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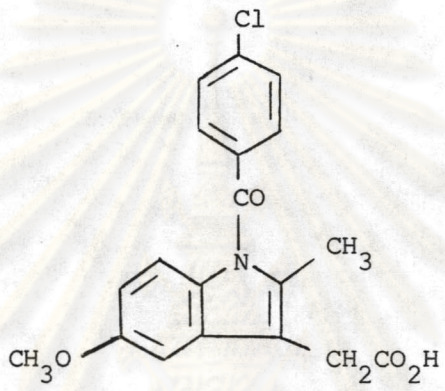
APPENDIX

Indomethacin (8,29-33)

Synonyms : Indometacine (MK 615)

Proprietary Names : Inacid, Indocid, Indocin, etc

Chemical formula :



1-(p-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid [53-86-1]

$C_{19}H_{16}ClNO_4$ (357.81)

Description : Pale-yellow to yellow-tan, crystalline powder that is odorless, or has a slight odor, and has a slightly bitter taste; light sensitive, stable in air and stable in heat under the usual prevailing temperature conditions, one polymorphic form melts at about 155℃, the other at about 162℃. pKa 4.5

Solubility : Practically insoluble in water; soluble 1 gm in 50 ml of alcohol, 30 ml of chloroform and 40 ml of ether, soluble in acetone and castor oil, soluble in alkaline solutions but with decomposition. Stable in neutral or slightly acidic media.

Uses : Indomethacin has analgesic, anti-inflammatory and antipyretic actions. It is used in the treatment of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and other rheumatic disorders. It is also used in the treatment of acute gout.

Doses : The usual initial dose is 25 mg two to four times daily with food, increared, if required, to 150 to 200 mg. In acute gout, 50 mg may be given 3-4 times daily. The optimum dose for PDA is 0.2 mg/kg body weight.

Indomethacin is readily absorbed from the gastro-intestinal tract; peak plasma concentrations are reached ½ to 2 hours after dose. More than 90% is bound to plasma proteins. It is metabolised in the liver and kidney and is excreted in the urine, mainly as the glucuronide, and to a much lesser extent in the faeces. It is also excreted in milk. Most-frequent untoward action is gastrointestinal reactions. The drug is contraindicated in children, pregnant women and nursing mothers, patients with gastrointestinal problems, and in patients allergic to aspirin.

Table XIV : Observed Solubilities of Indomethacin (I) in Various Mixed Solvents at 30℃

1. Glycerine and Water system

Glycerine(%)	Water(%)	Specific Gravity		Dilution	Average Absorbance		Solubilities of I.(μg/ml)	
		mixed solvent	I.solution	factor	0 day	2 months	0 day	2 months
10	90	1.0261	1.0251	16.67	0.046	0.045	33.33	32.54
20	80	1.0565	1.0558	16.67	0.044	0.045	31.75	32.54
30	70	1.0821	1.0811	16.67	0.059	0.060	43.65	44.44
40	60	1.1112	1.1102	16.67	0.052	0.050	38.09	36.51
50	50	1.1394	1.1385	16.67	0.057	0.061	42.06	45.24
60	40	1.1658	1.1641	16.67	0.079	0.078	59.52	58.73
70	30	1.1913	1.1893	25	0.061	0.062	67.86	69.05
80	20	1.2151	1.2131	25	0.089	0.087	101.19	98.81
90	10	1.2371	1.2333	25	0.123	0.125	141.67	144.05
100	0	1.2576	1.2486	25	0.173	0.173	201.19	201.19

2. Propylene Glycol and Water System

Propylene Glycol(%)	Water(%)	Specific Gravity		Dilution	Average Absorbance		Solubility of I.(µg/ml)	
		mixed solvent	I.solution	factor	0 day	2 months	0 day	2 months
10	90	1.0065	1.0068	250	0.040	0.041	428.57	440.48
20	80	1.0162	1.0141	250	0.037	0.039	392.86	416.67
30	70	1.0225	1.0231	250	0.034	0.032	357.14	333.33
40	60	1.0295	1.0301	250	0.034	0.034	357.14	357.14
50	50	1.0350	1.0359	333.33	0.031	0.034	428.57	476.19
60	40	1.0383	1.0392	333.33	0.045	0.044	650.79	634.92
70	30	1.0393	1.0412	333.33	0.087	0.088	1317.46	1333.33
80	20	1.0391	1.0401	2000	0.031	0.033	2571.43	2761.90
90	10	1.0370	1.0398	2000	0.063	0.064	5619.05	5714.28
100	0	1.0338	1.0367	5000	0.051	0.051	11190.48	11190.48

3. Polyethylene Glycol 400 and Water System

PEG 400 (%)	Water(%)	Specific Gravity		Dilution	Average Absorbance		Solubility of I.(µg/ml)	
		mixed solvent	I.solution	factor	0 day	2 months	0 day	2 months
10	90	1.0166	1.0169	16.67	0.042	0.041	30.16	29.37
20	80	1.0354	1.0351	25	0.044	0.045	47.62	48.81
30	70	1.0522	1.0515	25	0.096	0.096	109.52	109.52
40	60	1.0704	1.0702	100	0.075	0.074	338.09	333.33
50	50	1.0869	1.0873	500	0.042	0.043	904.76	928.57
60	40	1.1011	1.1019	1000	0.118	0.119	5428.57	5476.19
70	30	1.1117	1.1143	4000	0.060	0.062	10666.67	11047.62
80	20	1.1183	1.1251	5000	0.054	0.053	11904.76	11666.67
90	10	1.1214	1.1292	10000	0.098	0.098	44761.90	44761.90
100	0	1.1221	1.1306	10000	0.102	0.103	46666.67	47142.86

4. Alcohol and Water System

Alcohol (%)	Water(%)	Specific Gravity		Dilution	Average Absorbance		Solubility of I.(µg/ml)	
		mixed solvent	I.solution	factor	0 day	2 months	0 day	2 months
10	90	0.9864	0.9869	250	0.045	0.046	488.09	500.00
20	80	0.9737	0.9752	250	0.049	0.047	535.71	511.90
30	70	0.9604	0.9608	250	0.048	0.047	523.81	511.90
40	60	0.9459	0.9476	250	0.058	0.057	642.86	630.95
50	50	0.9275	0.9293	250	0.109	0.108	1250.00	1238.09
60	40	0.9070	0.9117	2000	0.033	0.035	2761.90	2952.38
70	30	0.8834	0.8865	2000	0.062	0.062	5523.81	5523.28
80	20	0.8585	0.8638	2000	0.104	0.106	9523.81	9714.28
90	10	0.8315	0.8403	5000	0.082	0.081	18571.43	18333.33
100	0	0.8018	0.8141	5000	0.092	0.094	20952.38	21428.57

5. Sorbitol Solution and Water System

Sorbitol Solution(%)	Water(%)	Specific Gravity		Dilution	Average Absorbance		Solubility of I.(µg/ml)	
		mixed solvent	I.solution	factor	0 day	2 months	0 day	2 months
10	90	1.0311	1.0308	12.5	0.035	0.035	18.45	18.45
20	80	1.0627	1.0620	12.5	0.036	0.034	19.05	17.86
30	70	1.0933	1.0919	12.5	0.033	0.035	17.26	18.45
40	60	1.1239	1.1235	12.5	0.038	0.038	20.24	20.24
50	50	1.1553	1.1548	12.5	0.041	0.039	22.02	20.83
60	40	1.1854	1.1853	12.5	0.050	0.052	27.38	28.57
70	30	1.2148	1.2148	12.5	0.055	0.056	30.36	30.95
80	20	1.2444	1.2442	12.5	0.088	0.089	50.00	50.59
90	10	1.2726	1.2723	12.5	0.067	0.067	37.50	37.50
100	0	1.2985	1.3001	12.5	0.092	0.091	52.38	51.78

6. Polyethylene Glycol 200 and Water System

PEG 200 (%)	Water(%)	Specific Gravity		Dilution	Average Absorbance		Solubility of I.(µg/ml)	
		mixed solvent	I.solution	factor	0 day	2 months	0 day	2 months
10	90	1.0165	1.0167	50	0.164	0.163	380.95	378.57
20	80	1.0332	1.0338	50	0.152	0.154	352.38	357.14
30	70	1.0507	1.0508	100	0.088	0.086	400.00	390.48
40	60	1.0682	1.0685	100	0.119	0.119	547.62	547.62
50	50	1.0837	1.0842	500	0.053	0.054	1166.67	1190.48
60	40	1.0975	1.0977	500	0.122	0.123	2809.52	2833.33
70	30	1.1081	1.1096	2000	0.091	0.091	8285.71	8285.71
80	20	1.1154	1.1205	2000	0.127	0.128	11714.28	11809.52
90	10	1.1199	1.1265	2000	0.184	0.182	17142.86	16952.38
100	0	1.1229	1.1300	2000	0.147	0.148	13619.05	13714.28

7. 1,4 Dioxane and Water System

1,4-Dioxane (%)	Water(%)	Specific Gravity		Dilution	Average Absorbance		Solubility of I.(µg/ml)	
		mixed solvent	I.solution	factor	0 day	2 months	0 day	2 months
10	90	1.0086	1.0081	100	0.108	0.108	495.24	495.24
20	80	1.0170	1.0158	100	0.108	0.106	495.24	485.71
30	70	1.0242	1.0227	100	0.135	0.125	623.81	576.19
40	60	1.0307	1.0290	500	0.061	0.052	1357.14	1142.86
50	50	1.0342	1.0338	500	0.147	0.109	3404.76	2500.00
60	40	1.0381	1.0456	2000	0.126	0.087	11619.05	7904.76
70	30	1.0382	1.0463	5000	0.100	0.051	22857.14	11190.48
80	20	1.0365	1.0451	5000	0.106	0.084	24285.71	19047.62
90	10	1.0369	1.0413	5000	0.129	0.079	29761.90	17857.14
100	0	1.0380	1.0374	5000	0.121	0.065	27857.14	14523.81

Buffer Systems (34)

A Sorensen's Phosphate Buffer System.

Solution A : Sodium Acid Phosphate Solution (0.15 M)

Sodium acid phosphate, anhydrous	8.00 gm
Sterile distilled water, q.s.	1000 ml

Solution B : Disodium Phosphate Solution (0.15 M)

Disodium phosphate, anhydrous	8.47 gm
Sterile distilled Water, q.s.	1000 ml

pH	Solution A (ml)	Solution B (ml)
5.9	90	10
6.5	70	30
7.0	40	60
7.4	20	80
8.0	5	95

Polynomial Regression (25)

This is the most frequently used curvilinear response model in practice, because of its ease in handling as a special case of the general linear regression model.

Polynomial Regression Models

Polynomial regression models can contain one, two, or more than two independent variables. Furthur, the independent variable can be present in various powers.

One Independent Variable-Second Degree has been used in this investigation because the true response function is unknown, but a second degree polynomial is a good approximation to the true function.

The model is written as :

$$y_i = \beta_o + \beta_1 x_i + \beta_2 x_i^2 + \varepsilon_i \qquad \text{(Eq. 24)}$$

As can be seen, the independent variable appears in the second degree. The response function for model (Eq. 24) is

$$E(y) = \beta_o + \beta_1 x + \beta_2 x^2 \qquad \text{(Eq. 25)}$$

which is a parabola and is frequently called a quadratic response function.

The regression coefficient β_o represents the mean response of y when $x = 0$ if the scope of the model includes $x = 0$ Otherwise,

β_o has no separate meaning of its own in the model. The regression coefficient β_1 is often called the linear effect coefficient while β_2 is called the curvature effect coefficient.

Fitting of Model

The least squares normal equations for the second-order polynomial are

$$x'xb = x'y$$

where;

$$b = \begin{bmatrix} b_o \\ b_1 \\ b_2 \end{bmatrix}, \quad x'x = \begin{bmatrix} n & \Sigma x_i & \Sigma x_i^2 \\ \Sigma x_i & \Sigma x_i^2 & \Sigma x_i^3 \\ \Sigma x_i^2 & \Sigma x_i^3 & \Sigma x_i^4 \end{bmatrix}, \quad x'y = \begin{bmatrix} \Sigma y_i \\ \Sigma x_i y_i \\ \Sigma x_i^2 y_i \end{bmatrix}$$

This yields the normal equations in terms of the algebraic version as :

$$\begin{aligned} \Sigma y_i &= nb_o + b_1 \Sigma x_i + b_2 \Sigma x_i^2 \\ \Sigma x_i y_i &= b_o \Sigma x_i + b_1 \Sigma x_i^2 + b_2 \Sigma x_i^3 \\ \Sigma x_i^2 y_i &= b_o \Sigma x_i^2 + b_1 \Sigma x_i^3 + b_2 \Sigma x_i^4 \end{aligned} \qquad \text{(Eq. 26)}$$

Analysis of Variance Results

ANOVA Table for second-order polynomial model.

Source of variation	SS	df	MS
Regression	$SSR = b'x'y' - n\bar{y}^2$	2	$MSR = SSR/2$
Error	$SSE = y'y - b'x'y'$	n-3	$MSE = SSE/n-3$
Total	$SSTO = y'y - n\bar{y}^2$	n-1	

where; $b' = [b_o\ b_1\ b_2]$, $\bar{y} = \Sigma y_1/n$, $y'y = \Sigma y_i^2$

Coefficient of Multiple Determination (R^2)

For a descriptive measure of the degree of relation between x_i and y_i, the R^2 is used and calculated using an equation

$$R^2 = \frac{SSR}{SSTO} \qquad \text{(Eq. 27)}$$

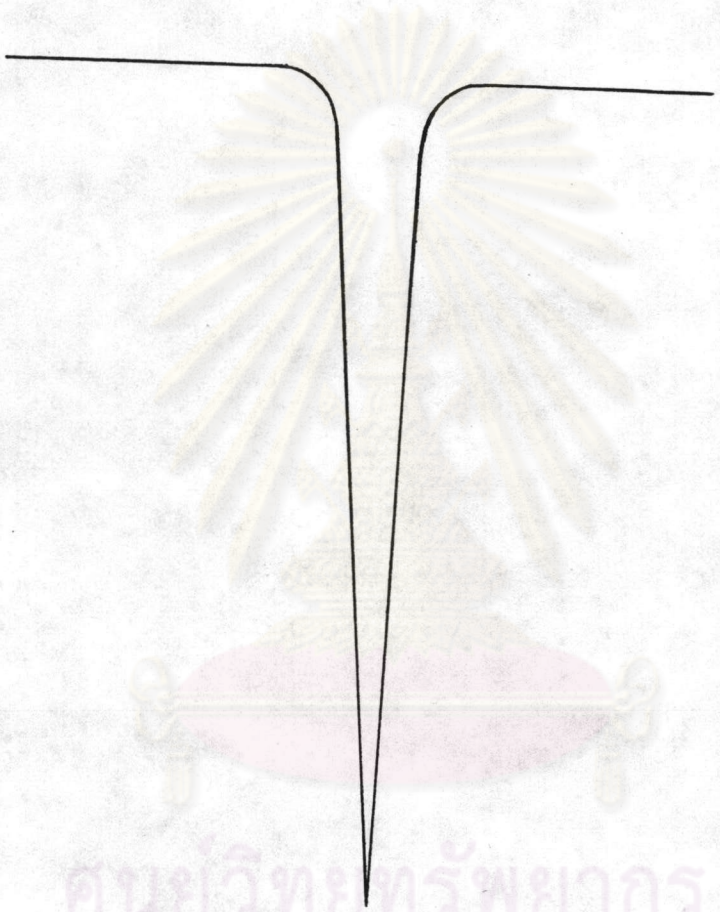


Figure 9 : Thermogram of indomethacin obtained using DSC, sensitivity 2 $mcal.sec^{-1}$

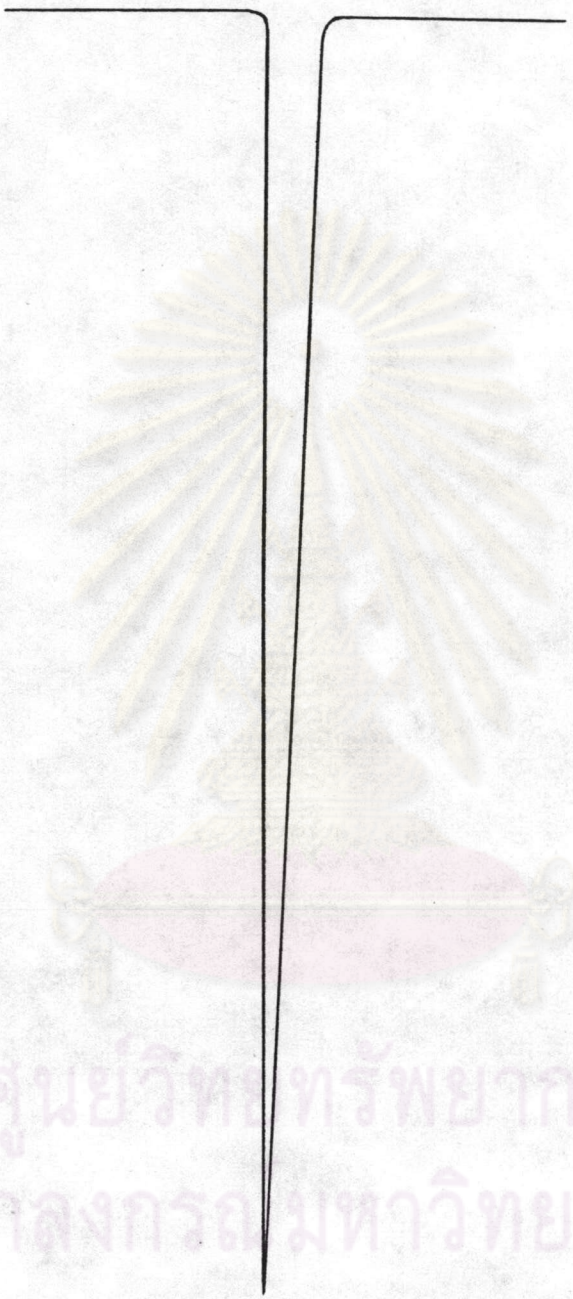


Figure 10 : Thermogram of indium obtained using DSC, sensitivity 1 mcal.sec^{-1}

VITA

Miss Patcharin Sukjit received a Bachelor of Sciences in Pharmacy from Chulalongkorn University in 1979. At present, she works as a pharmacist in Department of Pharmacy, Ramathibodee Hospital, Bangkok, Thailand.