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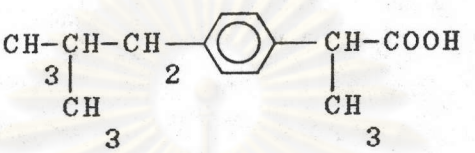
APPENDICES

APPENDIX A

Drug and Carriers Used in This Investigation

Ibuprofen (35-38)



2-(4-Iso-butylphenyl) propionic acid

Description A white or almost white powder or crystals with a characteristic odour and a slight taste.

Melting Point 75-77.5 °C

Apparent pKa 5.2

Solubility -practically insoluble in water.
-soluble 1 in 1 ml of chloroform, 1 in 1.5 ml of alcohol and acetone, 1 in 2 ml of ether.
-soluble in aqueous solutions of alkali hydroxides and carbonates.

Use analgesic, antipyretic, anti-inflammatory.
In low doses, it is effective in the management of mild to moderate pain and fever. In higher doses, it is anti-inflammatory, used in treatment of rheumatoid arthritis, osteoarthritis and other musculoskeletal disorders.

Dose 600 to 1200 mg daily in divided doses.
Maximum total daily dosage is 2400 mg.

Adverse Effects the most common adverse effects are gastrointestinal disturbances. Others are allergic reaction, dizziness, nervousness, etc.

Pharmacokinetics Ibuprofen is absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 2 hours after ingestion. Ibuprofen is extensively (99%) bound to plasma proteins and has a half-life of about 2 hours. It is rapidly excreted in the urine mainly as metabolites and their conjugates.

Polyethylene glycol (Macrogols, Polyoxyethylene glycols, PEG, Lutrol E®) (1, 50)

They are mixtures of condensation polymers of ethylene oxides and water. The molecular weight, indicated by the number in the name, vary from 200 to over 20000 and the molecular weight fractions used for solid dispersions vary from 1000 (soft unctious solids) to 20000 (hard brittle crystals) (1).

PEG 4000

Average molecular weight 3100 to 3700.

Description an almost tasteless, creamy-white, hard, wax-like solid or flakes or white free-flowing powder with a faint characteristic odour.

Melting point 53-56 °C.

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

PEG 6000

Average molecular weight 5000 to 7000.

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

Melting point about 60 °C.

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

Use - stabilizers of emulusion, water-miscible bases for ointments, bases for suppositories.
- tablet lubricants, binders and coating (PEG 6000).
- higher molecular weight PEGs have been extensively used as water soluble carriers to solid dispersion with poorly water-soluble drugs.

LD_{50} Orally in rats (51) PEG 4000 : 59 g/kg (divided doses)
PEG 6000 : >50 g/kg

Polyvinylpyrrolidone (Povidone, Polyvidone, PVP, Kollidon®, Plasdone®) (1,52)

Description a fine white or very slightly cream-coloured, odourless or almost odourless, tasteless powder. It is hygroscopic.

Melting point over 275 °C with decomposition (1).

Solubility - soluble in water, alcohol, chloroform and isopropyl alocohol.

- practically insoluble in acetone and ether.

The viscosity in aqueous solution, relative to water, is expressed as a K-value, ranging from 10 to 95.

Use - suspending and dispersing agent.

- tablet binding, granulating and film-coating agent.
- carrier for solvent-prepared solid dispersions.

Cross-linked Polyvinylpyrrolidone (Polyvinylpolypyrrolidone, Crospovidone, PVPP, Kollidon CL®, Polyplasdone XL®)

Description white, fine tasteless powder with faint characteristic odour.

Solubility - insoluble in water and conventional solvents.

Molecular weight cannot be determined since it is insoluble in all conventional solvents.

Use tablet disintegrant.

Urea (Carbamide) (53)

Urea is a normal physiological metabolite and, despite being a mild diuretic, is generally regarded as nontoxic and pharmacologically inert.

Description colourless, slightly hygroscopic, odourless or almost odourless, prismatic crystals or pellets, or white crystalline powder, with a cooling saline taste.

Melting point 132-135°C.

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 osmotic diuretic with a low renal threshold.

Absoption fairly rapidly absorbed from the gastrointestinal tract.

Mannitol (54)

A hexahydric alcohol related to mannose. It is isomeric with sorbitol.

Description A white odourless crystalline powder or granules with a sweetish taste.

Melting point 165 to 169°C.

Solubility -soluble 1 in 6 ml of water and 1 in 18 ml of glycerol.
-slightly soluble in alcohol and pyridine.
-practically insoluble in chloroform and ether.
-soluble in solutions of alkali carbonates and hydroxides.

Use -diluent and excipient in pharmaceutical preparations.
-osmotic diuretic (intraveuous infusion).

Absorption only small amounts are absorbed from the gastrointestinal tract.

APPENDIX B

Determination of Minimum Proportion of Carrier for Each Dispersion System

According to the fact that bulk volume of the carrier have to be more than, or at least, equal to that of the drug powder in order to homogeneously disperse or entrap the drug molecules in the carrier, the minimum proportions of drug and carriers using in this study had to be determined from their bulk densities.

$$\text{bulk density} = \frac{\text{weight}}{\text{bulk volume}}$$

The bulk density can be determined by 3-tap method (55) :

A sample of about 50 ml of powder; which has previously been passed through a U.S.Standard No.20 sieve, is carefully introduced into a 100-ml graduated cylinder. The cylinder is dropped onto a hard wood surface 3 times from a height of 1 inch at 2-second intervals. The bulk density is then obtained by deviding the weight of the sample in grams by the final volume in ml of the sample contained in the cylinder.

Table 19 Bulk Density of Ibuprofen and Some Carriers Used in This Study

Compound	Bulk Density*	Bulk Volume (ml of 1 g)
IBU	0.4705	2.125
PEG 4000	0.6308	1.585
PEG 20000	0.6026	1.659
Urea	0.7545	1.325

* the average of three determinations

As a result of bulk volumes from Table 19, the minimum IBU:carrier ratio for each solid dispersion system should be 1:2.

APPENDIX C

Standard Curve

Table 20 Typical Standard Curve Data for Ibuprofen Concentrations in Carbondioxide-Free Deionized Water Estimated Using Linear Regression

Standard No.	Concentration (mcg/ml)	Optical Density at 222 nm	Inversely estimated concentration (mcg/ml)		% Theory
1	1.0	0.049	0.946		94.60
2	2.0	0.096	2.017		100.85
3	5.0	0.232	5.117		102.34
4	7.5	0.341	7.602		101.36
5	10.0	0.451	10.109		101.09
6	12.5	0.557	12.525		100.20
7	15.0	0.664	14.964		99.76
8	20.0	0.880	19.888		99.44
				Mean	99.96
				S.D.	2.35
				C.V.	2.36%

1. $r^2 = 0.9998$, $a = 0.04387$, $b = 0.00751$ ($Y = aX + b$)

2. Inversely estimated concentration = (Optical Density - 0.00751)/0.04387

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

4. Coefficient of variation (C.V.) = $\frac{\text{S.D.}}{\text{Mean}} \times 100$

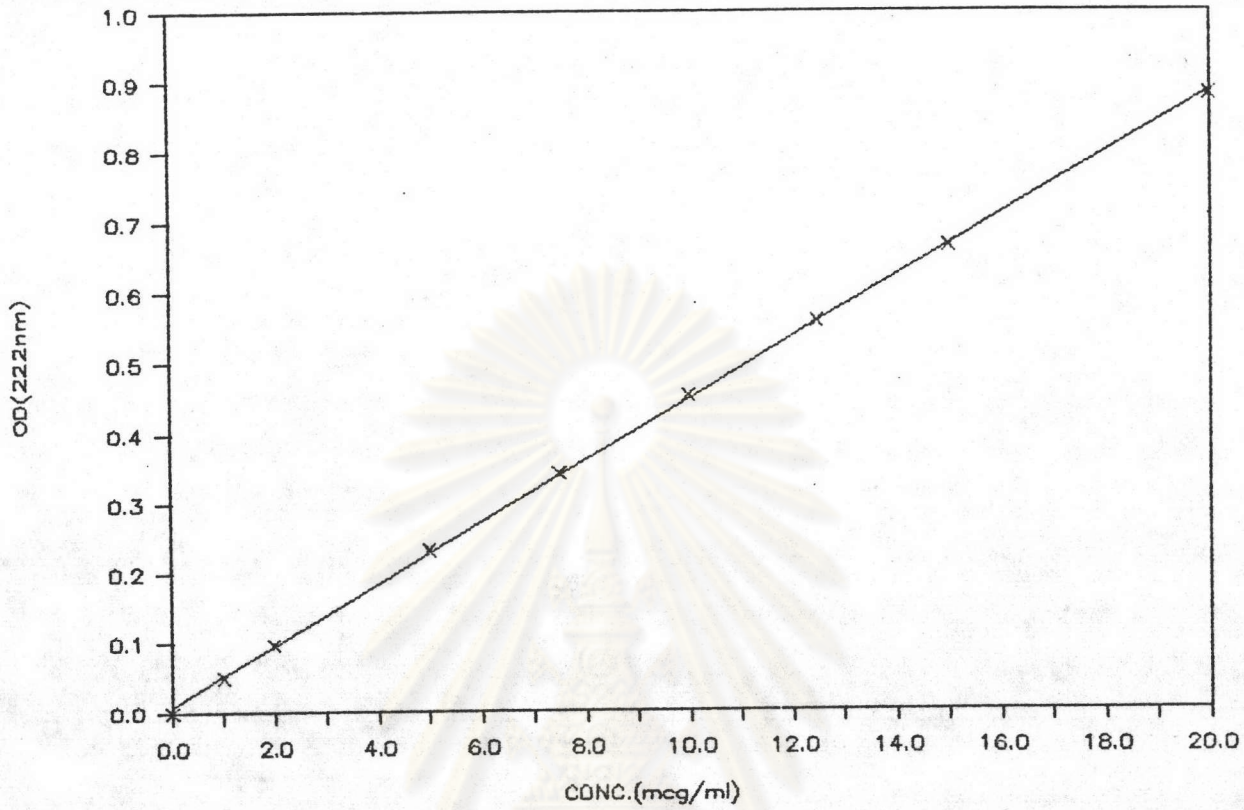


Figure 13 Typical standard curve for ibuprofen concentration in carbondioxide-free deionized water.

$Y = 0.04387\ X + 0.00751 \qquad (r^2 = 0.9998)$

APPENDIX D

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. Testing the Concentration Difference of Two Means

(by Student's t-test)

Let μ_1, μ_2 = Population means

$\bar{X}_1, \bar{X}_2$ = Sample means

σ_1^2, σ_2^2 = Population variances

s_1, s_2 = Sample standard deviation

N_1, N_2 = Sample size

The null hypothesis $H_0 : \mu_1 = \mu_2$

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

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

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.

4. Analysis of Variance (ANOVA)

Table 21 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.

VITA

Miss Panida Asavapichayont was born on November 15, 1961, in Bangkok. She got her degree in Bachelor of Science in Pharmacy in 1984 from Faculty of Pharmaceutical Science, Chulalongkorn University.