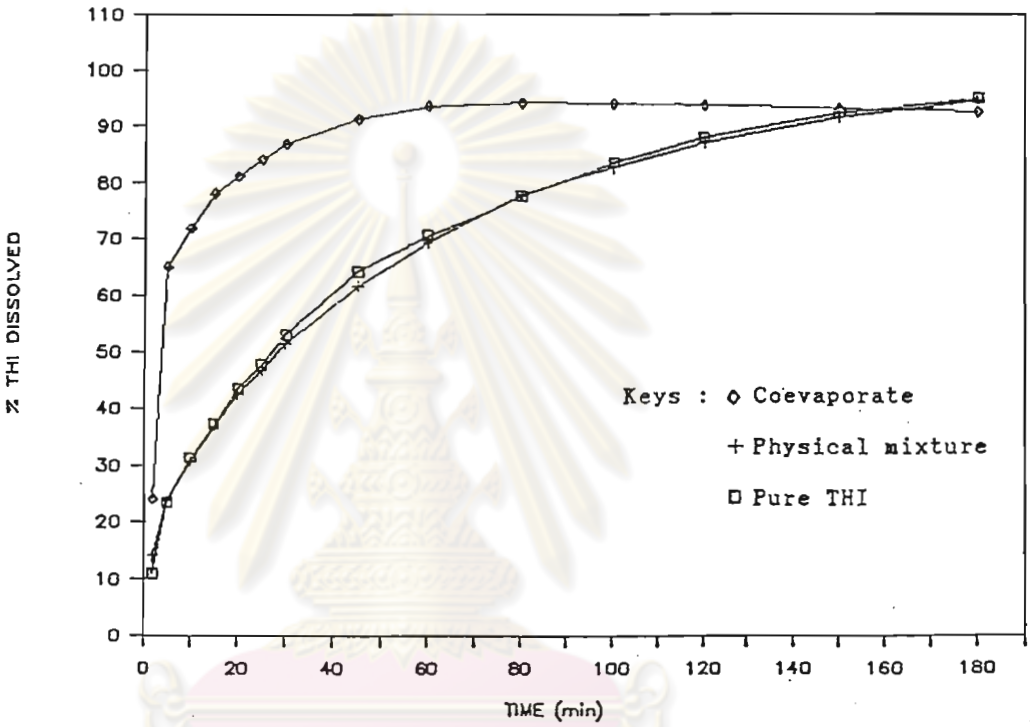


Figure 41 Dissolution Profiles of Thiamphenicol from 1:1 THI-PEG 4000 System at pH 7.5

Table 40 In Vitro Dissolution of Thiamphenicol from 1:1 THI-PEG 4000 Coevaporate, Physical Mixture and Prue Drug at pH 7.5.

Time (min)	Percent Thiamphenicol Dissolved		
	1[a]	2[b]	3[c]
5	65.05[d] (3.00)[e]	23.84 (1.62)	23.46 (0.61)
10	71.91 (4.06)	30.86 (0.88)	31.45 (0.65)
15	78.18 (2.06)	37.04 (1.90)	37.39 (0.81)
30	86.90 (3.07)	51.40 (1.20)	53.14 (1.34)
45	91.25 (2.83)	61.70 (1.85)	64.36 (1.91)
60	95.54 (0.99)	69.52 (1.74)	70.75 (2.04)
120	93.61 (0.21)	87.04 (2.06)	88.03 (1.59)
180	92.36 (0.18)	94.30 (2.87)	94.81 (0.71)
Kd^{f} (hr^{-1})	3.40 (0.28)	1.29 (0.07)	1.23 (0.11)

[a] Coevaporate

[b] Physical mixture

[c] Pure drug

[d] The mean of six determinations

[e] Standard error

[f] Dissolution rate constant

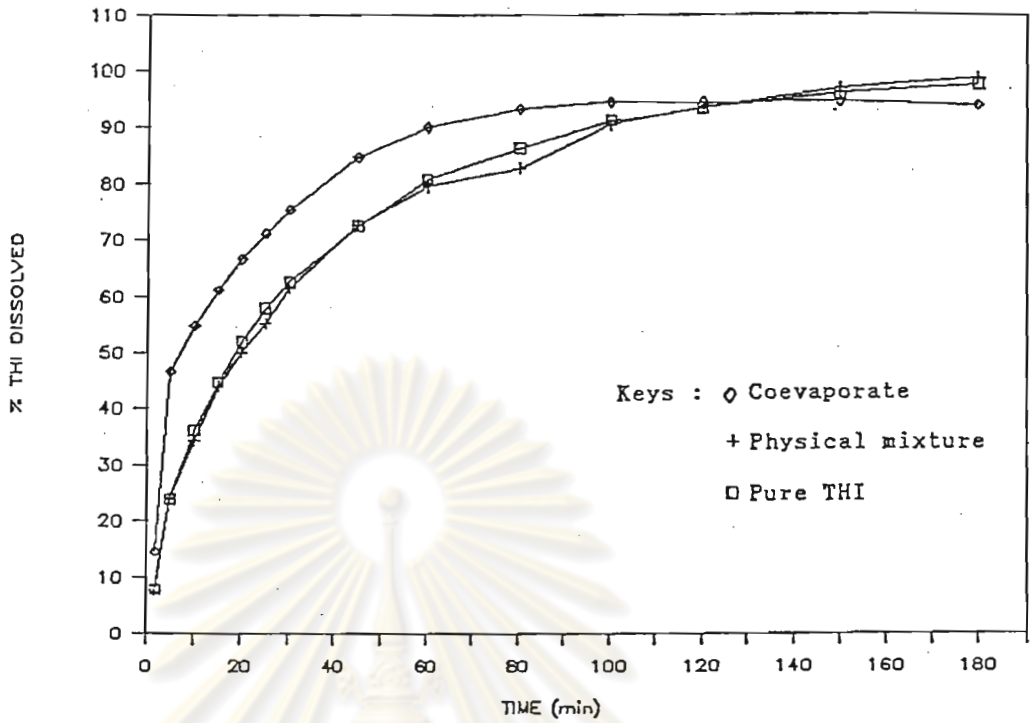


Figure 42 Dissolution Profiles of Thiamphenicol from 1:1 THI-PEG 6000 System at pH 1.5

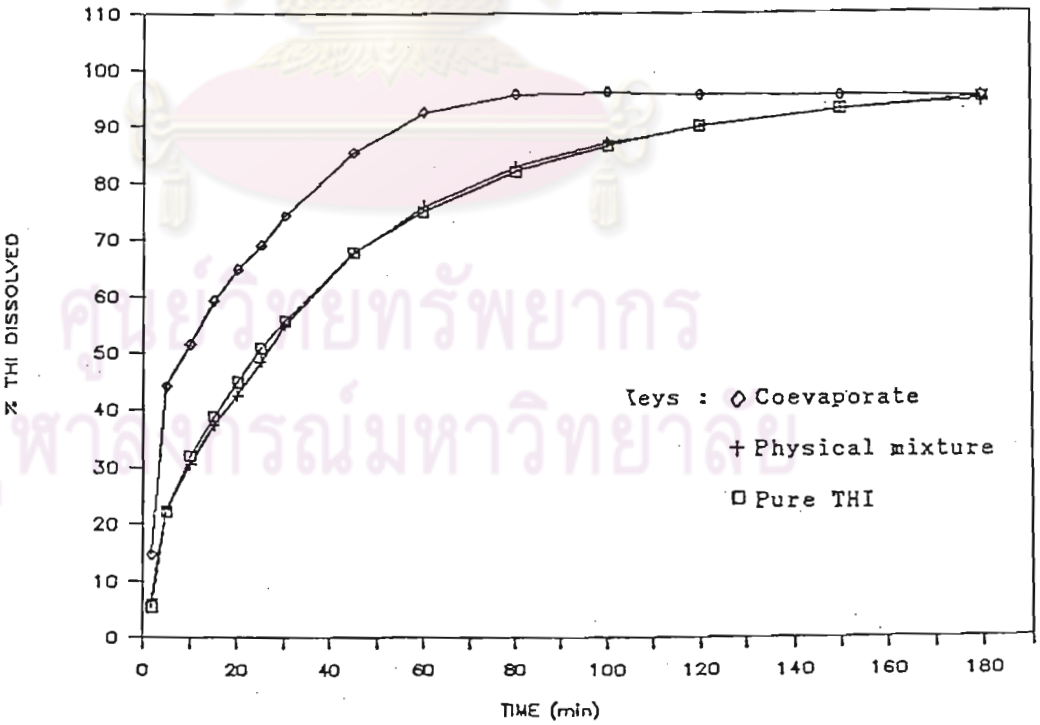


Figure 43 Dissolution Profiles of Thiamphenicol from 1:1 THI-PEG 6000 System at pH 4.5.

Table 41 In Vitro Dissolution of Thiamphenicol from 1:1 THI-PEG 6000 Coevaporate, Physical Mixture and Pure Drug at pHs 1.5 and 4.5

Time (min)	Percent Thiamphenicol Dissolved					
	pH 1.5			pH 4.5		
	1[a]	2[b]	3[c]	1	2	3
5	46.68[d] (2.63)[e]	24.56 (0.75)	23.97 (0.57)	43.30 (2.34)	22.46 (0.43)	23.25 (0.45)
10	54.85 (2.69)	35.02 (1.40)	36.16 (0.78)	51.58 (2.75)	30.54 (0.71)	32.10 (0.70)
15	61.18 (2.57)	44.85 (1.44)	44.75 (1.33)	59.29 (2.62)	37.49 (0.88)	39.05 (0.83)
30	75.34 (1.71)	62.57 (3.00)	62.47 (2.01)	74.28 (2.36)	54.92 (1.18)	55.68 (1.16)
45	84.78 (1.47)	74.07 (3.70)	72.40 (2.09)	85.47 (2.26)	67.67 (1.33)	67.88 (1.88)
60	90.04 (0.95)	80.97 (3.73)	80.80 (1.89)	92.43 (1.66)	76.03 (1.26)	75.10 (1.06)
120	94.50 (0.13)	95.21 (3.27)	93.30 (1.26)	95.53 (0.15)	89.86 (0.91)	90.04 (0.63)
180	94.01 (0.29)	99.72 (2.98)	97.59 (0.52)	95.08 (0.10)	94.27 (0.56)	94.92 (0.55)
Kd[f] (hr^{-1})	3.18 (0.22)	1.61 (0.07)	1.66 (0.16)	3.34 (0.36)	1.58 (0.55)	1.48 (0.17)

[a] Coevaporate

[b] Physical mixture

[c] Pure drug

[d] The mean of six determinations

[e] Stantdard error

[f] Dissolution rate contstant

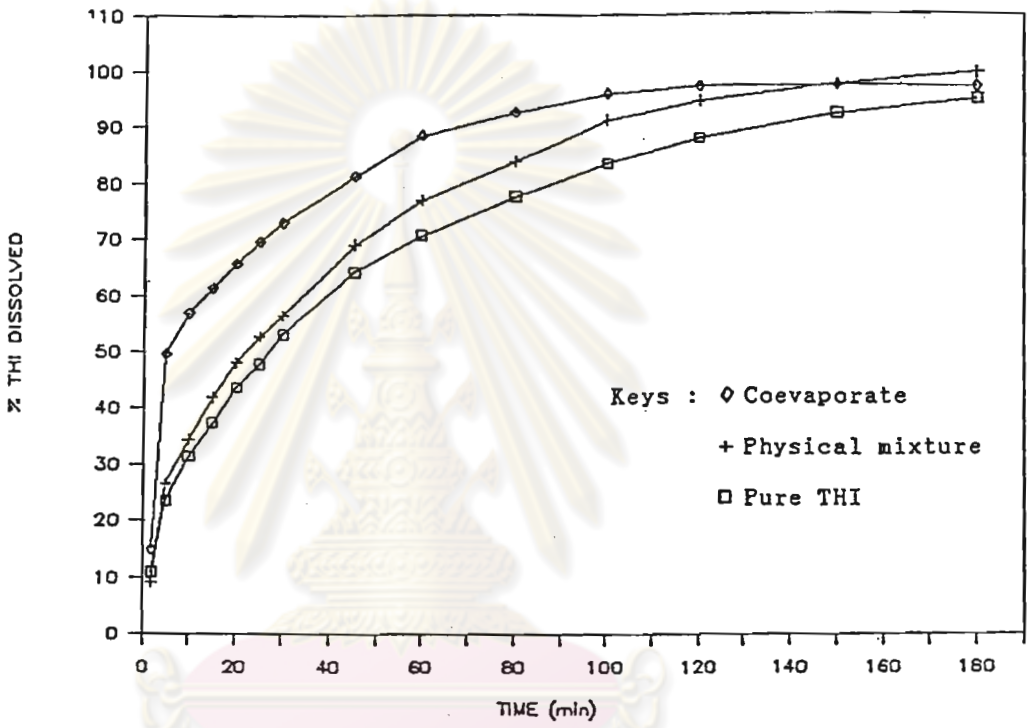


Figure 44 Dissolution Profiles of Thiamphenicol from 1:1 THI-PEG 6000 System at pH 7.5

Table 42 In Vitro Dissolution of Thiamphenicol from 1:1 THI-PEG 6000 Coevaporate, Physical Mixture and Prue Drug at pH 7.5.

Time (min)	Percent Thiamphenicol Dissolved		
	1[a]	2[b]	3[c]
5	65.05[d] (3.00)[e]	23.84 (1.62)	23.46 (0.61)
10	71.91 (4.06)	30.86 (0.88)	31.45 (0.65)
15	78.18 (2.06)	37.04 (1.90)	37.39 (0.81)
30	86.90 (3.07)	51.40 (1.20)	53.14 (1.34)
45	91.25 (2.83)	61.70 (1.85)	64.36 (1.91)
60	95.54 (0.99)	69.52 (1.74)	70.75 (2.04)
120	93.61 (0.21)	87.04 (2.06)	88.03 (1.59)
180	92.36 (0.18)	94.30 (2.87)	94.81 (0.71)
Kd[f] (hr^{-1})	3.40 (0.28)	1.29 (0.07)	1.23 (0.11)

[a] Coevaporate

[b] Physical mixture

[c] Pure drug

[d] The mean of six determinations

[e] Standard error

[f] Dissolution rate constant

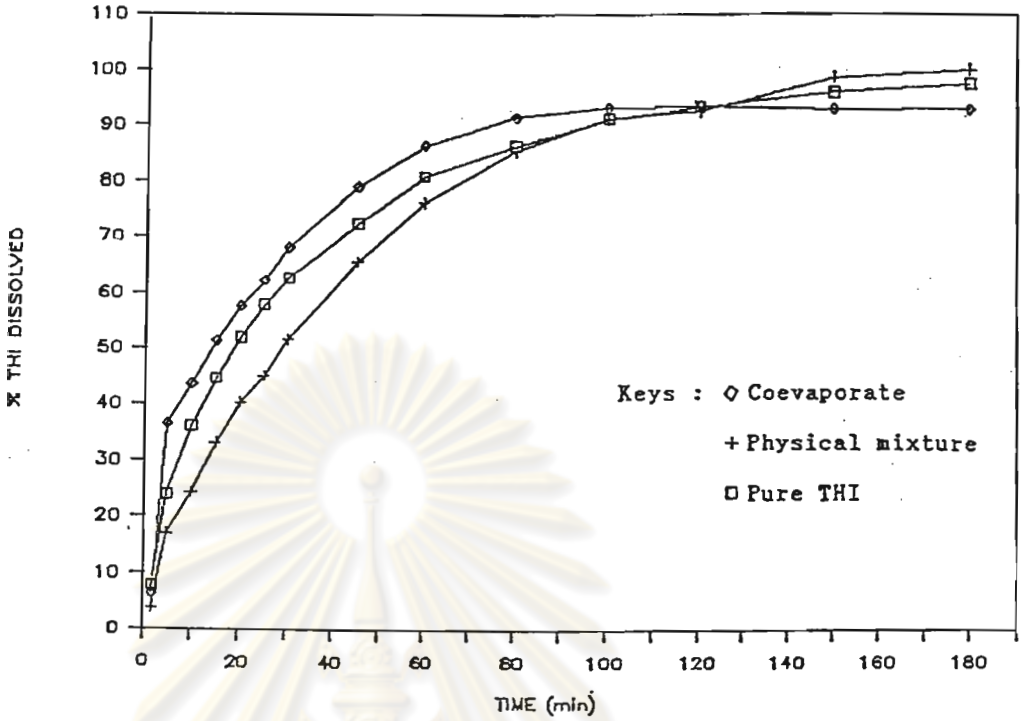


Figure 45 Dissolution Profiles of Thiamphenicol from 1:1 THI-PEG 20000 System at pH 1.5

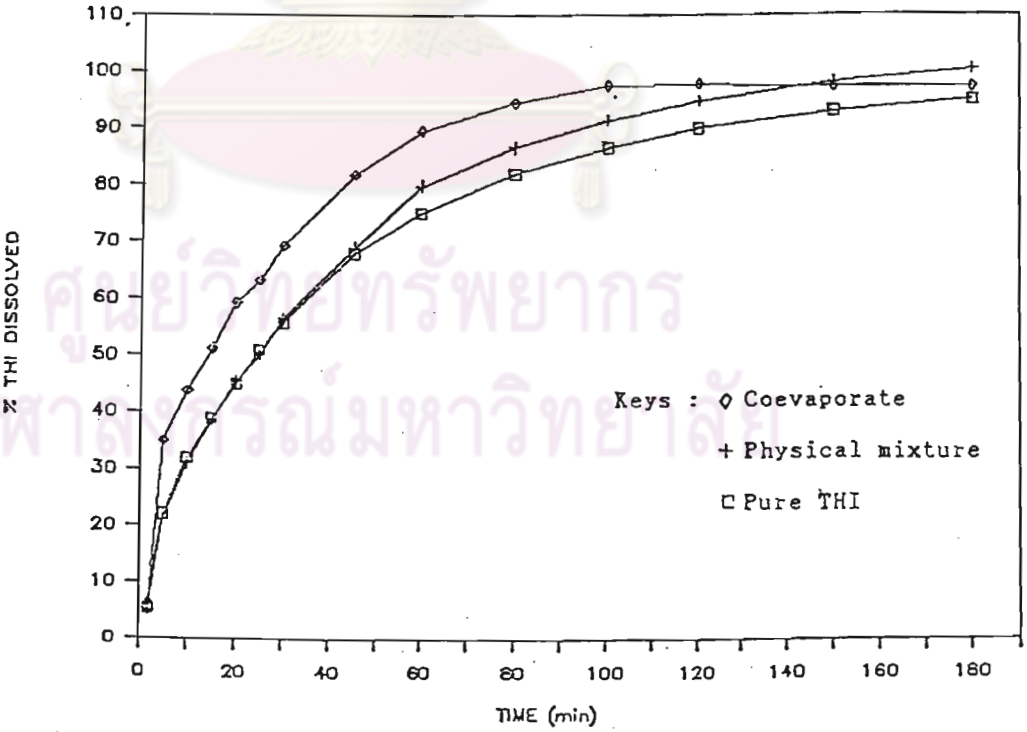


Figure 46 Dissolution Profiles of Thiamphenicol from 1:1 THI-PEG 20000 System at pH 4.5

Table 43 In Vitro Dissolution of Thiamphenicol from 1:1 THI-PEG 20000 Coevaporate, Physical Mixture and Pure Drug at pHs 1.5 and 4.5

Time (min)	Percent Thiamphenicol Dissolved					
	pH 1.5			pH 4.5		
	1[a]	2[b]	3[c]	1	2	3
5	36.60[d] (3.02)[e]	21.22 (1.88)	23.97 (0.57)	35.05 (4.03)	17.00 (0.90)	23.25 (0.45)
10	43.77 (2.44)	30.98 (2.09)	36.16 (0.78)	43.90 (4.32)	24.28 (1.17)	32.10 (0.70)
15	51.43 (2.96)	38.57 (2.34)	44.75 (1.33)	51.26 (4.80)	33.21 (1.32)	39.05 (0.83)
30	68.11 (3.42)	56.27 (3.19)	62.47 (2.01)	69.24 (5.48)	51.68 (2.28)	55.68 (1.16)
45	79.13 (2.92)	69.05 (3.27)	72.40 (2.09)	81.88 (4.63)	65.60 (2.41)	67.88 (1.88)
60	86.41 (2.33)	79.87 (3.56)	80.80 (1.89)	89.64 (3.15)	76.13 (2.57)	75.10 (1.06)
120	93.64 (0.83)	94.72 (1.91)	93.30 (1.26)	97.78 (0.29)	92.58 (2.29)	90.04 (0.63)
180	93.22 (0.75)	100.25 (0.62)	97.59 (0.52)	97.12 (0.25)	100.03 (1.53)	94.92 (0.55)
Kd[f] (hr^{-1})	2.90 (0.30)	1.55 (0.11)	1.66 (0.16)	3.05 (0.13)	1.56 (0.08)	1.48 (0.17)

[a] Coevaporate

[b] Physical mixture

[c] Pure drug

[d] The mean of six determinations

[e] Stantdard error

[f] Dissolution rate contstant

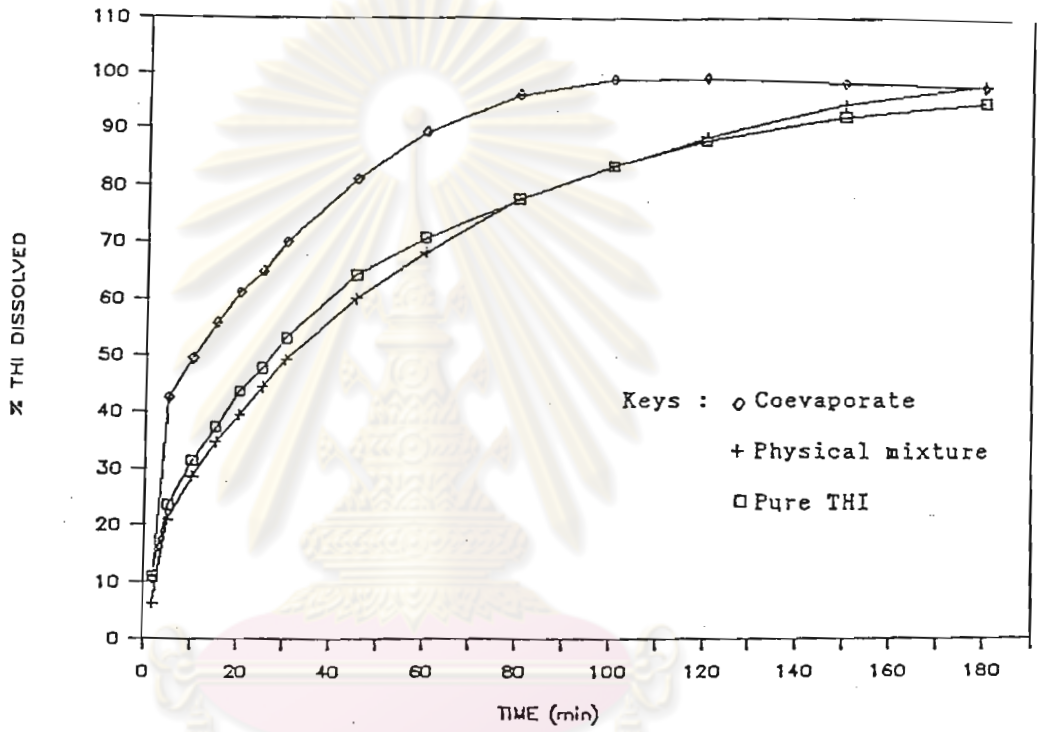


Figure 47 Dissolution Profiles of Thiamphenicol from 1:1 THI-PEG 20000 System at pH 7.5

Table 44 In Vitro Dissolution of Thiamphenicol from 1:1 THI-PEG 20000 Coevaporate, Physical Mixture and Prue Drug at pH 7.5.

Time (min)	Percent Thiamphenicol Dissolved		
	1[a]	2[b]	3[c]
5	42.60[d] (2.71)[e]	20.89 (0.95)	23.46 (0.61)
10	49.92 (2.97)	28.54 (1.15)	31.45 (0.65)
15	55.79 (3.29)	34.78 (1.26)	37.39 (0.81)
30	70.03 (3.39)	49.31 (1.80)	53.14 (1.34)
45	81.21 (2.77)	60.01 (2.04)	64.36 (1.91)
60	89.29 (2.08)	68.15 (2.31)	70.75 (2.04)
120	99.35 (0.23)	88.59 (2.17)	88.03 (1.59)
180	97.67 (0.22)	94.81 (2.03)	94.81 (0.71)
Kd[f] (hr^{-1})	2.47 (0.15)	1.22 (0.05)	1.23 (0.11)

[a] Coevaporate

[b] Physical mixture

[c] Pure drug

[d] The mean of six determinations

[e] Standard error

[f] Dissolution rate constant

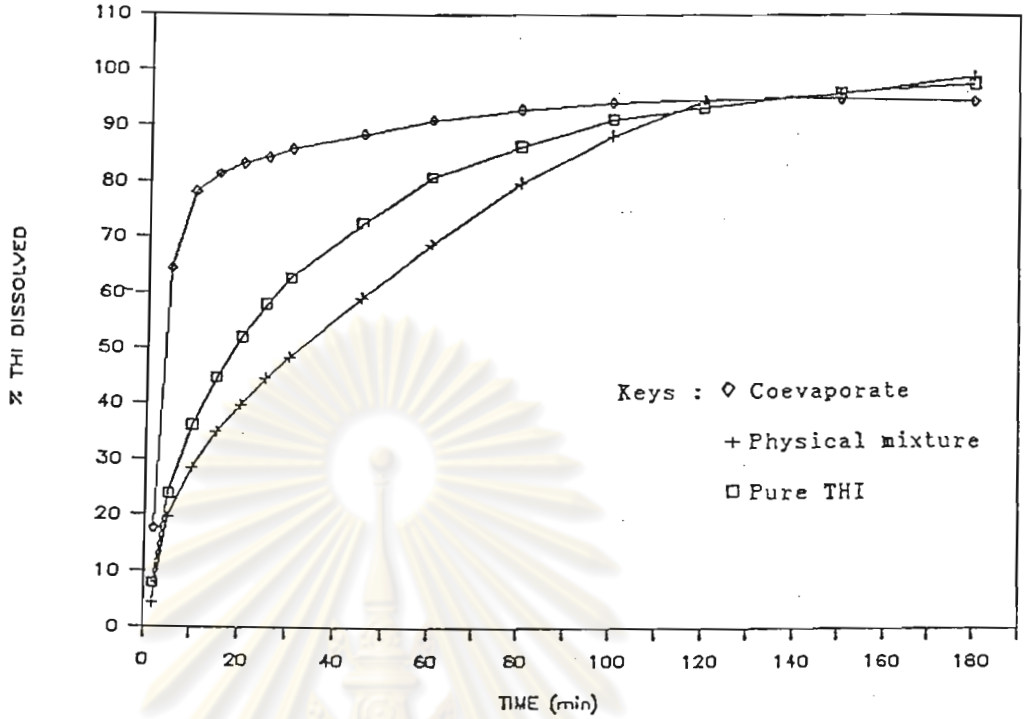


Figure 48 Dissolution Profiles of Thiamphenicol from 1:1 THI-PVP K-90 System at pH 1.5.

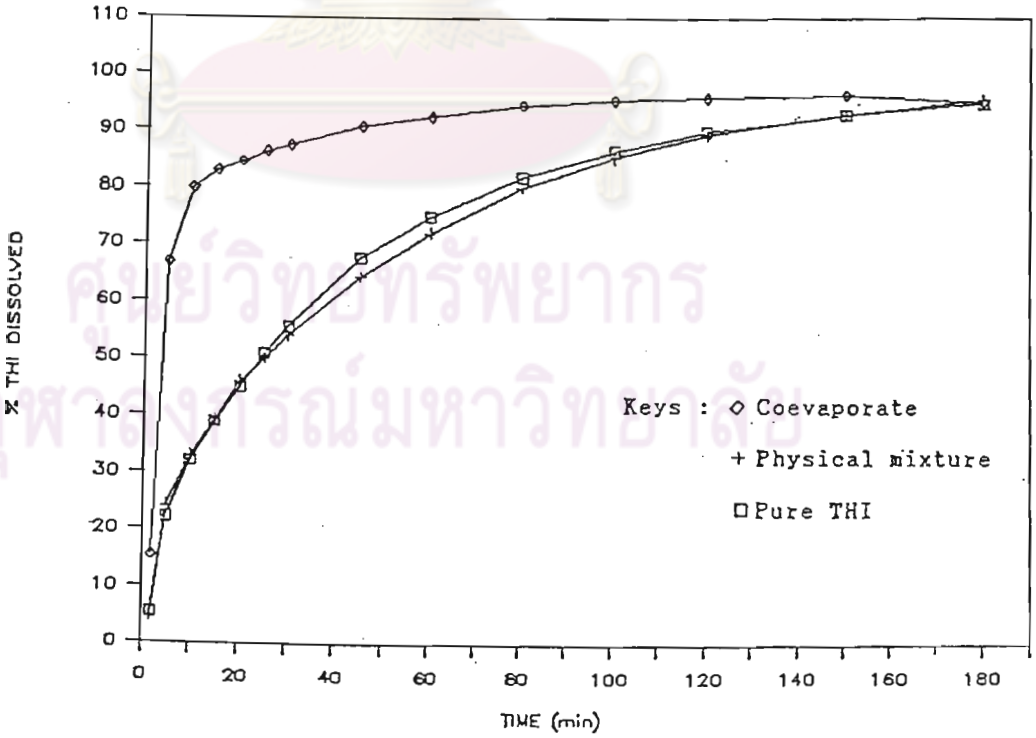


Figure 49 Dissolution Profiles of Thiamphenicol from 1:1 THI-PVP K-90 System at pH 4.5

Table 45 In Vitro Dissolution of Thiamphenicol from 1:1 THI-PVP K-90 Coevaporate, Physical Mixture and Pure Drug at pHs 1.5 and 4.5

Time (min)	Percent Thiamphenicol Dissolved					
	pH 1.5			pH 4.5		
	1[a]	2[b]	3[c]	1	2	3
5	64.36[d] (3.12)[e]	27.69 (0.25)	23.97 (0.57)	67.93 (1.62)	24.13 (1.03)	23.25 (0.45)
10	78.15 (2.59)	35.29 (0.29)	36.16 (0.78)	79.92 (1.73)	33.02 (1.41)	32.10 (0.70)
15	81.48 (2.44)	45.13 (0.22)	44.75 (1.33)	83.08 (1.59)	39.40 (1.75)	39.05 (0.83)
30	85.21 (2.05)	62.19 (0.20)	62.47 (2.01)	87.48 (1.19)	53.97 (2.11)	55.68 (1.16)
45	88.43 (1.62)	72.64 (0.18)	72.40 (2.09)	90.92 (0.73)	64.59 (1.98)	67.88 (1.88)
60	90.97 (1.58)	78.81 (0.14)	80.80 (1.89)	92.55 (0.89)	72.26 (1.77)	75.10 (1.06)
120	94.67 (0.51)	93.62 (0.22)	93.30 (1.26)	95.94 (0.24)	89.36 (1.41)	90.04 (0.63)
180	94.49 (0.17)	99.12 (0.65)	97.59 (0.52)	95.11 (0.18)	95.51 (1.66)	94.92 (0.55)
Kd[f] (hr^{-1})	3.08 (0.20)	1.44 (0.05)	1.66 (0.16)	2.32 (0.32)	1.34 (0.04)	1.48 (0.17)

[a] Coevaporate

[b] Physical mixture

[c] Pure drug

[d] The mean of six determinations

[e] Stantdard error

[f] Dissolution rate contstant

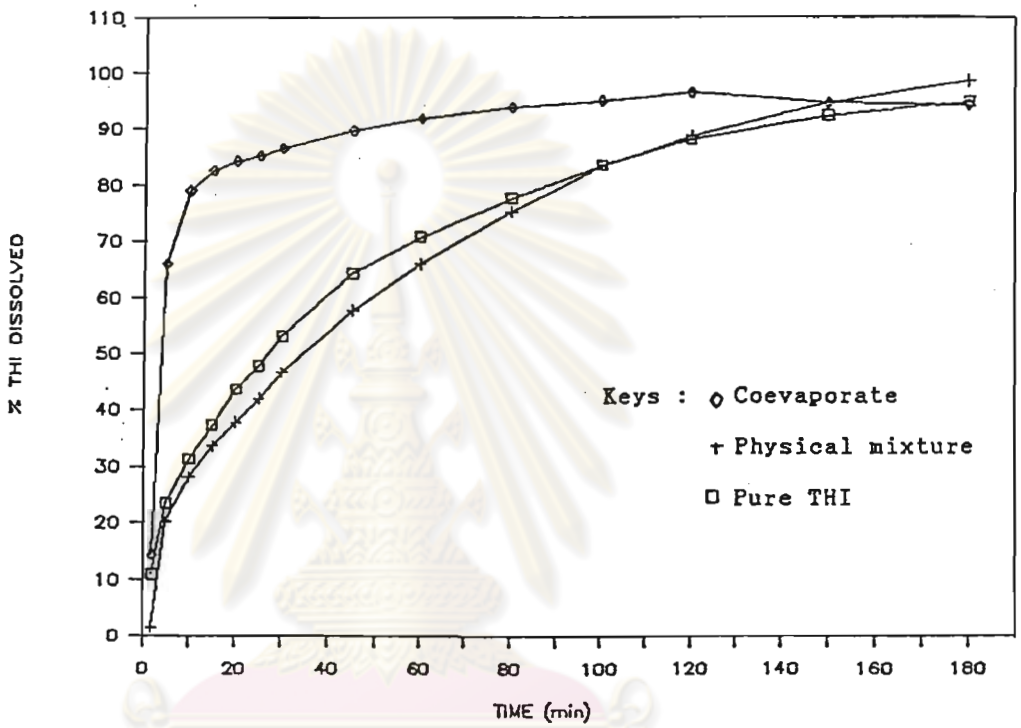


Figure 50 Dissolution Profiles of Thiamphenicol from 1:1 THI-PVP K-90 System at pH 7.5

Table 46 In Vitro Dissolution of Thiamphenicol from 1:1 THI-PVP K-90 Coevaporate, Physical Mixture and Prue Drug at pH 7.5.

Time (min)	Percent Thiamphenicol Dissolved		
	1[a]	2[b]	3[c]
5	66.04[d] (2.35)[e]	20.26 (0.42)	23.46 (0.61)
10	79.05 (2.01)	28.27 (0.33)	31.45 (0.65)
15	82.63 (1.94)	33.77 (0.62)	37.39 (0.81)
30	86.53 (1.77)	46.66 (1.07)	53.14 (1.34)
45	89.58 (1.53)	57.66 (1.40)	64.36 (1.91)
60	91.79 (1.34)	65.98 (1.51)	70.75 (2.04)
120	96.33 (0.48)	88.61 (0.81)	88.03 (1.59)
180	94.15 (0.82)	94.43 (0.72)	94.81 (0.71)
Kd[f] (hr^{-1})	2.34 (0.25)	1.14 (0.03)	1.23 (0.11)

[a] Coevaporate

[b] Physical mixture

[c] Pure drug

[d] The mean of six determinations

[e] Standard error

[f] Dissolution rate constant

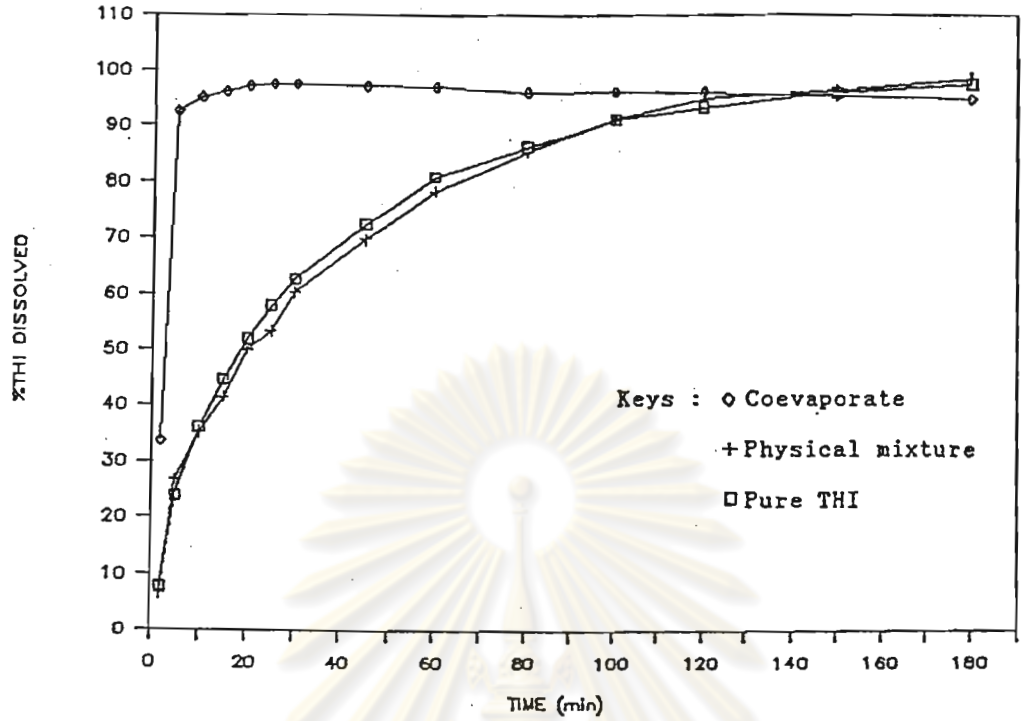


Figure 51 Dissolution Profiles of Thiamphenicol from 1:1 THI-PVP K-30 System at pH 1.5

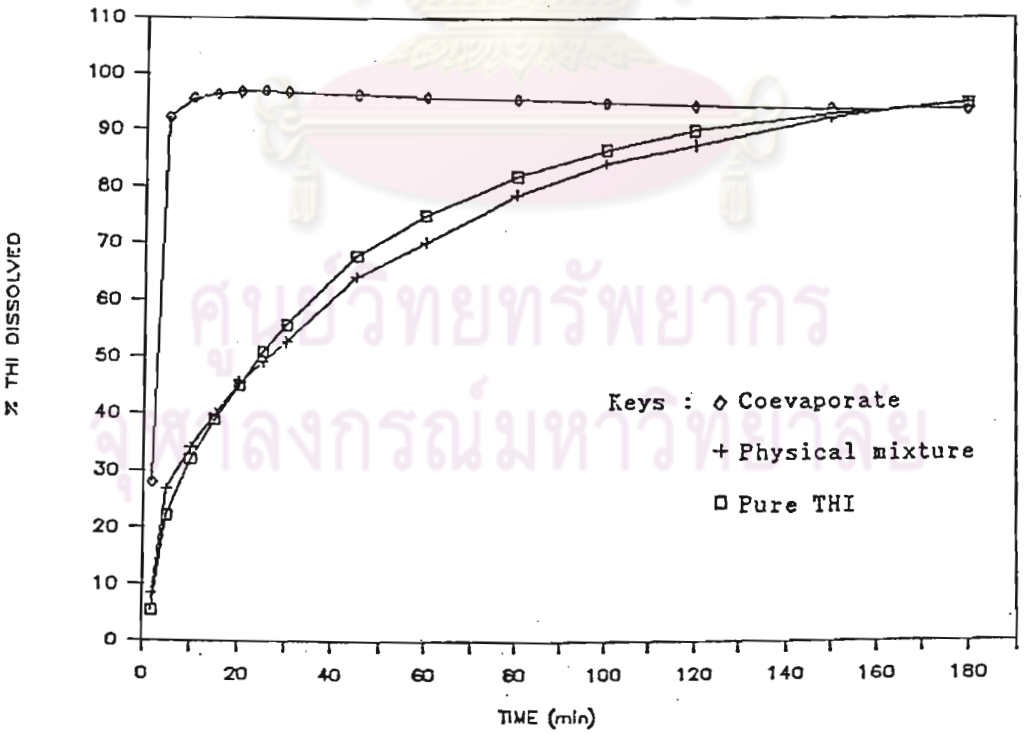


Figure 52 Dissolution Profiles of Thiamphenicol from 1:1 THI-PVP K-30 System at pH 4.5

Table 47 In Vitro Dissolution of Thiamphenicol from 1:1 THI-PVP K-30 Coevaporate, Physical Mixture and Pure Drug at pHs 1.5 and 4.5

Time (min)	Percent Thiamphenicol Dissolved					
	pH 1.5			pH 4.5		
	1[a]	2[b]	3[c]	1[a]	2[b]	3[c]
5	93.29[d] (2.42)[e]	27.33 (0.21)	23.97 (0.57)	92.15 (1.98)	26.58 (0.50)	23.25 (0.45)
10	97.97 (0.31)	35.94 (0.26)	36.16 (0.78)	95.65 (1.31)	34.95 (0.40)	32.10 (0.70)
15	98.11 (0.31)	42.47 (0.26)	44.75 (1.33)	96.43 (1.05)	41.45 (1.01)	39.05 (0.83)
30	97.20 (0.26)	61.47 (0.08)	62.47 (2.01)	96.68 (0.36)	56.76 (1.22)	55.68 (1.16)
45	96.67 (0.28)	71.17 (0.29)	72.40 (2.09)	96.36 (0.13)	66.89 (1.27)	67.88 (1.88)
60	96.25 (0.29)	79.85 (0.24)	80.80 (1.89)	95.86 (0.15)	73.59 (1.49)	75.10 (1.06)
120	95.04 (0.46)	96.96 (0.23)	93.30 (1.26)	94.21 (0.18)	89.59 (1.30)	90.04 (0.63)
180	93.83 (0.55)	99.57 (0.19)	97.59 (0.52)	93.63 (0.13)	97.01 (1.93)	94.92 (0.55)
Kd[f] (hr^{-1})	2.90 (0.30)	1.55 (0.11)	1.66 (0.16)	3.05 (0.13)	1.56 (0.08)	1.48 (0.17)

[a] Coevaporate

[b] Physical mixture

[c] Pure drug

[d] The mean of six determinations

[e] Stantdard error

[f] Dissolution rate contstant

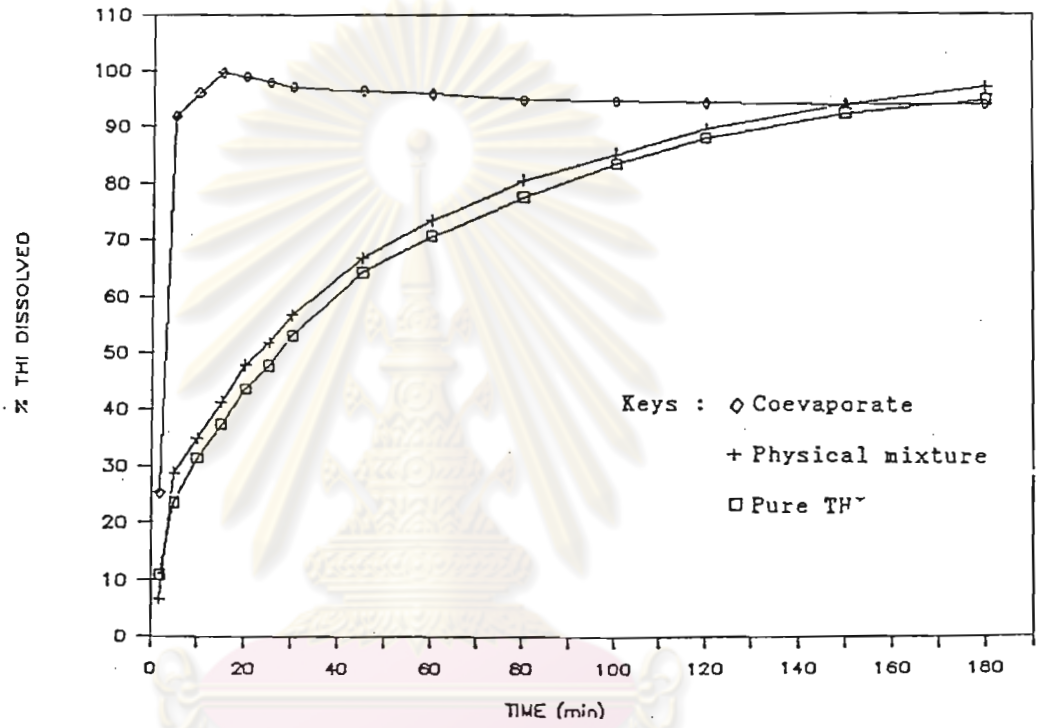


Figure 53 Dissolution Profiles of Thiamphenicol from 1:1 THI-PVP K-30 System at pH 7.5

Table 48 In Vitro Dissolution of Thiamphenicol from 1:1 THI-PVP K-30 Coevaporate, Physical Mixture and Prue Drug at pH 7.5.

Time (min)	Percent Thiamphenicol Dissolved		
	1[a]	2[b]	3[c]
5	91.86[d] (0.47)[e]	26.79 (0.37)	23.46 (0.61)
10	96.02 (0.34)	34.19 (0.34)	31.45 (0.65)
15	99.75 (0.29)	40.10 (0.44)	37.39 (0.81)
30	97.08 (0.12)	52.74 (1.24)	53.14 (1.34)
45	96.49 (0.11)	64.14 (1.28)	64.36 (1.91)
60	95.92 (0.13)	70.28 (1.31)	70.75 (2.04)
120	94.24 (0.75)	87.37 (0.91)	88.03 (1.59)
180	93.87 (0.12)	94.93 (0.78)	94.81 (0.71)
Kd^{f} (hr^{-1})	21.20 (0.75)	1.27 (0.50)	1.23 (0.11)

[a] Coevaporate

[b] Physical mixture

[c] Pure drug

[d] The mean of six determinations

[e] Standard error

[f] Dissolution rate constant

Table 49 The Statistical Comparisons of Percent THI Dissolved at Various Times and Dissoltion Rate Constants (Kd) from Various THI Dispersion Systems and Pure THI (TC1-TC5, TP1-TP5, TO) at pH 1.5 Using one - way ANOVA.

Time (min)	Source of Variation	d.f[a]	SS[b]	MS[c]	F[d]
5	Treatment	10	31335.90	3133.59	113.07
	Error	55	1524.23	27.71	
	Total	65	32860.10		
15	Treatment	10	23028.70	2302.87	81.99
	Error	55	1544.62	28.08	
	Total	65	24573.30		
30	Treatment	10	10583.10	1058.31	32.29
	Error	55	1802.26	32.76	
	Total	65	12385.40		
60	Treatment	10	2919.25	291.92	12.30
	Error	55	1305.54	23.73	
	Total	65	4224.78		
120	Treatment	10	332.19	33.22	3.70
	Error	55	493.20	8.96	
	Total	65	825.39		
Kd (hr^{-1})	Treatment	10	32.38	3.23	10.63
	Error	55	16.75	0.31	
	Total	65	49.13		

[e] $F_{0.05\ (\ 10,55\ )} = 2.01$

[f] $F_{0.10\ (\ 10,55\ )} = 1.72$

[a] Degree of freedom

[b] Sum of square error

[c] Mean square error

[d] Variation ratio

[e,f] F obtained from the table

Table 50 The Statistical Comparisons of Percent THI Dissolved at Various Times and Dissoltion Rate Constants (Kd) from Various THI Dispersion Systems and Pure THI (TC1-TC5, TP1-TP5, TO) at pH 4.5 Using one - way ANOVA.

Time (min)	Source of Variation	d.f[a]	SS[b]	MS[c]	F[d]
5	Treatment	10	33592.40	3359.24	175.99
	Error	55	1049.80	19.08	
	Total	65	34642.20		
15	Treatment	10	27137.30	2713.73	90.55
	Error	55	1648.21	29.76	
	Total	65	28785.50		
30	Treatment	10	15725.40	1572.54	41.01
	Error	55	2108.87	38.34	
	Total	65	17834.30		
60	Treatment	10	6658.01	665.80	34.88
	Error	55	1049.91	19.08	
	Total	65	7707.92		
120	Treatment	10	1299.91	129.99	16.62
	Error	55	430.21	7.82	
	Total	65	1730.12		
Kd (hr^{-1})	Tretment	10	49.03	4.87	19.10
	Error	55	14.12	0.26	
	Total	65	63.14		

[e] $F_{0.05\ (\ 10,55\ )} = 2.01$

[f] $F_{0.10\ (\ 10,55\ )} = 1.72$

[a] Degree of freedom

[b] Sum of square error

[c] Mean square error

[d] Variation ratio

[e,f] F obtained from the table

Table 51 The Statistical Comparisons of Percent THI Dissolved at Various Times and Dissoltion Rate Constants (Kd) from Various THI Dispersion Systems and Pure THI (TC1-TC5, TP1-TP5, TO) at pH 7.5 Using one - way ANOVA.

Time (min)	Source of Variation	d.f[a]	SS[b]	MS[c]	F[d]
5	Treatment	10	34287.30	3428.73	234.40
	Error	55	804.53	14.62	
	Total	65	35091.90		
15	Treatment	10	30927.10	3092.71	142.45
	Error	55	1194.09	21.71	
	Total	65	32121.20		
30	Treatment	10	18642.70	1864.27	86.81
	Error	55	1181.18	21.48	
	Total	65	19823.90		
60	Treatment	10	7274.91	727.49	29.82
	Error	55	1341.66	24.39	
	Total	65	8616.57		
120	Treatment	10	1199.32	119.93	5.48
	Error	55	1203.17	21.87	
	Total	65	2402.49		
Kd (hr^{-1})	Treatment	10	34.66	3.46	456.34
	Error	55	0.41	0.01	
	Total	65	35.07		

[e] $F_{0.05\ (\ 10,55\ )} = 2.01$

[f] $F_{0.10\ (\ 10,55\ )} = 1.72$

[a] Degree of freedom

[b] Sum of square error

[c] Mean square error

[d] Variation ratio

[e,f] F obtained from the table

Table 52 The Statistical Comparisons of Percent THI Dissolved at Various times and Dissoltion Rate Constants (Kd) from Various THI Dispersion Systems and Pure THI (TC1-TC5, TP1-TP5, T0) at pH 1.5 Using T-test.

	Comparative Percent THI Dissolved at time (min)										Kd (hr^{-1})	
	5		15		30		60		120			
Prep	TP1	TC1	TP1	TC1	TP1	TC1	TP1	TC1	TP1	TC1	TP1	TC1
T0	-	++	+	++	-	++	-	++	+	++	-	+
TP1		++		++		++		++		-		++
	TP2	TC2	TP2	TC2	TP2	TC2	TP2	TC2	TP2	TC2	TP2	TC2
T0	-	++	-	++	-	++	-	++	-	-	-	++
TP2		++		++		++		++		-		++
	TP3	TC3	TP3	TC3	TP3	TC3	TP3	TC3	TP3	TC3	TP3	TC3
T0	-	++	-	-	-	-	-	-	-	-	-	++
TP3		++		+		+		-		-		++
	TP4	TC4	TP4	TC4	TP4	TC4	TP4	TC4	TP4	TC4	TP4	TC4
T0	++	++	-	++	-	++	-	++	-	-	+	-
TP4		++		++		++		++		-		+
	TP5	TC5	TP5	TC5	TP5	TC5	TP5	TC5	TP5	TC5	TP5	TC5
T0	++	++	-	++	-	++	-	++	+	-	+	++
TP5		++		++		++		++		++		++
	TC2	TC3	TC2	TC3	TC2	TC3	TC2	TC3	TC2	TC3	TC2	TC3
TC1	-	++	-	+	-	+	-	-	++	++	-	-
TC2		+		+		-		-		-		-
	TC4	TC5	TC4	TC5	TC4	TC5	TC4	TC5	TC4	TC5	TC4	TC5
TC1	-	++	-	++	-	++	-	-	++	++	-	+
TC2	++	++	++	++	+	++	-	++	-	-	-	+
	TC4	TC5	TC4	TC5	TC4	TC5	TC4	TC5	TC4	TC5	TC4	TC5
TC3	++	++	++	++	++	++	-	++	-	-	-	+
TC4		++		++		++		++		-		+

+ = Significant difference ($p < 0.10$)
++ = Significant difference ($p < 0.05$)
- = Not Significant difference ($p > 0.10$)

Table 53 The Statistical Comparisons of Percent THI Dissolved at Various Times and Dissoltion Rate Constants (Kd) from Various THI Dispersion Systems and Pure THI (TC1-TC5, TP1-TP5, T0) at pH 4.5 Using T-test.

	Comparative Percent THI Dissolved at time (min)										Kd (hr^{-1})	
	5		15		30		60		120			
Prep.	TP1	TC1	TP1	TC1	TP1	TC1	TP1	TC1	TP1	TC1	TP1	TC1
T0	-	++	-	++	-	++	-	++	-	++	-	++
TP1		++		++		++		++		++		++
	TP2	TC2	TP2	TC2	TP2	TC2	TP2	TC2	TP2	TC2	TP2	TC2
T0	-	++	-	++	-	++	-	++	-	++	-	++
TP2		++		++		++		++		++		++
	TP3	TC3	TP3	TC3	TP3	TC3	TP3	TC3	TP3	TC3	TP3	TC3
T0	+	+	-	+	-	+	-	++	-	++	-	++
TP3		++		++		+		++		+		++
	TP4	TC4	TP4	TC4	TP4	TC4	TP4	TC4	TP4	TC4	TP4	TC4
T0	-	++	-	++	-	++	-	++	-	++	-	+
TP4		++		++		++		++		++		++
	TP5	TC5	TP5	TC5	TP5	TC5	TP5	TC5	TP5	TC5	TP5	TC5
T0	+	++	-	++	-	++	+	++	+	++	-	++
TP5		++		++		++		++		++		++
	TC2	TC3	TC2	TC3	TC2	TC3	TC2	TC3	TC2	TC3	TC2	TC3
TC1	++	++	+	+	-	-	-	-	+	-	-	-
TC2		-		-		-		-		+		-
	TC4	TC5	TC4	TC5	TC4	TC5	TC4	TC5	TC4	TC5	TC4	TC5
TC1	++	++	+	++	-	+	-	-	+	++	-	++
TC2	++	++	++	++	++	++	-	-	-	++	+	++
	TC4	TC5	TC4	TC5	TC4	TC5	TC4	TC5	TC4	TC5	TC4	TC5
TC3	++	++	++	++	+	++	-	-	++	++	-	++
TC4		++		++		++		++		++		++

+ = Significant difference ($p < 0.10$)
++ = Significant difference ($p < 0.05$)
- = Not Significant difference ($p > 0.10$)

Table 54 The Statistical Comparisons of Percent THI Dissolved at Various Times and Dissoltion Rate Constants (Kd) from Various THI Dispersion Systems and Pure THI (TC1-TC5, TP1-TP5, TO) at pH 7.5 Using T-test.

	Comparative Percent THI Dissolved at time (min)										Kd (hr^{-1})	
	5		15		30		60		120			
Prep.	TP1	TC1	TP1	TC1	TP1	TC1	TP1	TC1	TP1	TC1	TP1	TC1
TO	-	++	-	++	-	++	-	++	-	++	-	++
TP1		++		++		++		++		++		++
	TP2	TC2	TP2	TC2	TP2	TC2	TP2	TC2	TP2	TC2	TP2	TC2
TO	+	++	-	++	-	++	+	++	+	++	-	++
TP2		++		++		++		++		+		++
	TP3	TC3	TP3	TC3	TP3	TC3	TP3	TC3	TP3	TC3	TP3	TC3
TO	-	++	-	++	-	++	-	++	-	++	-	++
TP3		++		++		++		++		++		++
	TP4	TC4	TP4	TC4	TP4	TC4	TP4	TC4	TP4	TC4	TP4	TC4
TO	++	++	-	++	+	++	-	++	-	++	-	++
TP4		++		++		++		++		++		++
	TP5	TC5	TP5	TC5	TP5	TC5	TP5	TC5	TP5	TC5	TP5	TC5
TO	++	++	+	++	-	++	-	++	-	-	-	++
TP5		++		++		++		++		-		++
	TC2	TC3	TC2	TC3	TC2	TC3	TC2	TC3	TC2	TC3	TC2	TC3
TC1	++	++	++	++	++	++	++	-	++	++	-	+
TC2		-		-		-		-		+		-
	TC4	TC5	TC4	TC5	TC4	TC5	TC4	TC5	TC4	TC5	TC4	TC5
TC1	-	++	-	++	-	+	-	-	+	-	+	++
TC2	++	++	++	++	++	++	-	-	-	-	-	++
	TC4	TC5	TC4	TC5	TC4	TC5	TC4	TC5	TC4	TC5	TC4	TC5
TC3	++	++	++	++	++	++	-	+	++	-	-	++
TC4		++		++		++		+		-		++

+ = Significant difference ($p < 0.10$)
++ = Significant difference ($p < 0.05$)
- = Not Significant difference ($p > 0.10$)

(TC1, TC2, TC3, TC4 and TC5) gave statistically significant higher dissolution rates and extents than the corresponding physical mixtures and pure drug alone. Within 10 minutes all the coevaporates exhibited more than 50 % THI dissolved except TC3 that gave 43.76 and 43.90 % THI dissolved at pHs 1.5 and 4.5, respectively. The percentage THI dissolved from TO were 36.15, 32.10 and 31.45 % within 10 minutes at pHs 1.5, 4.5 and 7.5, respectively.

Comparing among the coevaporates with various types of carriers, the dissolution profiles were illustrated in Figures 54 - 56. The statistical comparisons for the dissolution parameters of each preparation using t - test were also presented in Tables 52 - 54. The results showed that TC5 gave the fastest dissolution rate followed by TC4, TC1, TC2 and finally TC3. The maximum THI released were achieved during the first 10 minutes and after 60 minutes from TC5 and from other coevaporates, respectively. The pure THI powder dissolved completely after 180 minutes

Hence, THI-PVP K-30 systems were selected for further studies like the previous NPX studies.

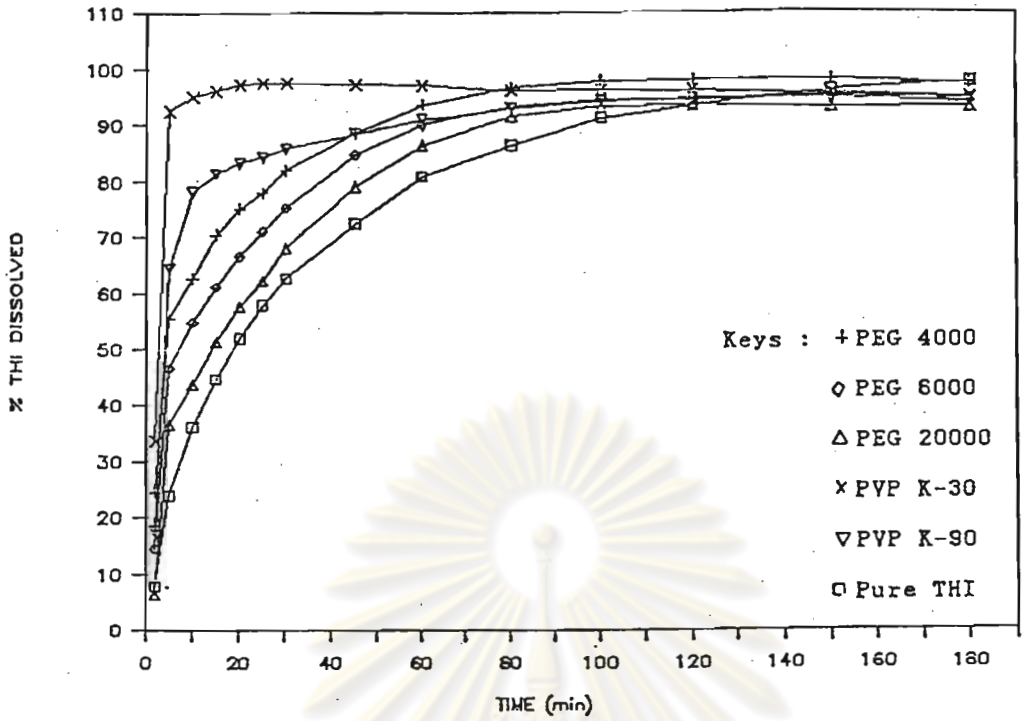


Figure 54 Dissolution Profiles of Thiamphenicol from 1:1 THI Coevaporates with various types of carriers at pH 1.5

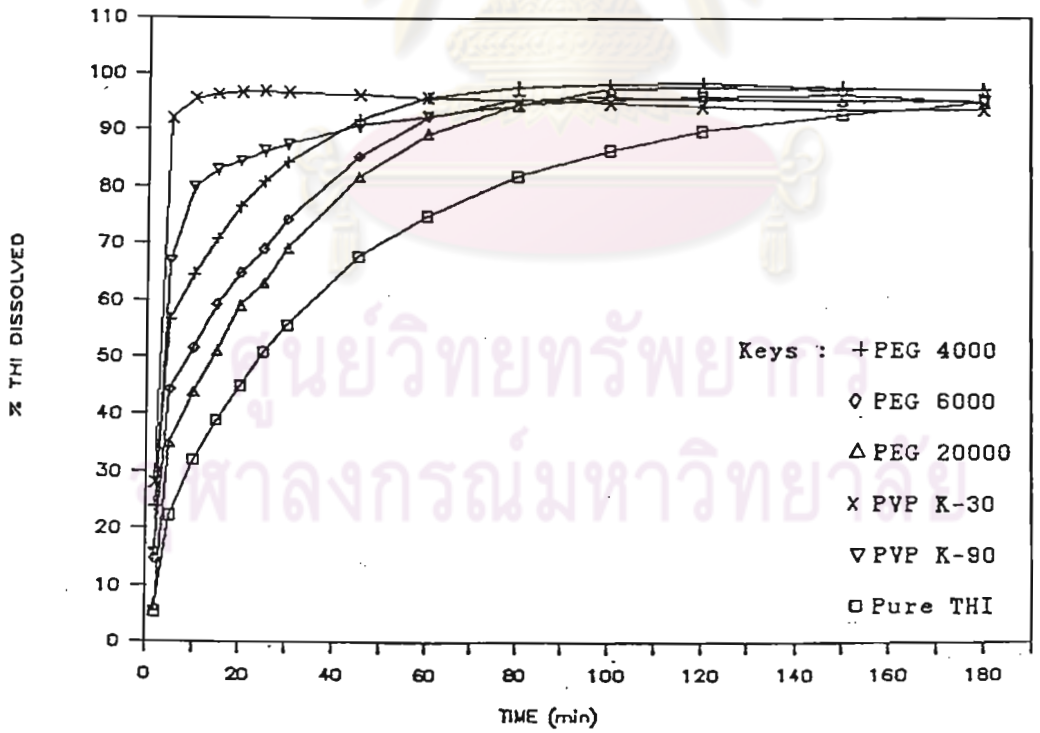


Figure 55 Dissolution Profiles of Thiamphenicol from 1:1 THI Coevaporates with various types of carriers at pH 4.5

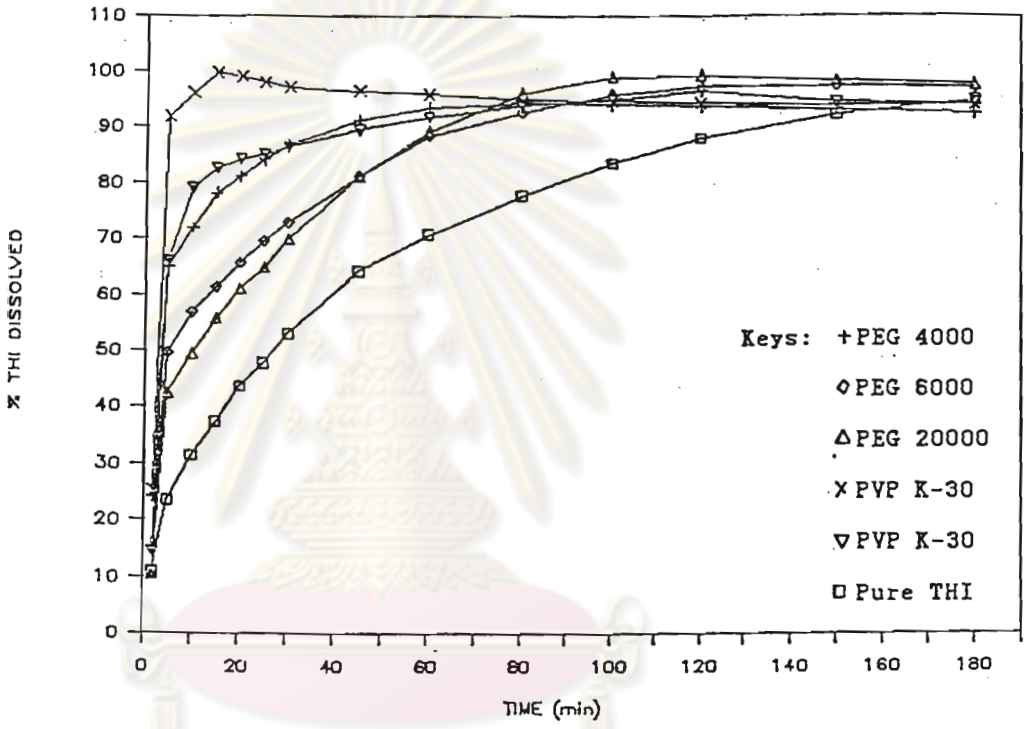


Figure 56 Dissolution Profiles of Thiamphenicol from 1:1 THI Coevaporates with various types of carriers at pH 7.5

The THI-PVP K-30 coevaporates were newly prepared with various ratios of drug:carrier i.e. 1:0.75, 1:0.50 and 1:0.25. The codes used for these preparations were as follows :

Code	Preparation
TC6	1:0.75 THI-PVP K-30 Coevaporate
TC7	1:0.50 THI-PVP K-30 Coevaporate
TC8	1:0.25 THI-PVP K-30 Coevaporate

TC6 had the same external characteristic as that obtained from TC5 previouesly prepared. The products obtained from TC6 and TC7 were nonsticky white powders.

Figures 57 - 59 and Tables 55 - 57 showed the dissolution profiles of THI-PVP K-30 coevaporates with various ratio of drug:carrier (TC5-TC8) compared to the 1:1 physical mixture (TP5) and pure THI (T0) in all dissolution mediums. The statistical comparisons for the dissolution parameters of these preparations using one-way ANOVA and t - test were presented in Tables 58 - 61.

The results revealed that TC6 gave statistically significant higher dissolution rates and extens than TC7 and TC8 ($p < 0.05$) in all pH of dissolution mediums. There were no statistically significal difference of dissolution between TC5 and TC6 ($p > 0.10$) at pHs 1.5 and 4.5. However, TC6 gave statistically significant higher dissolution rates than TC5 at pH 7.5. ($p < 0.10$)

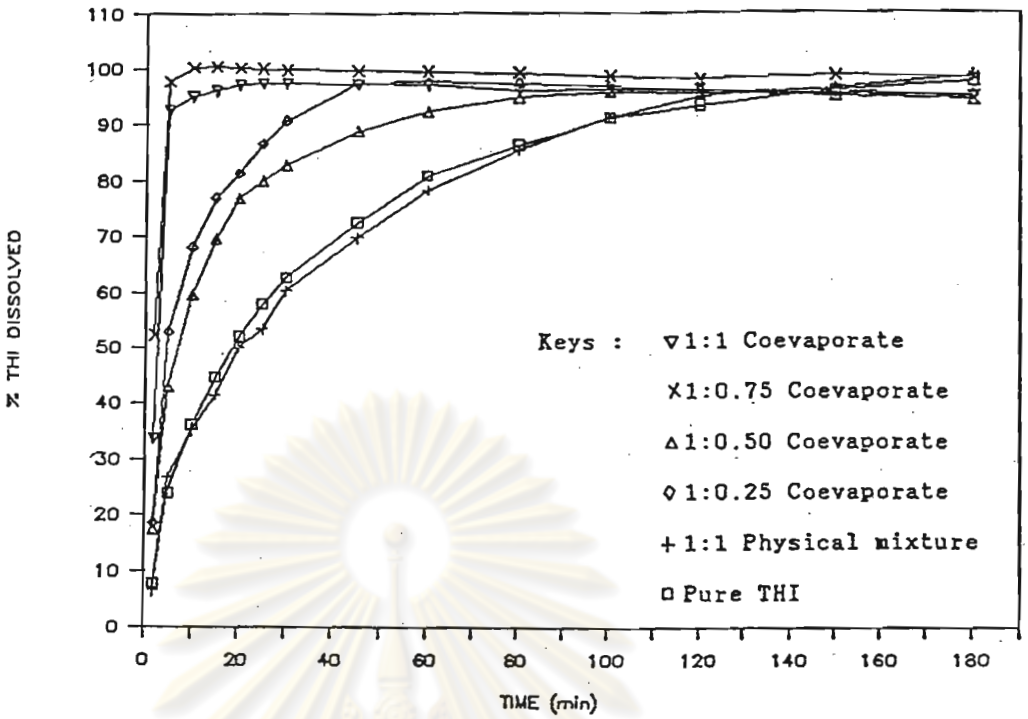


Figure 57 Dissolution Profiles of Thiamphenicol from THI-PVP K-30 Coevaporates with various ratios of Drug:Carrier at pH 1.5

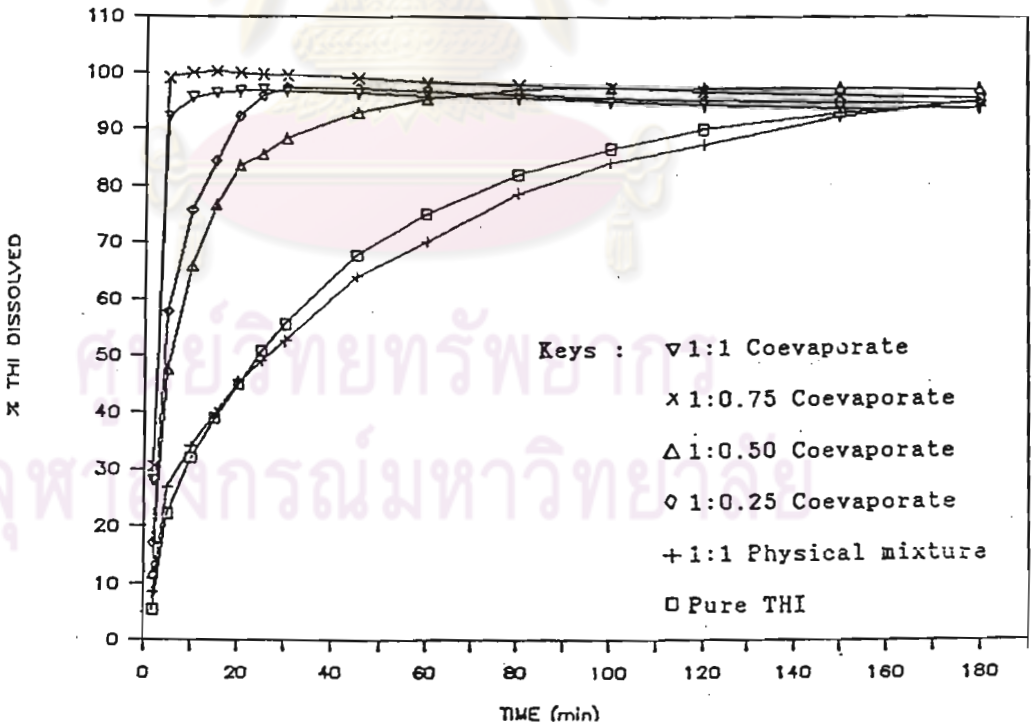


Figure 58 Dissolution Profiles of Thiamphenicol from THI-PVP K-30 Coevaporates with various ratios of Drug:Carrier at pH 4.5

Table 55 In Vitro Dissolution of Thiamphenicol from THI-PVP K-30 Coevaporates with Various Ratios of Drug : Carrier at pH 1.5

Time (min)	Percent Thiamphenicol Dissolved			
	Ratios of Drug:Carrier			
	1:1	1:0.75	1:0.50	1:0.25
5	93.29[a] (2.42)[b]	99.12 (0.34)	57.74 (3.33)	47.58 (4.05)
10	97.97 (0.31)	100.00 (0.06)	75.74 (3.09)	65.85 (5.37)
15	98.11 (0.31)	100.21 (0.13)	84.87 (2.87)	76.62 (5.77)
30	97.20 (0.26)	99.36 (0.15)	97.33 (0.21)	88.34 (4.27)
45	96.67 (0.28)	98.91 (0.19)	97.21 (0.17)	92.91 (2.64)
60	96.25 (0.29)	98.43 (0.08)	96.71 (0.15)	95.27 (1.27)
120	95.04 (0.46)	96.89 (0.08)	96.09 (0.10)	95.61 (0.31)
180	93.83 (0.55)	96.17 (0.16)	94.72 (0.22)	97.12 (0.15)
Kd[c] (hr^{-1})	44.92 (0.70)	42.21 (0.62)	9.20 (0.78)	6.56 (1.51)

[a] The mean of six determinations

[b] Standard error

[c] Dissolution rate constant

Table 56 In Vitro Dissolution of Thiamphenicol from THI-PVP K-30 Coevaporates with Various Ratios of Drug : Carrier at pH 4.5

Time (min)	Percent Thiamphenicol Dissolved			
	Ratios of Drug:Carrier			
	1:1	1:0.75	1:0.50	1:0.25
5	92.15[a] (1.98)[b]	97.31 (1.09)	52.82 (1.98)	42.99 (5.92)
10	95.65 (1.31)	100.04 (0.26)	68.24 (2.82)	59.60 (6.24)
15	96.43 (1.05)	100.19 (0.26)	77.07 (3.41)	69.68 (5.92)
30	96.68 (0.36)	99.34 (0.87)	90.71 (2.61)	82.88 (4.36)
45	96.36 (0.13)	98.84 (0.12)	97.37 (0.53)	88.85 (2.93)
60	95.86 (0.15)	98.43 (0.08)	97.65 (0.07)	92.39 (1.62)
120	94.21 (0.18)	96.86 (0.06)	96.09 (0.10)	95.61 (0.31)
180	93.63 (0.13)	96.13 (0.15)	94.96 (0.09)	94.26 (0.32)
Kd^{c} (hr^{-1})	25.14 (5.22)	36.86 (4.52)	7.96 (0.99)	5.50 (1.90)

[a] The mean of six determinations

[b] Standard error

[c] Dissolution rate constant

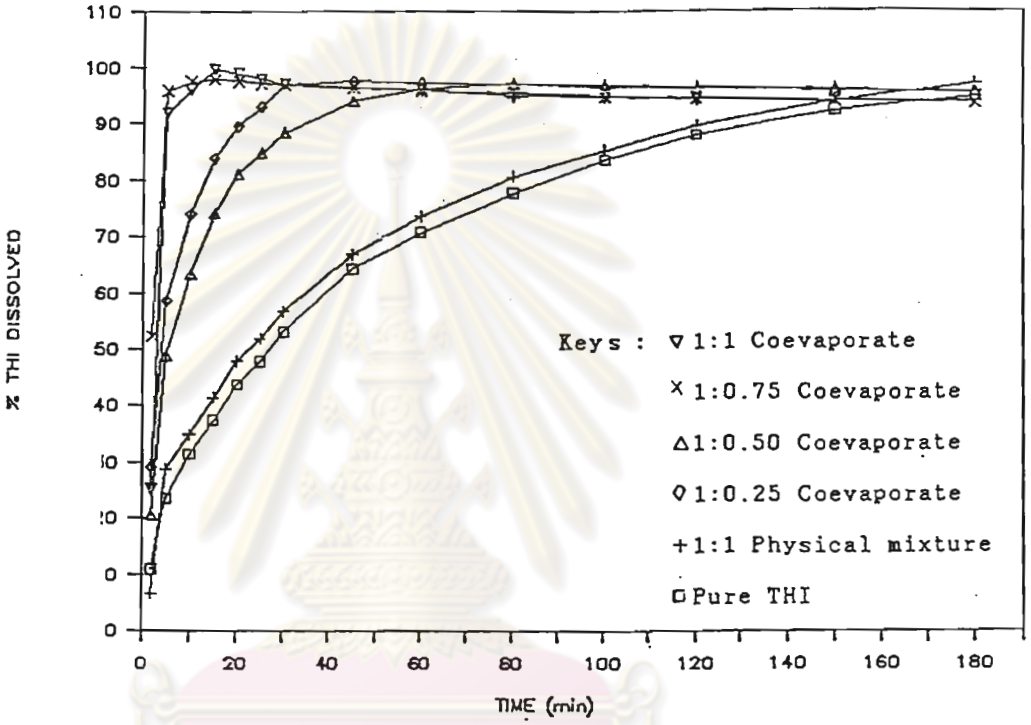


Figure 59 Dissolution Profiles of Thiamphenicol from THI-PVP K-30 Coevaporates with various ratios of Drug:Carrier at pH 7.5

Table 57 In Vitro Dissolution of Thiamphenicol from THI-PVP K-30 Coevaporates with Various Ratios of Drug : Carrier at pH 7.5

Time (min)	Percent Thiamphenicol Dissolved			
	Ratios of Drug:Carrier			
	1:1	1:0.75	1:0.50	1:0.25
5	91.86[a] (0.47)[b]	95.86 (1.00)	58.57 (2.29)	48.88 (2.88)
10	96.02 (0.34)	97.61 (0.25)	73.98 (3.94)	63.46 (2.90)
15	99.75 (0.29)	97.69 (0.25)	83.92 (4.31)	74.18 (3.40)
30	97.08 (0.12)	97.40 (0.56)	97.10 (0.74)	88.52 (2.92)
45	96.49 (0.11)	97.12 (0.59)	97.71 (0.10)	94.23 (1.92)
60	95.92 (0.13)	96.78 (0.58)	97.33 (0.14)	96.23 (0.88)
120	94.24 (0.75)	95.34 (0.53)	96.15 (0.12)	96.52 (0.22)
180	93.87 (0.12)	95.34 (0.85)	96.65 (0.15)	95.61 (0.17)
Kd^{c} (hr^{-1})	21.20 (0.75)	34.63 (4.09)	6.01 (0.97)	5.32 (0.09)

[a] The mean of six determinations

[b] Standard error

[c] Dissolution rate constant

Table 58 The Statistical Comparisons of Percent THI Dissolved at Various Times and Dissoltion Rate Constants (Kd) from THI-PVP K-30 Coevaporates with Various Ratios of Drug: Carrier, 1:1 Physical Mixture and Pure THI (TC5-TC8, TP5, TO) at pH 1.5 Using one - way ANOVA.

Time (min)	Source of Variation	d.f[a]	SS[b]	MS[c]	F[d]
5	Treatment	5	30748.70	6149.73	131.27
	Error	30	1394.79	46.49	
	Total	35	32143.50		
15	Treatment	5	18878.30	3775.66	67.34
	Error	30	1682.02	56.06	
	Total	35	20560.31		
30	Treatment	5	8580.70	1716.14	73.06
	Error	30	704.64	23.48	
	Total	35	9285.33		
60	Treatment	5	2207.61	441.52	69.44
	Error	30	190.74	6.35	
	Total	35	2398.35		
120	Treatment	5	57.12	11.42	5.90
	Error	30	58.02	1.93	
	Total	35	115.14		
Kd (hr^{-1})	Treatment	5	98.93	19.79	20.57
	Error	30	28.81	6.96	
	Total	35	127.79		

[e] $F_{0.05\ (\ 5,30\ )} = 2.53$

[f] $F_{0.10\ (\ 5,30\ )} = 2.05$

[a] Degree of freedom

[b] Sum of square error

[c] Mean square error

[d] Variation ratio

[e,f] F obtained from the table

Table 59 The Statistical Comparisons of Percent THI Dissolved at Various Times and Dissoltion Rate Constants (Kd) from THI-PVP K-30 Coevaporates with Various Ratios of Drug: Carrier, 1:1 Physical Mixture and Pure THI (TC5-TC8, TP5, TO) at pH 4.5 Using one - way ANOVA.

Time (min)	Source of Variation	d.f[a]	SS[b]	MS[c]	F[d]
5	Treatment	5	31325.10	6265.02	192.32
	Error	30	977.26	32.57	
	Total	35	32302.40		
15	Treatment	5	22705.10	4541.02	102.65
	Error	30	1327.15	44.24	
	Total	35	24032.30		
30	Treatment	5	14109.00	2821.81	133.68
	Error	30	633.22	21.10	
	Total	35	14742.30		
60	Treatment	5	5156.72	1031.34	219.23
	Error	30	141.12	4.70	
	Total	35	5297.84		
120	Treatment	5	898.14	179.63	92.17
	Error	30	58.46	1.94	
	Total	35	956.61		
Kd (hr^{-1})	Treatment	5	102.98	20.60	23.98
	Error	30	25.76	0.87	
	Total	35	128.78		

[e] $F_{0.05\ (\ 5,30\ )} = 2.53$

[f] $F_{0.10\ (\ 5,30\ )} = 2.05$

[a] Degree of freedom

[b] Sum of square error

[c] Mean square error

[d] Variation ratio

[e,f] F obtained from the table

Table 60 The Statistical Comparisons of Percent THI Dissolved at Various Times and Dissoltion Rate Constants (Kd) from THI-PVP K-30 Coevaporates with Various Ratios of Drug: Carrier, 1:1 Physical Mixture and Pure THI (TC5-TC8, TP5, TO) at pH 7.5 Using one - way ANOVA.

Time (min)	Source of Variation	d.f[a]	SS[b]	MS[c]	F[d]
5	Treatment	5	28969.70	5793.93	337.74
	Error	30	460.15	15.34	
	Total	35	29429.80		
15	Treatment	5	22805.70	4561.14	146.46
	Error	30	934.26	31.14	
	Total	35	23740.00		
30	Treatment	5	14401.00	2880.21	230.34
	Error	30	375.13	12.50	
	Total	35	14776.20		
60	Treatment	5	5355.58	1071.12	162.90
	Error	30	197.26	6.57	
	Total	35	5552.84		
120	Treatment	5	530.72	106.14	3.58
	Error	30	889.73	29.65	
	Total	35	1420.44		
Kd (hr^{-1})	Treatment	5	88.94	17.78	55.94
	Error	30	9.53	0.32	
	Total	35	98.48		

[e] $F_{0.05\ (\ 5,30\ )} = 2.53$

[f] $F_{0.10\ (\ 5,30\ )} = 2.05$

[a] Degree of freedom

[b] Sum of square error

[c] Mean square error

[d] Variation ratio

[e,f] F obtained from the table

Table 61 The Statistical Comparisons of Percent THI Dissolved at Various Times and Dissoltion Rate Constants (Kd) from THI-PVP K-30 Coevaporates with Various Ratios of Drug: Carrier, and Pure THI (TC5-TC8, TO) Using T -test.

A. at pH 1.5

	Comparative Percent THI Dissolved at time (min)										Kd (hr^{-1})	
	5		15		30		60		120			
Prep.	TO	TC5	TO	TC5	TO	TC5	TO	TC5	TO	TC5	TP5	TC5
TC6	++	++	++	++	++	++	++	++	++	++	++	-
TC7	++	++	++	++	++	-	++	++	++	++	++	+
TC8	++	++	++	+	++	-	++	-	+	++	+	+
	TC7	TC8	TC7	TC8	TC7	TC8	TC7	TC8	TC7	TC8	TC7	TC8
TC6	++	++	++	++	++	++	++	+	++	-	++	++
TC7		-		-		-		-		++		-

B. at pH 4.5

Prep.	TO	TC5	TO	TC5	TO	TC5	TO	TC5	TO	TC5	TO	TC5
TC6	++	-	++	++	++	++	++	++	-	++	++	-
TC7	++	++	++	++	++	+	++	-	+	+	++	+
TC8	+	++	++	++	++	+	++	+	+	-	-	+
	TC7	TC8	TC7	TC8	TC7	TC8	TC7	TC8	TC7	TC8	TC7	TC8
TC6	++	++	++	++	+	+	++	++	++	++	++	++
TC7		-		-		-		+		-		-

C. at pH 7.5

Prep.	TO	TC5	TO	TC5	TO	TC5	TO	TC5	TO	TC5	TO	TC5
TC6	++	++	++	++	++	-	++	-	++	-	++	+
TC7	++	++	++	++	++	-	++	++	++	-	++	++
TC8	++	++	++	++	++	+	++	-	++	-	++	++
	TC7	TC8	TC7	TC8	TC7	TC8	TC7	TC8	TC7	TC8	TC7	TC8
TC6	++	++	+	++	-	+	++	-	++	++	++	++
TC7		+		-		+		-		-		-

+ = Significant difference ($p < 0.10$)
++ = Significant difference ($p < 0.05$)
- = Not Significant difference ($p > 0.10$)

2.2. In Vitro Absorption Studies

Typical Standard curves of THI in artificial plasma fluids pHs 7.5 and 9.0 were shown in Figures 60 - 61 and Tables 62 - 63, respectively. TC6 was studied compared to TO. The representative increasing of THI in phase II (artificial plasma fluids) absorbed from the test preparations in phase I (artificial gastric or intestinal fluids) were illustrated in Figures 62 - 64 and Table 64. The absorption of THI from TC6 through the artificial membranes was faster than from TO, hence the apparent absorption rate contstants of TC6 was statistically significant higher than TO's in all pH of artificial gastro-intestinal fluids ($p < 0.05$).

The correlation test between the apparent absorption and dissolution rate constants of THI from the test preparations were demonstrated in Figure 65. The result showed that there were statistically significant correlation of both parameters. ($p < 0.05$)

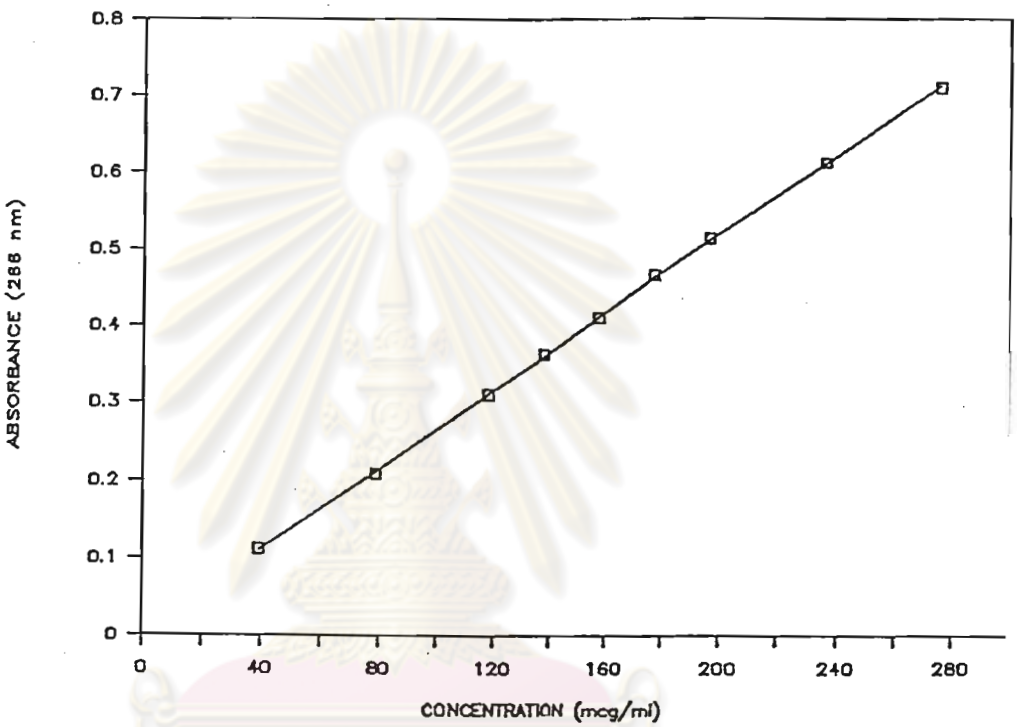


Figure 60 Typical Standard curve for Thiamphenicol concentration vs. absorbance in Artificial Plasma Fluid pH 7.5 estimated using linear regression

Table 62 Typical Standard Curve Data for Thiamphenicol Concentrations in Artificial Plasma Fluid pH 7.5 Estimated Using Linear Regression[1]

Standard No.	Conc. (mcg/ml)	Absorbance at 266 nm	Inversely estimated[2] Conc.(mcg/ml)	%Theory[3]
1	39.44	0.111	39.53	100.23
2	78.88	0.208	77.67	98.47
3	118.32	0.311	118.17	99.88
4	138.04	0.363	138.62	100.42
5	157.76	0.411	157.50	99.83
6	177.48	0.466	179.12	100.93
7	197.20	0.513	197.61	100.21
8	236.64	0.612	236.54	99.96
9	276.08	0.710	275.07	99.64
			Mean	99.95
			S.D.	0.67
			C.V.[4]	0.67 %

1. $r^2 = 0.9998$

2. Inversely estimated concentration $= \frac{\text{Absorbance} - 0.0105}{0.0025}$

3. %Theory $= \frac{\text{Inversely estimated concentration}}{\text{known concentration}} \times 100$

4. C.V. $= \frac{\text{S.D.}}{\text{Mean}} \times 100$

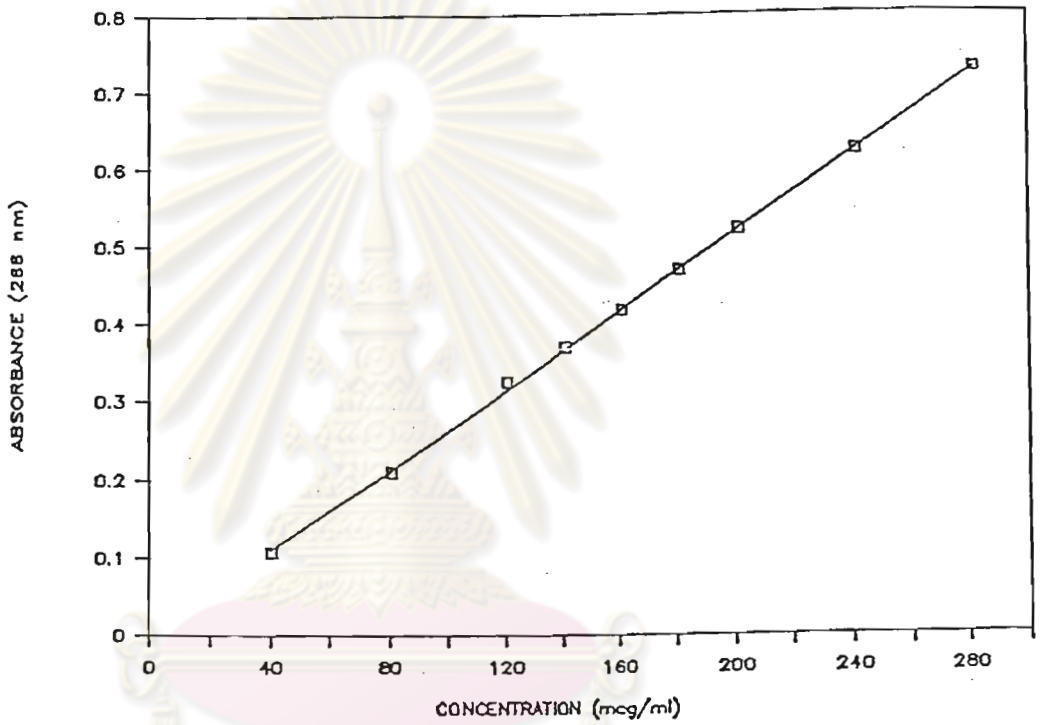


Figure 61 Typical Standard curve for Thiamphenicol concentration vs. absorbance in Artificial Plasma Fluid pH 9.0 estimated using linear regression

Table 63 Typical Standard Curve Data for Thiamphenicol Concentrations in Artificial Plasma Fluid pH 9.0 Estimated Using Linear Regression[1]

Standard No.	Conc. (mcg/ml)	Absorbance at 266 nm	Inversely estimated[2] Conc.(mcg/ml)	%Theory[3]
1	40.32	0.107	39.15	97.09
2	80.64	0.210	79.62	98.74
3	120.96	0.324	124.43	102.87
4	141.12	0.369	142.11	100.70
5	161.28	0.416	160.56	99.57
6	181.44	0.467	180.62	99.55
7	201.60	0.520	201.45	99.93
8	241.92	0.621	241.14	99.68
9	282.24	0.726	282.41	100.06
			Mean	99.80
			S.D.	1.53
			C.V.[4]	1.53 %

1. $r^2 = 0.9996$

2. Inversely estimated concentration $= \frac{\text{Absorbance} - 0.0074}{0.0025}$

3. $\%\text{Theory} = \frac{\text{Inversely estimated concentration}}{\text{known concentration}} \times 100$

4. $\text{C.V.} = \frac{\text{S.D.}}{\text{Mean}} \times 100$

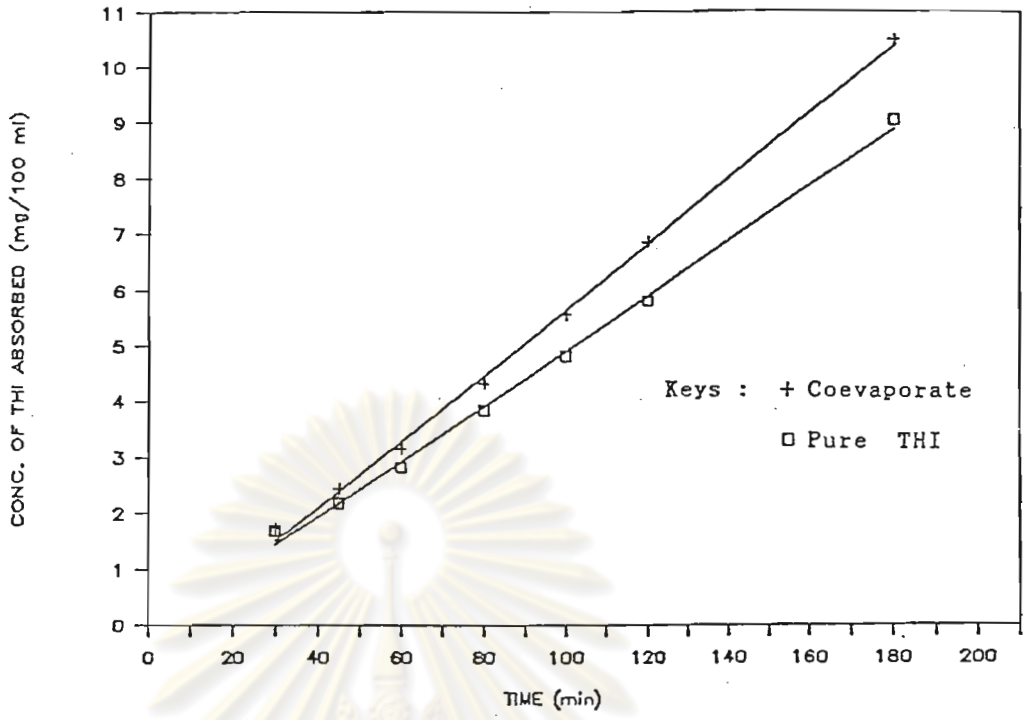


Figure 62 In Vitro Representative Increasing of Mean THI Concentration (in Phase II) Absorbed from 1:0.75 THI-PVP K-30 Coevaporate and Pure THI in Artificial Gastric Fluid pH 1.5

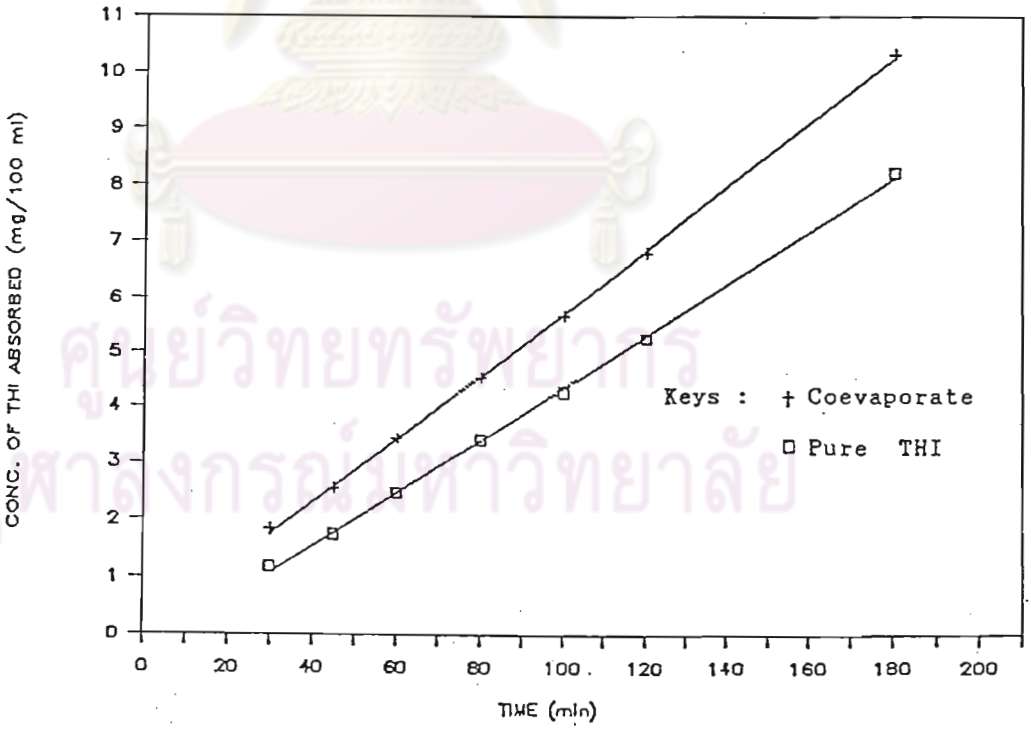


Figure 63 In Vitro Representative Increasing of Mean THI Concentration (in Phase II) Absorbed from 1:0.75 THI-PVP K-30 Coevaporate and Pure THI in Artificial Gastric Fluid pH 4.5

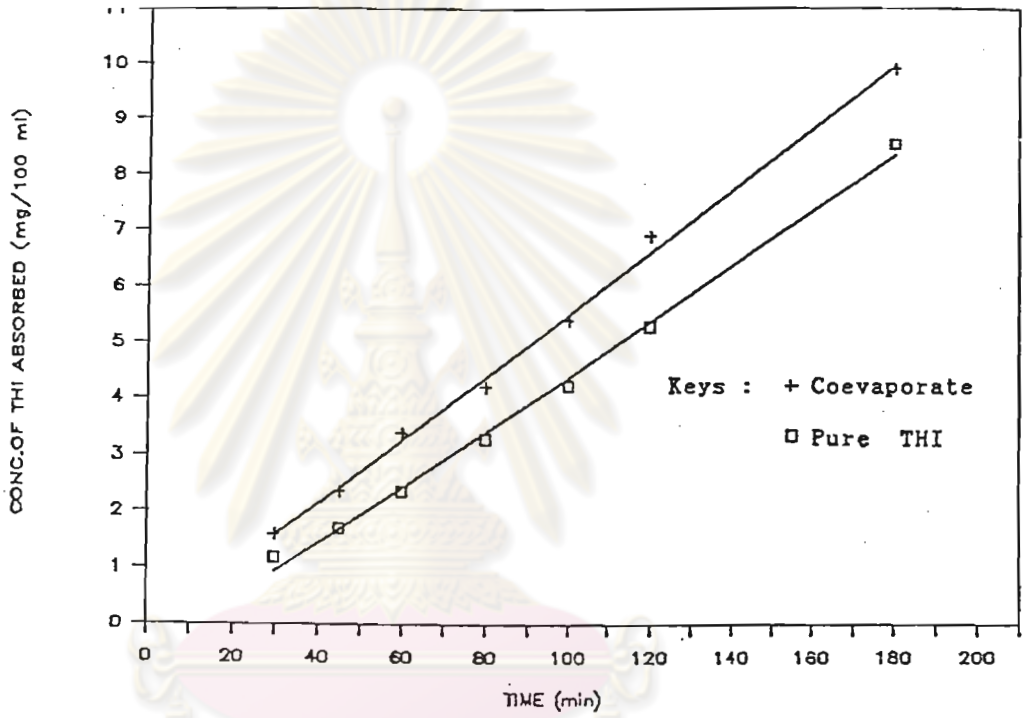


Figure 64 In Vitro Representative Increasing of Mean THI Concentration (in Phase II) Absorbed from 1:0.75 THI-PVP K-30 Coevaporate and Pure THI in Artificial Intestinal Fluid pH 7.5

Table 64 In Vitro Absorption Data of Thiamphenicol from 1:0.75 THI-PVP K-30 Coevaporate and Pure THI in Artificial Gastrointestinal Fluids pHs 1.5, 4.5 and 7.5

Time (min)	Concentration of Thiamphenicol Absorbed in Phase II (mg/100ml)					
	pH 1.5		pH 4.5		pH 7.5	
	1[a]	2[b]	1	2	1	2
30	1.75[c] (0.20)[d]	1.69 (0.12)	1.83* (0.12)	1.18 (0.10)	1.59 (0.04)	1.15 (0.17)
45	2.44 (0.06)	2.18 (0.12)	2.55* (0.18)	1.75 (0.08)	2.38 (0.10)	1.70 (0.13)
60	3.17 (0.04)	2.83 (0.10)	3.44** (0.08)	2.48 (0.06)	3.39 (0.03)	2.53 (0.42)
80	4.33* (0.09)	3.85 (0.02)	4.56** (0.10)	3.42 (0.06)	4.26* (0.05)	3.38 (0.05)
100	5.56* (0.12)	4.82 (0.04)	5.68** (0.20)	4.27 (0.04)	5.40** (0.01)	4.22 (0.02)
120	6.86* (0.23)	5.80 (0.08)	6.80** (0.21)	5.25 (0.04)	6.84** (0.05)	5.27 (0.05)
180	10.48** (0.16)	9.04 (0.06)	10.32** (0.05)	8.22 (0.02)	9.92** (0.05)	8.55 (0.05)
Ci_o[e] (mg%)	241.09 (0.69)	247.66 (1.84)	249.34 (0.69)	240.47 (1.53)	250.04 (1.63)	248.43 (1.58)
Ki[f] (hr^{-1})	0.07** (0.01)	0.05 (0.01)	0.06** (0.01)	0.04 (0.01)	0.06** (0.00)	0.04 (0.01)

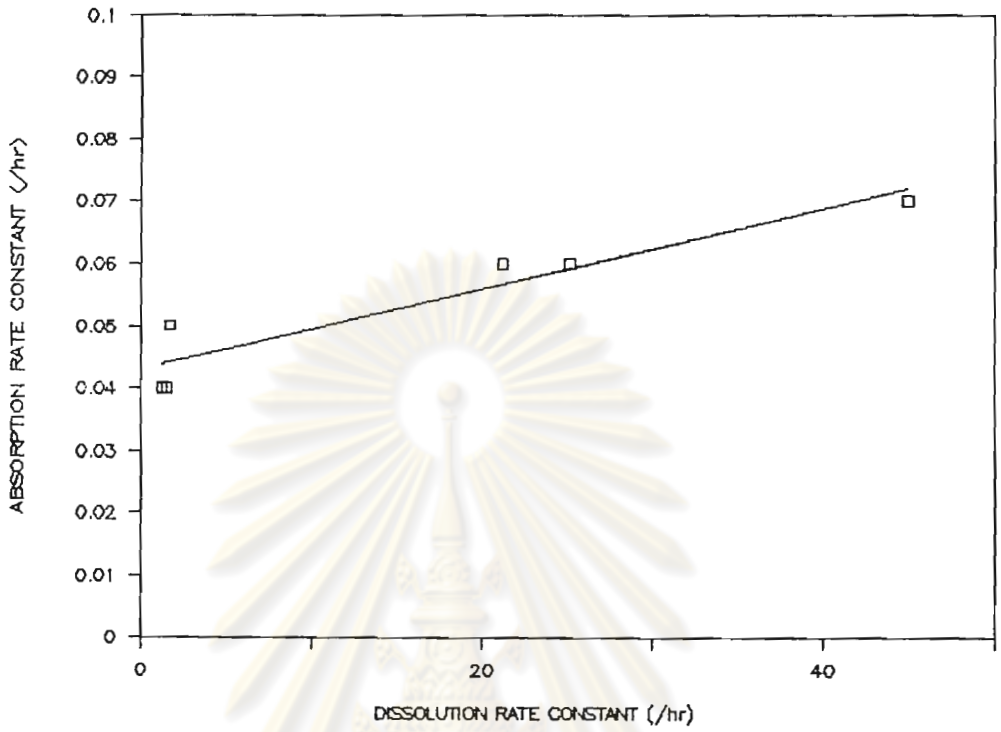
[a] Coevaporate [b] Pure drug

[c] The mean of two determinations [d] Standard error

[e] Starting concentration [f] In vitro absorption rate constant

* Significant higher than pure THI's ($p < 0.10$)

** Significant higher than pure THI's ($p < 0.05$)



Samples		Kd (hr^{-1})	Ki (hr^{-1})
Pure drug	at pH 1.5	1.66	0.05
	4.5	1.48	0.04
	7.5	1.23	0.04
Coevaporate	at pH 1.5	44.92	0.07
	4.5	25.14	0.06
	7.5	21.20	0.06
Correlation coefficient		0.94	
Degree of freedom		4	
t-value		5.68	
p-value		($p < 0.05$)	

Figure 65 Correlation between In Vitro Absorption Rate Constant (Ki) and Dissolution Rate Constant (Kd) of Thiamphenicol

2.3. Physical Characteristic Studies

2.3.1. X-ray Diffraction Studies

X-ray diffraction patterns of pure THI, PVP K-30, their physical mixture (TP5) and their coevaporates with various ratio of drug:carrier (TC5-TC8) were presented in Figure 66. Pure THI showed the diffraction peaks indicated to have crystalline forms. On the contrary, PVP K-30 exhibited no diffraction peaks that proved to have amorphous forms. The marked differance in the x-ray diffraction patterns of the physical mixture and coevaporates in these systems were observed. TP5 had the pattern containing the diffraction peaks of the drug. The diffraction patterns of TC5 and TC6 showed disappearance of those diffraction peaks that demonstrated the complete lack of crystallinity in these systems. However, in the patterns of TC7 and TC8, some of diffraction peaks were remained which demonstrated some crystalline forms of the drug in thes systems.

2.3.2. Differential Thermal Analysis

The thermograms of pure THI, PVP K-30, their physical mixture (TP5) and coevaporate (TC6) were shown in Figure 67. The thermogram of pure drug gave the characteristic melting endotherm at about 168°C. The thermogram of PVP K-30 showed a melting endotherm at about 73 °C. The thermograms of TP5 illustrated endotherms of

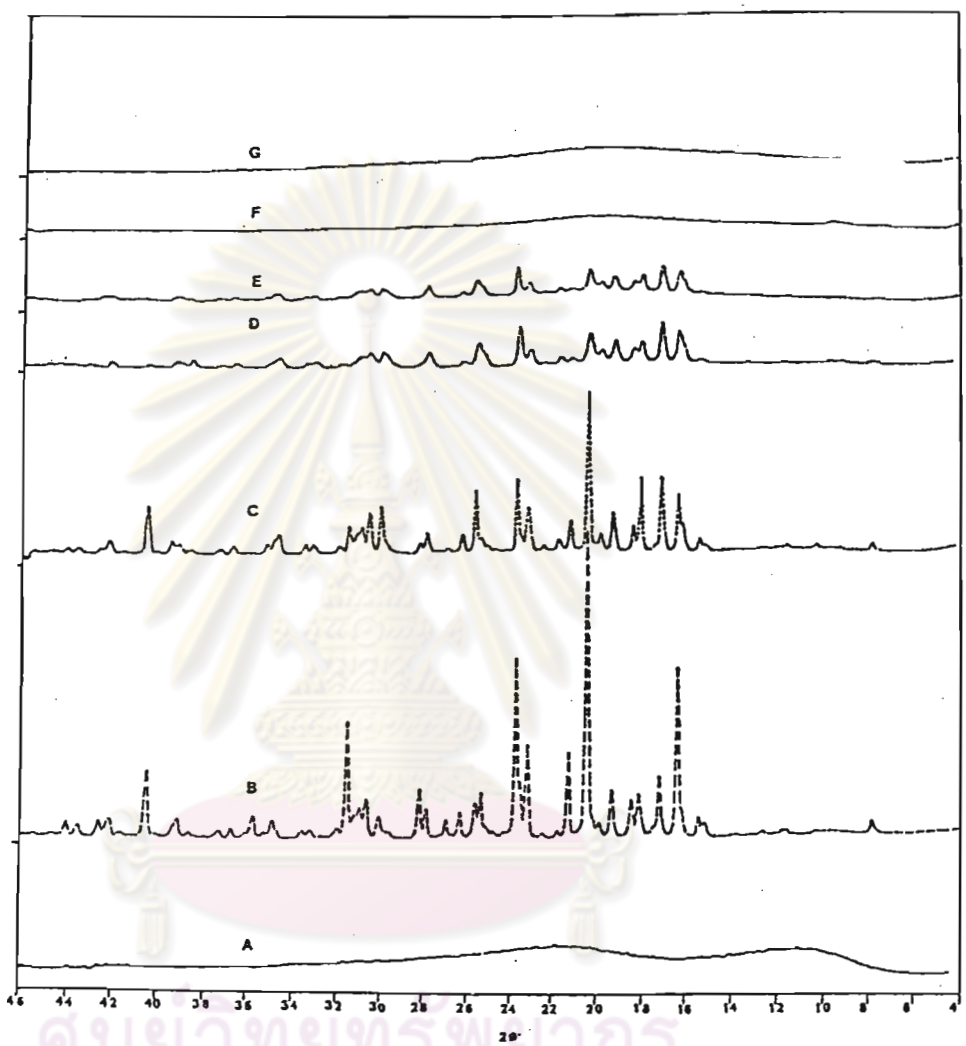


Figure 66 X-Ray Diffraction Patterns of THI-PVP K-30 System

(A) PVP K-30

(B) Pure THI

(C) 1:1 Physical Mixture

(D) 1:0.25 Coevaporate

(E) 1:0.50 Coevaporate

(D) 1:0.75 Coevaporate

(D) 1:1 Coevaporate

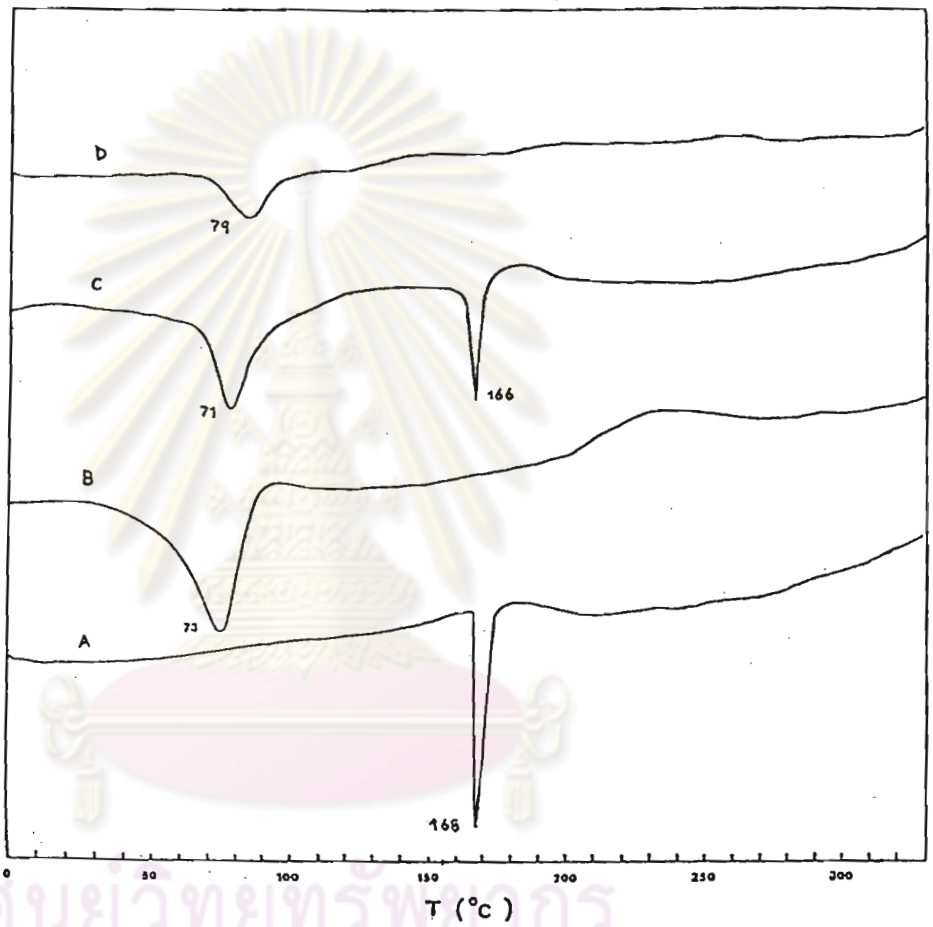


Figure 67 Differential Thermograms of 1:0.75 THI-PVP K30 System

(A) Pure THI

(B) PVP K-30

(C) Physical Mixture

(D) Coevaporate

both THI and PVP K-30. In the thermogram of TC6, endothermic peak of the drug disappeared. From this DTA result,it was reconfirmed that thiamphenicol is present in the amorphous form in PVP matrix.

CHAPTER IV

DISCUSSION AND CONCLUSION

The dissolution rates of naproxen and thiamphenicol powders are slow. This may be a result of their hydrophobicities and occurence of aggregation and agglomeration. Dissolution rate of naproxen was greater in dissolution medium pH 7.5 than pHs 4.5 and 1.5, respectively. But the contrary result was obtained for thiamphenicol. These are expected because of the difference of acid - base properties of the drugs. Naproxen is a weak acid (pKa = 4.3) (6) but thiamphenicol is a weak base that can form salts with acids such as hydrochloric or glycinic acid (7). Most of the acidic drug is ionized in the dissolution medium at the higher pH value. On the contrary, most of the basic drug is ionized in the dissolution medium at the lower pH value.

The coevaporates and physical mixtures of both drugs were prepared with various types of polymeric water-soluble carriers i.e. PEG 4000, 6000 , 20000, PVP K-30 and K-90. The observation obtained in the present studies demonstrated that all coevaporates with these polymers increased the dissolution of both naproxen and thiamphenicol. But in the cases of the physical mixtures, the increasing of dissolution was seen only for naproxen.

The 1:1 physical mixtures of naproxen and each

types of polymer systems showed increasing of dissolution rate as compared with the pure drug. This is likely due to the abilities of the water-soluble polymers to enhance the wettability (1,3,8) of hydrophobic naproxen particles. Since it is frequently difficult to disperse finely divided drug powders in a liquid because of entrapped or adsorbed air or some other contaminants (1,3). The polymers are readily soluble in an aqueous medium. Upon exposure of these systems to an aqueous medium, the polymers rapidly dissolved and a complete wetting of the drug occured at the same time and in this manner the effective surface area was increased, thereby increase the dissolution rate.

On the other hand, the physical mixtures of thiamphenicol and these polymers showed no enhancement in the dissolution rate and extent as compared to the pure drug. The dissolution of the drug from these systems, especially in PEG 20000 and PVP K-90 systems, were retarded. This could be attributed to the assumption of bulk effect due to the presence of the polymers in solution (9). Since the dissolution of the drug may be diffusion controled, therefore the increasing of viscosity due to the polymers incorpolated would reduce the diffusion rate of the drug in diffusion layer and also reduce the dissolution rate (1,9).

By comparing between the coevaporate and the corresponding physical mixture in each type of carrier

system. The similar results were obtained for both naproxen and thiamphenicol that the coevaporats exhibited faster dissolution than the corresponding physical mixtures as well as the pure control drugs. This could be explained on the basis that the two component systems are probably more intimately associated with one other than they are in physical mixture (8). Besides, both drug and carrier, initially, occur in solution and as the solvent is stripped from the solution a supersaturated system is formed (8). Finally, supersaturated solution loses enough solvent so that a very rapid precipitation of solute occurs. Such rapid crystallization is commonly known to cause the formation of very fine particles and herein seem to be the effectiveness of coevaporate system (3,8).

Furthermore, by comparing among the coevaporates with various types of carriers fixed at the same ratio 1:1 of drug:carrier. Large difference of dissolution behavior among these preparations were observed in both naproxen and thiamphenicol. Therefore, the physico-chemical nature of the polymers may play a predominant role in the dissolution of the drugs from these systems (10).

Polyethylene glycols are crystalline, inert and water-soluble polymer with two parallel helixes in a unit cell (1,11). Their high solubilities in a wide range of organic solvents favor solvent methods since highly concentrated PEG solutions are viscous and retard crystallization of drugs. During dissolution of the

dispersions, PEG may also wet the dispersed drug and promote dissolution rates (3). These compounds have the advantage for being spectroscopically transparant in the visible and UV regions. Therefore, assays and dissolution rate studies of drug - PEGs solid dispersions can be directly and easily achieved without complications due to an extraction procedures (3).

Polyvinylpyrrolidone (PVP) is also a high molecular weight polymer. Since PVP melts at temperatures only in excess of 275 C with decomposition, the drug-PVP solid dispersions can only be prepared by the solvent method. PVP is also soluble in a variety of organic solvents (1), an advantage in accommodating various drugs which posses limited solubility properties. The theories of dissolution from PVP dispersions have been comprehensively examined (12) and dissolution from the polymer proceed via wetting and hydrating of polymer surface which leads to swelling (1).

This investigation showed that PVP systems are more suitable carriers for enhancing the dissolution of both naproxen and thiamphenicol than PEG systems. This is because the fastest and highest dissolution rate and extent of the both drugs were obtained from PVP K-30 followed by PVP K-90, PEGs 4000, 6000, and 20000 coevaporates, respectively. These results also indicated the influence of the polymers molecular weight on dissolution of the drugs from their coevaporates. As can

be seen, the dissolution rate of the drugs decreased as the molecular weight of either PVP or PEG increased

Since there are many grades of PEG avilable, several researchers have attempted to quantify the effect of molecular weight on dissolution. The dissolution rates of pure polymers, without drugs, were inversely related to the molecular weight (1,13) i.e. the dissolution rate decreased as the molecular weight increased. Similar finding, the dissolution rate of drugs dispersed in PEG decreased as the molecular weight of the polymers increased were found for hydroflumethiazide (1), indomethacin (1), sulphadimidine (14) and tolbutamide (15). Such effects are probably explained on the basis of the dissolution rate of the PEG weight fraction themselves and also that the incorporation of a drug into the PEG may, for low molecular weight dispersion, produce a eutectic temperature below 37 C, thereby allowing melting of the dispersion to occur prior to dissolution and further increase dissolution rate (1). However, for other drugs the reverse trend that dissolution rate decrease with decreasing molecular weight are observed such as PEG dispersion includes those with papaverine (16), sulphamethoxydiazine (17).

The effect of molecular weight of PVP on the release of drug is more closely defined than for PEG. Generally, as the molecular weight of PVP increase the dissolution rate of drugs released from dispersion

decrease. This may be explained on the basis that as the molecular weight increases, the viscosities of the polymer solutions increase (thereby retarding dissolution) and the solubilities of polymer decrease (1). Similarly the process of swelling, before dissolution is foreshortened as the molecular weight decrease (1). The dissolution rates of many other PVP solid dispersed drugs decrease with increasing weight. Examples include sulphathiazole (12), sulphadimidine (18), chloramphenicol (19), and furosemide (20)

An attempt was made to find the coevaporate with the best dissolution whereas using the less amount of carrier. The effect of PVP K-30 weight fraction on dissolution of naproxen and thiamphenicol has also been studied. Results demonstrated that there was significantly progessive increase in the average percentage naproxen dissolved corresponding to the increased weight fraction of PVP K-30 in the coevaporates from the ratio 1:0.25 to 1:1 of naproxen:PVP K-30. This may be due to the fact that the heigher the dilution, the finer the crystalline size during precipitation wherein more drug can dissolved in the same environment (3). In case of thiamphenicol, the similar results were obtained from 1:0.25 to 1:0.75 ratio of thiamphenicol:PVP K-30. Furthermore, increasing the ratio to 1:1 showed insignificant decreasing of dissolution compared to the 1:0.75 ratio. This may be attributed to the fact that for 1:0.75 ratio of

thiamphenicol-PVP K-30 coevaporate, the amount of the carrier used had nearly reached their maximum solubilizing effect on the drug. Therefore, further increase in the amount of carrier to 1:1 ratio, the carrier might impart some viscosity around the drug particles. This effect would reduce the dissolution rate of the drug in the diffusion layer and hence retard the dissolution rate (1).

In conclusion, the best systems in this investigation for enhancing the dissolution of naproxen and thiamphenicol were 1:1 naproxen-PVP K-30 and 1:0.75 thiamphenicol-PVP K-30 coevaporates, respectively. Since they were the most economical systems and the hightest dissolution rates were obtained.

The in vitro absorption studies using Sartorious apsorption simulator (SM 16750) exhibited statistically significant higher absorption of the drugs from the coevaporates as compared to the pure drugs. However, only thiamphenicol system that there were significant correlation between dissolution and absorption rates.

In order to explain the increasing factors of dissolution and/or absorption of the drugs from the coevaporates, determination of physical characteristic of these systems using x-ray diffractometry and differential thermal analysis (DTA) were analyzed.

Figure 33 showed the powder x-ray diffraction patterns of naproxen-PVP K-30 dispersion systems.

Serveral sharp diffraction peaks were similarly presented in all pattern of the coevapolates with various ratio of drug:carrier and the 1:1 physical mixture . These patterns attributed to the presence of naproxen crystal dispersed in the amorphous form of PVP matrix. This appearance, especially in 1:1 ratio of the coevaporate, was supported by DTA that there was the existed endothermic peak of naproxen in the thermograms as showed in Figure 34. The shift of endothermic peaks may indicate eutectic property of this system. Hence, polymorphic modification did not contribute to the increased dissolution and also absorption rates of naproxen from the coevaporate. However, this could be explaind from several assumptions as follows :

1. Since rapid coprecipitation of drug and carrier during evaporating of solvent might result in the formation of very find particle, hence the specific surface area of drug particles might increase and so did the dissolution and absorption rates. (1,3,8)

2. A possible solubilization effect by the carrier may operate in the microenvironment (diffusion layer) immediately surrounding the drug particles in the early stage of dissolution since the carrier completely dissolves in a short time (1).

3. The absence of aggregation and agglomeration between fine crystallinities of the pure hydrophobic drug

may play a far more important role in increasing rates of dissolution and absorption (3).

4. Excellent wettability and dispersibility of the drug from the coevaporates with a water-soluble matrix, result in an increased dissolution rate of the drug in aqueous media (3).

5. An increased rate of dissolution and absorption may also occur if the drug crystallizes in a metastable form after solidification. A metastable, crystalline form has a higher solubility which, in turn, leads to a faster dissolution. (3)

On the other hand, the x-ray diffraction patterns of thiamphenicol-PVP K-30 dispersion systems were presented in Figure 66. These patterns demonstrated the absence of diffraction peaks of thiamphenicol in the coevaporates with the ratio of 1:0.75 and 1:1 which indicated that thiamphenicol was presented in the amorphous form. This was supported by the DTA of 1:0.75 thiamphenicol-PVP K-30 system. The thermograms showed in Figure 67 illustrated the disappeared endothermic peak of the drug in the coevaporate. The lack of the features characteristic of the endotherm of two components, indicates that an interaction occurs under these conditions (21). In addition, the appearence of physical characteristic of the coevaporates prepared were transparant, brittle and glassy. Hence, the formation of

glass solution or glass suspension may be obtained in the coevaporate. A glass solution is metastable. It can only produce weak and diffuse diffraction effects (1,3). In this sense a glass is also amorphous to x-ray diffraction (1).

The enhancement of dissolution and absorption rate of thiamphenicol from the coevaporate may be explained by the fact that the presence of the drug in amorphous or metastable form which have higher energy than crystalline form could promote higher dissolusion and absorption of the drug, in addition to the factors previously discussed.

Conclusion

Results of the present study indicated that a proposed technique, " coevaporation " , can be used as an alternative approach to enhance dissolution and absorption of the drugs that have the difference acid - base properties such as naproxen and thiamphenicol. In addition, such fast-dissolution of the coevaporates may improve bioavailability of drug and also reduce the possibility of local gastrointestinal irritation caused by certain drugs, allowing a short resident time in the gut (3).

However, further studies on the stabilities and the feasibility of using in manufacturing process, including in vivo evaluation of the coevaporates were suggested. Reduction of the dosages may be advised to

avoid the overdose toxicity.

Although, only two drugs were studied, it is believed that this useful technique could be applied to many other poorly water soluble drugs as well.

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APPENDICES

APPENDIX A

SOLID DISPERSIONS

The rate determining step in the absorption process for drugs of poor or slow solubility is generally their dissolution rates in gastro-intestinal fluids (1,3). Since drugs must dissolve before it can be absorbed. Enhancement dissolution properties generally increases the rate and extent of absorption and bioavailability of such drugs (3,22-24).

Several technique can be used to improve the dissolution properties of poorly soluble drugs, these include formation of polymorphs, salts, hydrates or solvates, complexation, surface adsorption and particle size reduction (1). Among these techniques, particle size reduction remains the most accepted method that can be easily and directly accomplished. However, fine particles may not always produce the expected faster dissolution and absorpion (2,3). This primarily results from the possible aggregation and agglomeration of the fine particles due to their increased surface energy and the subsequent stronger van der Waal's attraction between weak polar molecules or their poor wettability in water (3). These problems require better technologies in processing new drug delivery system.

In 1961, Sekiguchi and Obi (25) were the first to demonstrate the unique approach of solid dispersion to reduce particle size and increase dissolution rates. They prepared the eutectic mixture of sulfathiazole with the physiologically innert and easily soluble carrier, urea. The solid dispersion, obtained by solidification of the molten eutectic mixture, showed increased dissolution of sulfathiazole. Goldberg et al (26) reported a detail experimental and theoretical discussion of the advantage of solid solution over the eutectic mixture. This technique is now called the melt method.

In 1965, Tachibana and Nakamura (27) reported a new method for preparing solid dispersions (solvent method) of B - carotene in PVP. Chiou and Riegelman (28) later advocated the application of glass solution to increased dissolution rate. Since then, pharmaceutical application of solid dipersion systems were extensively studied and reviewed by a number of investigators (1-3). Therefore, a through understanding of this technique and principle will be essential in the effective application in drug-design technology.

Definition

The term "solid dispersion" was defined by Chiou and Riegeman (3) and refers to "the dispersion of one or more active ingredients in an inert carrier or matrix at solid state , prepared by the melting, solvent or melting-

solvent method". The selection of the carrier has an ultimate influence on the dissolution characteristic of the dispersed drug. Therefore:

- a poorly water soluble drug combined with a water-soluble carrier results in a fast release of the drug
- a good water-soluble drug combined with a slightly water-soluble carrier leads to a retardation of drug release from the matrix.

The solid dispersions may also called under various names, including solid solutions (3,26), eutectics (26), and coprecipitates or coevporates (29).

Selection of Suitable Carriers

A carrier chosen for dispersions to increase the dissolution rates of drugs should meet the following criteria (3) :

- freely water soluble with intrinsic rapid dissolution properties.
- pharmacologically inert.
- non-toxic.
- for melting method, it should meet these properties:
  : a melting point of not more than 200 C

: chemically, physically, and thermally stable.

: a relatively low vapor pressure, and

: miscibility with drug in liquid state.

- for solvent method, it should be soluble in a variety of organic solvents.

Some of the most frequently used ones are listed in Table 65 (1)

Table 65 Carrier Materials for Solid Dispersion.

Polyvinylpyrrolidone	Renex 650
Polyethylene glycol	Dextrose
Citric acid	Sucrose
Succinic acid	Galactrose
Pentaerythritol	Sorbitol
Pentaerythrityl tetraacetate	Moltose
Polyoxyethylene streate	Urea
Hydroxyalkylxanthins	Xylitol
Deoxycholic acid	Mannitol
Galactomannan	Polyoxamer
Methyl cellulose	Cyclodextrin

Method of Preparation

Solid dispersions can be obtained by three main procedures :

a. Melting method (fusion technique)

It consisted of melting the physical mixture of drug and water-soluble carrier by agitation, and then , by cooling, crushing, rapid solidification of the liquid obtained. This product is then crushed and calibrated (2,3). The drug must also dissolved in the molten carrier if the melting method is to be successful (3).

The advantage of this method is its simplicity and economy (3). However, it has the drawback of possible decomposition and evaporation of the constituents during melting at high temperature (3).

b. Solvent method (coprecipitation or coevporation technique)

In this method, the physical mixture of drug and carrier was dissolved in a common solvent, follow by evaporation of the solvent and pulverized the solid product which is usually called " coprecipitate " or " coevaporate " (1,3) .

This method dose not involve the risk of decomposition of component products by heat because most organic solvent require low temperature for their removal.

However, a certain number of drawbacks subsists : the choice of the solvent, the difficulty in complete removing solvent, the effect of solvent on the chemical stability of a drug and finally , the high cost of the process (1,3).

c. Melting-solvent method.

In this method, the drug is first dissolved in a suitable liquid solvent. The solution is incorporated directly into the melt of a carrier, and then the liquid solvent is removed to obtaine a solid dispersion (3).

This method has the advantage of both melting and solvent method. It has applied only to few drug-carrier systems such as spironolactone-PEG 6000 and griseofuvin-PEG 6000 (3).

Physical characteristics and Dissolution Properties

Chiou and Riegelman (3) classified the following six system as solid dispersions base on interaction between drug and carrier.

1. Simple eutectic mixtures

2. Solid solutions

3. Glass solutions and glass suspensions

4. Amorphous precipitates

5. Compound or complex formation between the drug and the carrier

6. Combination

1. Simple eutectic mixtures

Eutectics are prepared by rapid solidification of two melted components which show complete miscibility in the liquid state and negligible solid-solid solubility (1,3). Eutectic systems are characterized by crystalline components (1). Both components crystallize out simultaneously in very small particle size. The increase of the specific area due to the reduction of particle size generally increases rates of dissolution and absorption of poorly soluble drugs (3).

2. Solid solutions

A solid solution is simply represented a solid solute dissolved in a solid solvent. Often it is called a mixed crystal because the two components crytallize together in a homogeneous one phase system (3). A solid solution of poorly soluble drug in a rapidly soluble carrier achieves faster dissolution rates than an eutectic because the particle size of the drug in solid solution is reduced to a minimum state, i.e. its molecular size (3). In addition the absence of aggregation and agglomeration between hydrophobic drug particles contributes to faster release of the drug. Also a possible solubilization effect

by the carrier may operate in the microenvironment immediately surrounding the drug particle in form of a diffusion layer (3).

3. Glass solutions and glass suspensions

A glass solution is a homogeneous glassy system in which a solute dissolved in a glassy solvent (10). Glass solution is often characterized by transparancy and brittleness below the glass-transforming temperature. Glass produces only weak and diffuse diffraction effect, while crystallines can give strong and sharp diffraction effects (3). If a water-insoluble drug form a glass solution with a water-soluble, glass-forming carrier such as sucrose, dextrose, galactose (30), sorbitol (3), citric acid (31), and PVP (24,33), then the in situ dissolved drug is released into the aqueous medium rapidly because the carrier quickly dissolved upon exposure to the medium. The lattice energy in the glass solution is much less than in a solid solution because of its similarity with the liquid solution. Therefore, the dissolution rate of drugs in the glass solution is theoretically faster than the solid solution. (3)

4. Amorphous precipitations in a crytalline carrier

Preparation of dispersion may lead to the formation of amorphous deposits of the drug. These are metastable and convert on storage to more crytalline form (3). Since the amorphous form is the highest energy

Method for Determination of Solid Dispersion Systems

Mamy methods can give information regarding the physical nature of a solid dispersion system. In most case combination of several method are required. The commonly used methods are as the follow :

1. Thermal analysis includes :

- Differential Thermal Analysis (DTA) and Differential Scanning Calorimetry (DSC) : effective thermal method for study phase equilibria of pure compounds or mixture. Differential effects, associated with physical or chemical changes are automatically recorded as a function of temperature or time as the substance is heated at a uniform rate. In addition to thawing and melting , polymorphic transitions, evaporation, sublimation, dissolvation and other types of decomposition can be quantitative detected. (3)

- Thermomicroscopic method : polymerized microscopy with a hot stage to study diagram of binary systems (3).

2. X-ray Diffraction :

The intensity of the X-ray reflection from a sample is measured as a function of diffraction angles. The diffraction method is an important and efficient tool in study the physical nature of solid dispersion. It

detects in simple way crystalline and amorphous components. In simple eutectic system, diffraction peaks of each crystalline component can be found. In an interstitial solid solution, the diffraction of the solute component disappear. (3)

3. Dissolution Rate Determination :

This method gives interesting parameters in preparing solid dispersion system. In most cases solid dispersions cause an acceleration of dissolution in gastric fluids. Under standard conditions the degree of crystallinity can be studied. (3)

4. Thermodynamic Methods :

The phase diagrams of eutectic and solid solution systems can be evaluated by some thermodynamic parameters (1,3). The knowlage of heats of fusion, entropies and partial pressures at various composition enables the determination of the solubility gap below the solid-liquid equilibrium temperature (3).

Conclusion

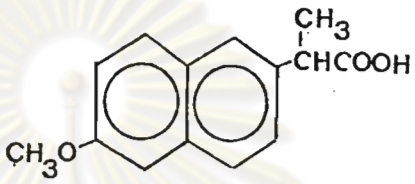
Solid dispersions have been studied over twenty years. Although they show advantages in many cases, very few preparations are so far marketed. Reasons for this are stability and technology problems. After shelf storage in many systems recrytallization occurs and significant change in dissolution rate of the rug appear (1,3).

The possibility or suitability of this technique for each drug should be directly and individually studied.

APPENDIX B

Drugs and Carriers Used in This Investigation

Naproxen (7,34, 36)



(6-Methoxy-2-naphthyl) propionic acid

Description A white or almost white, odourless or almost odourless, crystalline powder.

Melting Point about 156 °C

Apparent pKa 4.2

Solubility -practically insoluble in water.

-soluble 1 in 25 of alcohol, 1 in 15 of chloroform, 1 in 40 of ether, and 1 in 20 of methyl alcohol.

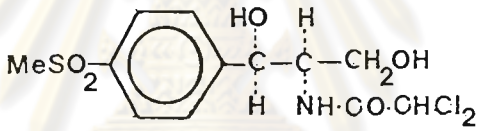
Use analgesic, antipyretic, and anti-inflammatory. It used in treatment of rheumatoid arthritis, and other rheumatic or musculoskeletal disorders, dysmenorrhoea and acute gout.

Dose 500 - 1000 mg daily in divided dose.

Adverse Effectes the most common adverse effects are gastrointestinal disturbances. Other are allergic reaction, dizziness, nervousness.

Pharmacokinetics Naproxen are readily absorbed from the gastrointestinal tract and peak plasma concentions are attained 2 to 4 hours after ingestion. At therapeutic concentration naproxen is more than 99% bound to plasma proteins and has a plasma half-life of between 12 and 15 hours. Approximately 95% of a dose is excreted in urine as naproxen and 6-O-desmethylnaproxen and their conjugates.

Thiamphenicol (36,37)



2,2 Dichloro-N-[(∝Rβ R)-β-hydroxy- ∝ -hydroxy-methyl-4-mesylphenethy] acetamide.

Description A fine white to yellowish-white odourless crystalline powder with a bitter taste.

Melting point 163-167 °C.

Solubility -slightly soluble in water, ether and ethyl acetate.

-soluble in methyl alcohol.

-very soluble in dimethylacetomide.

Use antibiotic, anti-infection.

Dose 1.5 g dialy in divided dose.

Adverse Effect Thiamphenicol is probably more liable to cause reversible depression of bone marrow than chloramphenicol but there have been fewer reports of aplasia so far.

Pharmacokinetics Thiamphenicol is absorped from the gastrointestinal tract and serum concentrations of 3 to 6 mcg/ml have been achieved 2 hours after a 500 mg dose. 50 to 70% of its oral dose is excreted unchanged in the urine in 24 hours, only 5 to 10 % is conjugated with glucuronic acid in the liver and also excreted in the bile.

Polyethylene Glycols (PEG) (1,38)

Polyethylene glycols are mixtures of condensation polymers of ethylene oxide and water. The molecular weight varies from 200 to 20000 that indicated by a number in the name.

PEG 4000

Description An almost tasteless, creamy-white, hard, wax-liked solid or flaskes or white free-flowing powder with a faint characteristic odour.

Average Molecular Weight 3100 to 3700.

Melting Point 53-56 °C.

Solubility -soluble 1 in 3 ml of water
-soluble 1 in 2 ml alcohol and chlorofrom
-practically insoluble in ether.

PEG 6000

Description An almost odourless, creamy-white, hard, wax-like solid or flakes or white free-following powder.

Averge Molecular Weight 5000 to 7000.

Melting Point about 60 °C.

Solubility -soluble 1 in 2 ml of water and chloroform.
-freely soluble in alcohol.
-practically insoluble in ether.

PEG 20000

Description A white odourless wax-like solid.

Average Molecular Weight 18000 to 22000.

Melting Point -

Solubility -soluble in water.
-freely soluble in alcohol and chloroform.
-practically insoluble in ether.

Use -stabilizers of emulsion, water-miscible bases for ointments, bases for suppositories.
-tablet binders and lubricants.
-water-soluble carriers for solid dispersion with poorly water-soluble drugs.

LD_{50} Orally in rats (55) PEG 4000 : 59 g/kg
PEG 6000 : >50 g/kg

Polyvinylpyrrolidone (PVP) (1,39)

Description A fine white or very slightly cream-coloured, odourless or almost odourless, tastless. The viscosity in aqueous solution, relative to water, is expressed as K-value, ranging from 10 to 95.

Melting Point over 275 C with decomposition.

Solubility -soluble 1 in 1 to 1.5 ml of water.
-soluble 1 in 10 to 12 ml of alcohol and 1 in 1.5 ml of boiling alcohol.
-practically insoluble in chloroform and ether.

Use -suspending and dispersing agent.
-tablet binding and granulating agent.
-carrier for solid dispersions.

Absorption and Fate Povidone does not appear to be absorbed from the gastro-intestinal tract and mainly excreted in urine, the rate being dependent upon the molecular weight.

APPENDIX C

Typical Dissolution Rate Determination

Dissolution Rate constants (Kd) of drugs could be calculated base on the assumption that the dissolution was first order process according to Equation 1.

$$\ln (B_{\infty} - Bt) = \ln B_{\infty} - kt \qquad \text{Eq...1}$$

Bt = amount of drug dissolved at time t

t = time

B_{∞} = maximum amount of drug dissolved at the last time

ln (B_{∞} - Bt) were ploted against time , which should give a straight line. (Figures 68,69) Dissolution rate constant (Kd) was the slope of the straight line (k) that could be calculated from the linear regression .

Examples for determining of dissolution rate constants of naproxen and thiamphenicol were shown in Tables .. and .., respectively.

Table 66 Example for Determination of Dissolution Rate Constant of Naproxen from It's powder at pH 1.5

TIME (min)	Bt (mg)	$\ln(B_\infty - Bt)$
2	2.52	3.05
5	4.17	2.97
10	9.85	2.63
15	15.66	2.08
20	18.69	1.61
25	19.95	1.33
30	21.09	0.98
45	22.35	0.33
60	22.86	-0.12
80	23.23	-0.68
100	23.36	-0.97
120	23.49	-1.38
150	23.74	ERR
180	23.74	ERR

Regression Output:

Constant	2.611351
Std Err of Y Est	0.460490
R Squared	0.920084
No. of Observations	12
Degrees of Freedom	10
X Coefficient(s)	-0.03805
Std Err of Coef.	0.003546

Kd = X Coefficient(s)

= 0.03805 min^{-1}

= 2.28 hr^{-1}

Figure 68 First Order Plot of Dissolution of Naproxen at pH 1.5

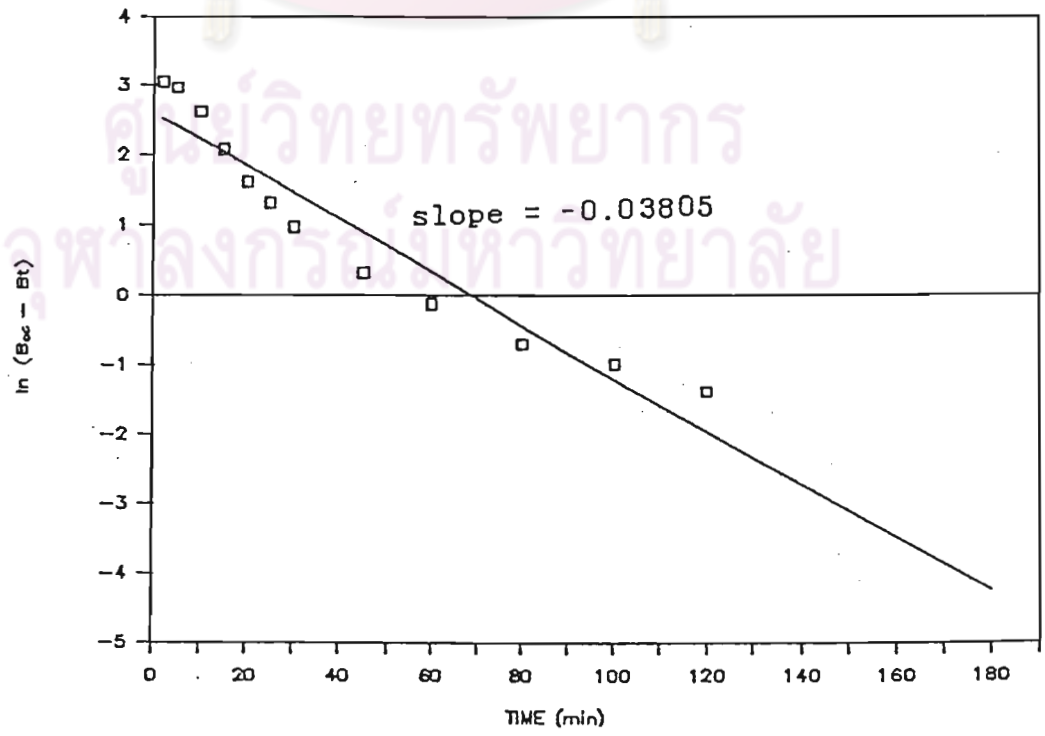


Table 67 Example for Determination of Dissolution Rate Constant of Thiamphenicol from It's powder at pH 1.5

TIME (min)	Bt (mg)	$\ln(B_\infty - Bt)$
2	7.85	5.41
5	23.96	5.21
10	38.15	5.03
15	44.74	4.88
20	51.99	4.73
25	57.89	4.59
30	62.65	4.46
45	72.41	4.14
60	80.81	3.73
80	86.37	3.33
100	91.21	2.76
120	93.29	2.37
150	96.46	1.04
180	97.59	ERR

Regression Output:

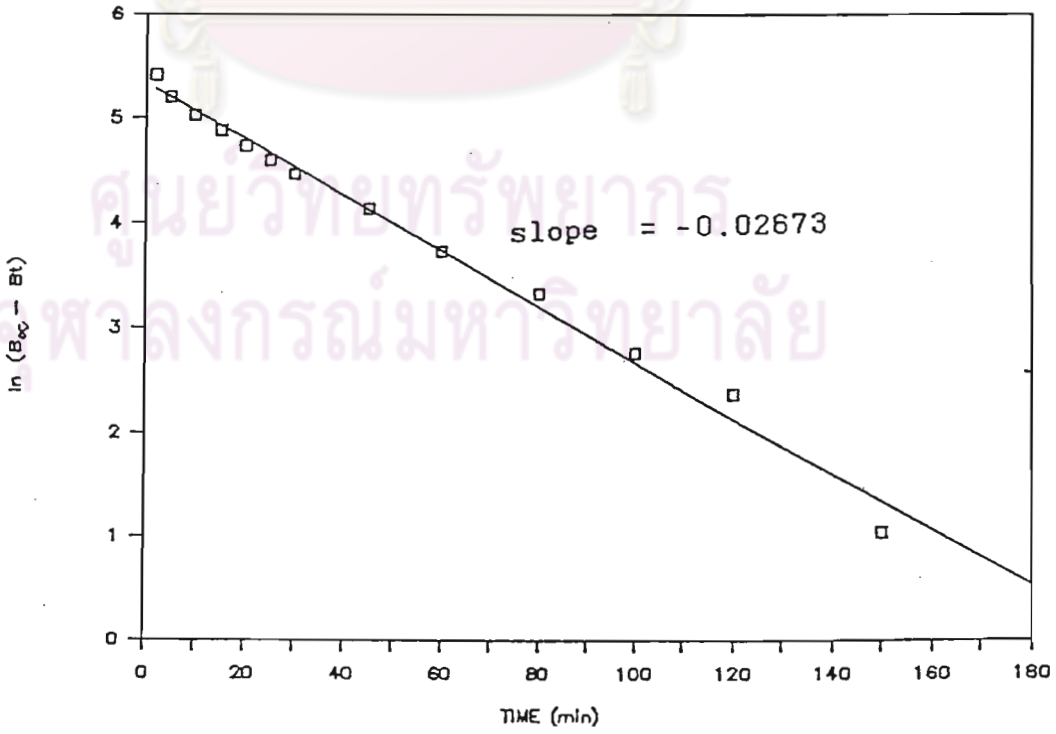
Constant	5.340187
Std Err of Y Est	0.135921
R Squared	0.989767
No. of Observations	13
Degrees of Freedom	11
X Coefficient(s)	-0.02673
Std Err of Coef.	0.000819

Kd = X Coefficient(s)

= 0.02673 min^{-1}

= 1.60 hr^{-1}

Figure 69 First Order Plot of Dissolution of Thiamphenicol at pH 1.5



APPENDIX D

Sartorius Absorption Simulator

Principle (40,41)

The SM 16750 Sartorius Absorption Simulator is a model, in which is simulated the in vivo passive transport of the drugs by diffusion through special artificial lipoid barriers. It was included that the apparatus provided a suitable adaptation to each drug (lipophily , ionisation) and is used mainly for the study of the absorption of new drug, and for the formulatory development of pharmaceutical preparations .

The apparatus consists principally of two containers for the artificial gastro-intestinal fluid (phase I) and artificial plasma (phase II) .(Figure 70)

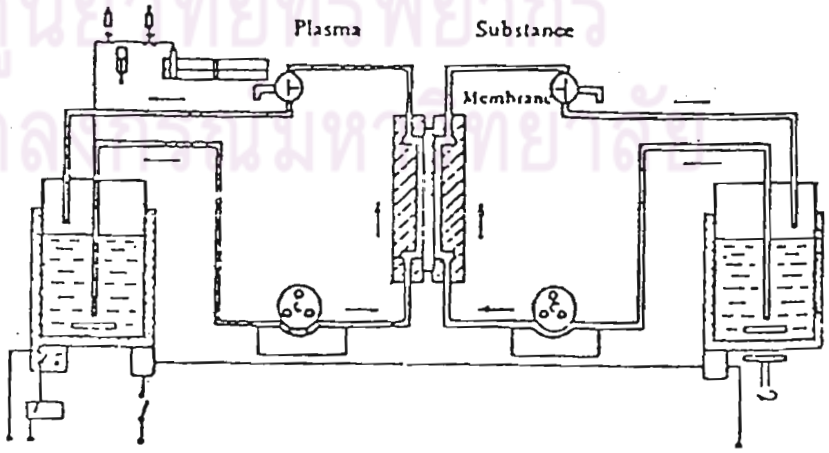


Figure 70 Schematic diagram of the SM 16750 Sartorius Model

Since it was only that the portion of a drug which was dissolved in phase I could be diffused , the model was applied by using a small filter attached the end of the tube connection . When the time began , the aqueous phases were circulated by a peristaltic pump. The temperature and flow rate should be checked during the experiment, $39 \pm 1\ ^{\circ}C$ and 10-15 $ml.min^{-1}$, respectively. Samples taken from each container at equal time intervals, were determined for the concentration of the drug. The rate of absorption of a drug from the gastro-intestinal tract can be expressed by the absorption rate constant , Ka or Ki. Similarly , the specific diffusion of a drug in the Absorption Simulator can be expressed as the diffusion rate constant ,Kdf . Because of these two quantities are found to be directly proportional to each other , the in vitro absorption rate constant ,Ki , can be calculated directly from the diffusion rate constant ,Kdf.

Evaluation of Results

The diffusion of a drug through the lipid barrier was a first order reaction . At the first period, the movement of the substance was predominately from phase I to phase II . Then back diffusion happened from phase II to phase I and finally the diffusion rates should be equal in both directions. The diffusion rate constant ,Kdf, was most easily determined during the first period because the increase in concentration of the drug in phase II usually had a linear relationship with the time .

Determination of the Starting Concentration , Ci_o.

The sum of drug concentrations in phase I and II were plotted against times , which should give a straight line paralleled to the abscissa. The starting concentration in phase I was obtained by extrapolation of the graph.(Figure 71)

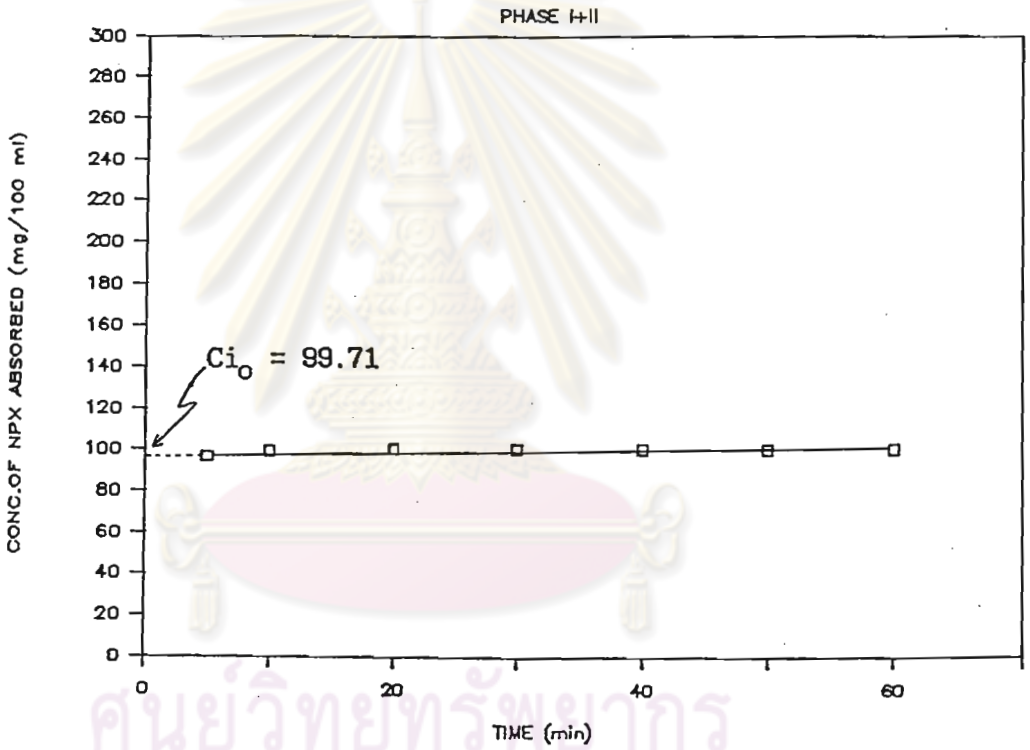


Figure 71 Determination of the Starting Concentration, Ci_o, Example for Absorption of Naproxen in Artificial intestinal fluid pH 7.5

Calculation of the Diffusion Rate Constant, Kdf.

A simple plot of the drug concentration in phase II or Cii against time at first period showed a straight line (Figure 72).

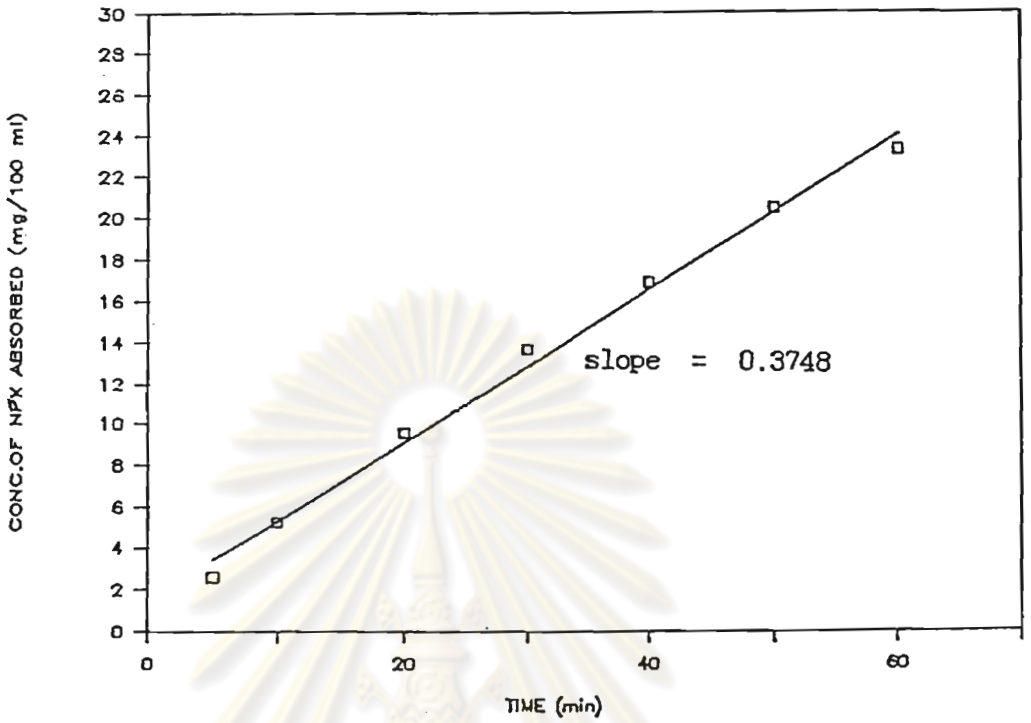


Figure 72 Determination of the Diffusion Rate Constant, Kdf, Example for Absorption of Naproxen in Artificial Intestinal Fluid pH 7.5

The diffusion rate contstant was calculated from the slope of this line according to Equation 2.

$$Kdf = \frac{(Cii_2 - Cii_1)}{(T_2 - T_1)} \cdot \frac{1}{Ci_o} \cdot \frac{Vii_o}{F} \quad (cm.min^{-1}) \qquad Eq...2$$

Ci_x = Drug concentration in phase II at time T_x $(mg.ml^{-1})$

Vii_o= Volume of the aqueous phase II at time T_o = 100 ml

F = Effective barrier area (cm^2) = 80 cm^2

T_x = Time (min)

Ci_o = Starting concentration (mg%)

Calculation of the In Vitro Absorption Rate Constant, Ki.

The in vitro absorption rate constants were calculated according to the Equation 3.

$$Ki = G \cdot (Kdf - Kdf_o) \qquad (min^{-1}) \qquad Eq...3$$

Ki = In vitro absorption rate constant (min^{-1})

Kdf = Diffusion rate constant $(cm.min^{-1})$

Kdf_o = Diffusion rate constant through the pores of the barriers with unfilled lipid phase $(cm.min^{-1})$

Absorption in	G-factor (cm^{-1})	Kdf_o ($cm.min^{-1}$)
Stomach	4.3	0.00007
Small intestine	10.0	0.00018

For example, the absorption from stomach and intestine naproxen were calculated :

Absorption from stomach (pH 1.5) :

According to Equation 2 and Equation 3, where the slope was 0.0258 $mg\%.min^{-1}$ (r^2=0.99), Vii_o was 100 ml, Ci_o was 3.31 mg%,F was 80 cm^2, G was 4.3 cm^{-1} and Kd_o was 0.00007 $cm.min^{-1}$,therefore

$$Kdf = \frac{0.0258 \times 100}{3.31 \times 80} = 0.0078 \quad cm.min^{-1}$$

$$Ki = 4.3 \times (0.0078-0.00007) = 0.0334 \quad min^{-1}$$

$$= 2.00 \quad hr^{-1}$$

Absorption from stomach (pH 4.5) :

According to Equation 2 and Equation 3, where the slope was 0.0662 mg%.min^{-1} (r^2=0.99), Vii_o was 100 ml, Ci_o was 9.64 mg%,F was 80 cm^2, G was 4.3 cm^{-1} and Kd_o was 0.00007 $cm.min^{-1}$,therefore

$$Kdf = \frac{0.0662 \times 100}{9.64 \times 80} = 0.0086 \quad cm.min^{-1}$$

$$Ki = 4.3 \times (0.0086-0.00007) = 0.0365 \quad min^{-1}$$

$$= 2.19 \quad hr^{-1}$$

Absorption from intestine (pH 7.5) :

According to Equation 2 and Equation 3, where the slope was 0.3748 mg%.min^{-1} (r^2=0.99), Vii_o was 100 ml, Ci_o was 99.71 mg%,F was 80 cm^2, G was 10 cm^{-1} and Kd_o was 0.00018 $cm.min^{-1}$,therefore

$$Kdf = \frac{0.3748 \times 100}{99.71 \times 80} = 0.0047 \quad cm.min^{-1}$$

$$Ki = 10 \times (0.0047 - 0.00018) = 0.0452 \quad min^{-1}$$

$$= 2.71 \quad hr^{-1}$$

Similarly, the absorption rate contstant of thiamphenicol and the coevaporates could be calculated.

APPENDIX E

STATISTICS

1. Mean ($\bar{X}$)

$$\bar{X} = \frac{\sum X}{N}$$

2. Standard Deviation (S.D.)

$$S.D. = \sqrt{\frac{\sum (X - \bar{X})^2}{N - 1}}$$

3. Standard Error (S.E.)

$$S.E. = \frac{S.D.}{\sqrt{N}}$$

4. Testing the Difference of Two Means.

(by T - test)

Let μ_1 , μ_2 = Population means

X_1 , X_2 = Sample means

σ_1 , σ_2 = Population variances.

s_1 , s_2 = Sample standard deviation

N_1 , N_2 = Sample size

The null hypothesis $H_o : \mu_1 = \mu_2$

The alternative hypothesis $H_a : \mu_1 \neq \mu_2$

The statistic t was given as $t = \dfrac{(\bar{X}_1 - \bar{X}_2) - (\mu_1 - \mu_2)}{S_p}$

First homogeneity of variance is tested for using the F test, which is defined as follows:

$$F = \frac{(s_1)^2}{(s_2)^2}$$

where $(s_1)^2$ = the larger of the two sample variances

$(s_2)^2$ = the smaller of the two sample variances

With this test we are evaluating the null hypothesis of no difference between the two population variances. If the F is not significant, the null hypothesis stands.

4.1 if $\sigma_1^2 \neq \sigma_2^2$

The statistic t was given as

$$t = \frac{\bar{X}_1 - \bar{X}_2}{S_p}$$

Where S_p^2 was the pooled variance

$$S_p^2 = \frac{(s_1)^2}{N_1} + \frac{(s_2)^2}{N_2}$$

With degree of freedom

$$d.f. = \frac{\left[\frac{s_1^2}{N_1} + \frac{s_2^2}{N_2}\right]^2}{\frac{\left[\frac{s_1^2}{N_1}\right]^2}{N_1 - 1} + \frac{\left[\frac{s_2^2}{N_2}\right]^2}{N_2 - 1}}$$

4.2 if $\sigma_1^2 = \sigma_2^2$

The test statistic for this case was

$$t = \frac{\bar{X}_1 - \bar{X}_2}{S_p}$$

Where the pooled variance

$$S_p^2 = \left[\frac{1}{N_1} + \frac{1}{N_2}\right]\left[\frac{\left[N_1 - 1\right] S_1^2 + \left[N_2 - 1\right] S_2^2}{N_1 + N_2 - 2}\right]$$

And degree of freedom

$$d.f. = N_1 + N_2 - 2$$

Comparing this t value with $t_{(tab)}$ for $\frac{\alpha}{2}$ that is obtained from the table

If $t > t_{(tab)}$, we reject the null hypothesis that $\mu_1 = \mu_2$ and accept the alternative hypothesis.

If t is not significant, the null hypothesis stands.

5. Correlation Coefficient Test

The correlation coefficient is a quantitative measure of the relation ship of correlation between two variable (X and Y)

$$r = \frac{N\sum XY - \sum X \sum Y}{\sqrt{[N\sum X^2 - (\sum X)^2][N\sum Y^2 - (\sum Y)^2]}}$$

where r = Corelation coefficient

N = the number of X, Y paris

Test of Zero Correlation

Let ρ = the true correlation coeffient, estimated by r

The null hypothesis $H_o : \rho = 0$

The alternative hypothesis $H_a : \rho \neq 0$

$$t_{n-2} = \frac{|r\sqrt{N-2}|}{\sqrt{1-r^2}}$$

The value of t is refered to a t distribution with (n-2) degree of freedom . If the t is not significant, the null hypothesis stands.

6. Analysis of Variance (ANOVA)

Analysis of Variance for Completely Randomized Design

Source of Variation	Sum of Squares	d.f.	Mean Square	Variation Ratio
Among-group (Treatment)	$\sum_{j=1}^{k} n_j (\bar{X}_{.j} - \bar{X}_{..})^2$	$k-1$	$\frac{SS_{among}}{k-1}$	$V.R. = \frac{MS_{among}}{MS_{within}}$
Within-group (Error)	$\sum_{j=1}^{k} \sum_{i=1}^{n_j} (X_{ij} - \bar{X}_{.j})^2$	$N-k$	$\frac{SS_{within}}{N-k}$	
Total	$\sum_{j=1}^{k} \sum_{i=1}^{n_j} (X_{ij} - \bar{X}_{..})^2$	$N-1$		

where X_{ij} = Observed value at Treatment j

$i = 1,2,\ldots,n$

$j = 1,2,\ldots,k$

$$T_{.j} = \sum_{i=1}^{n_j} X_{ij}$$

$$\bar{X}_{.j} = \frac{T_{.j}}{n_j}$$

$$T_{..} = \sum_{j=1}^{k} T_{.j}$$

$$\bar{X}.. = \frac{T..}{N}$$

$$N = \sum_{j=1}^{k} n_j$$

Comparing the V.R. value with the critical value F obtained from table at degree of freedom (k-1) and (N-k).

If $F > F_{(tab)}$, we reject the null hypothesis that $\mu_1 = \mu_2 = \mu_3 = \ldots = \mu_k$ and accept the alternative hypothesis.

If F is not significant, the null hypothesis stands.

VITAE

Miss Sirirat Pinsuwan was born on June 7, 1961, in Songkla, Thailand. She got her degree in Bachelor of Science in Pharmacy (first class honors) in 1985 from Faculty of Pharmacy, Prince of Songkla University.