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APPENDIX

APPENDIX 1

DETAILS OF SOME EXCIPIENTS

Indomethacin (Gilman, 1990)

1. Pharmacological Properties

Indomethacin has prominent antiinflammatory and analgesic-antipyretic properties similar to those of the salicylates.

The antiinflammatory effects of indomethacin are evident in patients with rheumatoid and other types of arthritis, including acute gout. Although indomethacin is more potent than aspirin, doses that are tolerated by patients with rheumatoid arthritis usually do not produce effects that are superior to those of salicylates. Indomethacin has analgesic properties distinct from its antiinflammatory effects, and there are evidences for both a central and peripheral actions. It is also an antipyretic.

Indomethacin is a potent inhibitor of the prostaglandin-forming cyclooxygenase; it also inhibits the motility of polymorphonuclear leukocytes. Like many other aspirin-like drugs, indomethacin uncouples oxidative phosphorylation in supratherapeutic concentrations and depresses the biosynthesis of mucopolysaccharides.

2. Pharmacokinetics and Metabolism

Indomethacin is rapidly and almost completely absorbed from the gastrointestinal tract after oral ingestion. The peak concentration in plasma is attained within 2 hours in the fasting subject but may be somewhat delayed when the drug is taken after meals. The concentrations in plasma required for an antiinflammatory effect have not been definitely determined but are probably less than 1 mcg/ml. Steady-state concentrations in plasma after long-term administration are approximately 0.5 mcg/ml. Indomethacin is 90 % bound to plasma proteins and also extensively bound to tissues. The concentration of the drug in the CSF is low, but its concentration in synovial fluid is equal to that in plasma within 5 hours of administration.

Indomethacin is largely converted to inactive metabolites, including those formed by O-demethylation (about 10 %), and N-deacylation. Some of these metabolites are detectable in plasma, and free and conjugated metabolites are eliminated in the urine, bile, and feces. There is enterohepatic cycling of the conjugates and probably of indomethacin itself. Ten to twenty percent of the drug is excreted unchanged in the urine, in part by tubular secretion. The half-life in plasma is variable, perhaps because of enterohepatic cycling, but averages about 3 hours.

3. Toxic Effects

A very high percentage (35 to 50 %) of patients receiving usual therapeutic doses of indomethacin experience untoward symptoms, and about 20 % must discontinue its use. Most adverse effects are dose related.

Gastrointestinal complaints and complications consist of anorexia, nausea, and abdominal pain. Single ulcers or multiple ulceration of the entire upper gastrointestinal tract, sometimes with perforations and hemorrhage, has been reported. Occult blood loss may lead to anemia in the absence of ulceration. Acute pancreatitis has also been reported. Diarrhoea may occur and is sometimes associated with ulcerative lesions of the bowel. Hepatic involvement is rare, although some fatal cases of hepatitis and jaundice have been reported. The most frequent CNS effect (indeed, the most common side effect) is severe frontal headache, occurring in 25 to 50 % of patients who take the drug for long periods. Dizziness, vertigo, light-headedness, and mental confusion are also frequent. Severe depression, psychosis, hallucinations, and suicide have occurred.

Hematopoietic reaction include neutropenia, thrombocytopenia, and, rarely, aplastic anemia. Platelet function is impaired by indomethacin. Hypersensitivity reactions are manifested as rashes, itching, urticaria, and, more seriously acute attacks of asthma. Patients sensitive to aspirin may exhibit cross-reactivity to

indomethacin. Indomethacin should not be used in pregnant women, nursing mothers, persons operating machinery, or patients with psychiatric disorders, epilepsy, or parkinsonism. It is also contraindicated in individuals with renal disease or ulcerative lesions of the stomach or intestines.

4. Preparations, Routes of Administration, and Dosage

Indometacin is available for oral use in capsules containing 25, 50 or 75 mg of the drug, and in sustained-release capsules (75 mg); it is also supplied in 50-mg suppositories and as an oral suspension (25 mg/ 5 ml).

The initial dose is 25 mg, two or three times daily, and this can be increased in 25- or 50-mg increments at weekly intervals until the total daily dose is 150 mg to 200 mg. Few patients tolerate more than 150 mg per day without severe side effects. Most patients respond within 4 to 6 days, but some require substantially longer treatment. The drug should be taken in divided portions with food or antacids or immediately after meals to lessen gastric distress. A dose of indomethacin taken with milk at bedtime is said to reduce the incidence of morning headache.

5. Therapeutic Uses

Because of the high incidence and severity of side effects associated with long-term administration, indometacin must not be routinely used as an analgesic or antipyretic. However, it has proven useful as an antipyretic in certain settings (e.g., Hodgkin's disease) when the fever has been refractory to other agents. Indomethacin has become an accepted part of the rheumatologist's armamentarium and a standard (together with aspirin) against which to measure the activity of other, newer drugs.

Indomethacin relieves pain, reduces swelling and tenderness of the joints, increases grip strength, and decreases the duration of morning stiffness. In these actions the drug is superior to placebo and equivalent to phenylbutazone; estimates of its potency relative to salicylates vary between 10 and 40 times higher. Overall, about two thirds of patients benefit from treatment with indomethacin; however, if 75 to 100 mg of the drug fails to provide benefit within 2 to 4 weeks, alternative therapy must be considered. The incidence and severity of side effects with indomethacin are particularly annoying, but a useful way of employing the undoubted potency of the drug, perhaps in combination with other and better tolerated daytime therapy, is to give a large single dose (up to 100 mg) at bedtime. This enables the patient to obtain a better-quality sleep, reduces the severity and

length of morning stiffness, and provides good analgesia until midmorning. The side effects of indomethacin are apparently better tolerated when it is given at night.

Indomethacin is often more effective than aspirin in the treatment of ankylosing spondylitis and osteoarthrosis. It is also very effective in the treatment of acute gout, although it is not uricosuric.

Patients with Bartter's syndrome have been successfully treated with indomethacin, as well as with other inhibitors of prostaglandin synthetase. The results are frequently dramatic; however, the condition of the patients may deteriorate rapidly when therapy is discontinued, and the long-term therapy necessary to control the disease requires administration of a drug that is better tolerated.

Cardiac failure in neonates caused by a patent ductus arteriosus may be controlled by the administration of indomethacin. A typical regimen involves the intravenous administration of 0.1 to 0.2 mg/kg every 12 hours for three doses. Successful closure can be expected in more than 70 % of neonates who are treated with the drug. Such therapy is indicated primarily in premature infants who weigh between 500 and 1750 g, who have a hemodynamically significant patent ductus arteriosus, and in whom other supportive maneuvers have been attempted. The principal limitation of this approach is renal toxicity, and therapy is stopped if the output of urine

falls below 0.6 ml/kg per hour. Renal failure, enterocolitis, thrombocytopenia, or hyperbilirubinemia contraindicates the use of indomethacin.

Poloxamer (Boylan, Cooper and Chowhan, 1986)

1. Nonproprietary Name

NF: Poloxamer.

2. Functional Category

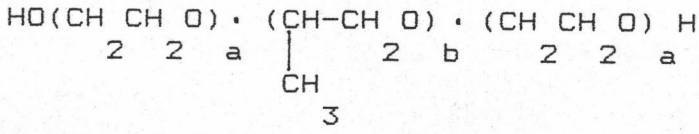
USP: Wetting and/or solubilizing agent; emulsifying and/or solubilizing agent.

3. Chemical Names and CAS Registry Number

Oxirane, methyl-, polymer with oxirane Polyethylene-propylene glycol α-Hydro-ω-hydroxypoly(oxyethylene) poly(oxypropylene) (27-31 moles) poly(oxyethylene) block copolymer(a = 2-130; b = 15-67) CAS registry number [9003-11-6].

4. Empirical Formula and Molecular Weight

Poloxamer 188 (pluronic F68) is one of a series of poly(oxyethylene), poly(oxypropylene) block polymers with the general empirical formula.



For poloxamer 188 (pluronic F68): a = 75 and b = 30, and average molecular weight = 8350.

For poloxamer 407 (pluronic F127): a = 98 and b = 67, and average molecular weight = 10000-14500.

5. Structural Formula

See above.

6. Commercial Availability

USA

BASF Wyandotte Corporation.

UK

A.B.M.Chemicals,Ltd.

BASF(UK)Ltd.

Diamond Shamrock U.K., Ltd.

Pechiney Ugine Kuhlmann Ltd.

7. Method of Manufacture

Propylene oxide is condensed onto a propylene glycol nucleus, followed by condensation of ethylene oxide onto both ends of the poly(oxypropylene) base.

8. Description

White, waxy, free-flowing prilled granules or cast solid; practically tasteless and odorless.

9. Pharmacopoeial Specifications

test	NF
pH (1 in 40 solution)	5.0-7.5.
Arsenic	< 3 ppm.
Heavy metals	< 0.002 %.
Average molecular weight	90.0-110.0 % of label (1,000-7,000).
	80.0-120.0 % of label (above 7,000).
Polyoxypropylene number	85.0-115.0 % of label.
Polyoxyethylene number	Within 1 of label.

10 Typical Properties

Antimicrobial action: nil; supports mold growth in aqueous solution.

Aqueous gellation concentration: between 60 and 90 % at room temperature.

Cloud point (Aqueous, 1 % and 10 %): more than 100°C.

Flash point: 260°C.

HLB value: 29.

Interfacial tension: 25°C, 0.1 % - 19.8 dynes/cm.; 0.01 % - 24.0 dynes/cm.

Loss on drying: 0.5 %.

Melting point: 52°C.

pH: between 6.0 and 7.4 (2.5 % w/v).

Solubility: soluble in water, dilute acids and ethyl alcohol; slightly soluble in toluene and xylene; insoluble in propylene glycol, perchloroethylene, glycerin, mineral oil and liquid paraffin.

Specific gravity: 1.06 g/cm^3 at 25°C.

Surface tension: 25°C, 0.1 % - 50.3 dynes/cm; 25°C, 0.01 % - 51.2 dynes/cm; 25°C, 0.001 % - 53.6 dynes/cm.

Viscosity: 1,000 cps at 77°C as a melt (Brookfield).

Hygroscopicity: very slight.

Flowability: free flowing.

11. Stability and Storage Conditions

Stable to aqueous acids, alkalis and metal ions.

12 Incompatibilities

Depending on the relative concentration, poloxamer 188 is incompatible with phenols and parabens.

13. Safety

The oral LD_{50} for five species of animals is greater than 15 g/kg of body weight. Directly applied to the eyes of rabbits in 5 % and 10 % concentrations, there

was no irratation. No incidents have been reported concerning skin irritation or sensitization. At concentrations of 5 %, 10 % and as a paste, there was no irritation or hyperemia in the gums of rabbits and dogs. No symptoms of toxicity were observed when injected IV into dogs at a dosage of 0.1 g/kg or into rabbits at a dosage of 1.0 g/kg. The IV LD_{50} is reported to be 5.5 g/kg for mice and 3.95 g/kg for rats when injected as a 5 % solution.

In a 14-day study of IV administration to rabbits at concentrations up to 0.5 g/kg/day, there were no over effects. A similar study with dogs showed no effects at dosage levels up to 0.5 g/kg/day. Over a range of 0.001 % to 10 %, no hemolysis of human blood cells was observed over 18 hours at 25°C. Poloxamer 188 has been used as an emulsifier and as a stabilizer for emulsions which have been safely injected intravenously. It is not metabolized in the body.

Rats fed 3 % or 5 % in their food for up to two years did not exhibit significant symptoms of toxicity. Rats receiving 7.5 % showed a decrease in growth rate.

14. Applications in Pharmaceutical Formulation or Technology

Use	Concentration (%)
Flavor solubilizer	0.3
Wetting agent	0.01-5

Use	Concentration (%)
Gelling agent	15-50
Spreading agent	1
Fat emulsifier	0.3
Stabilizing agent	1-5
Suppository base	4-6, 90
Tablet coating	10
Tablet excipient	5-10
Fluorocarbon emulsifier	2.5

Polyoxyethylene Sorbitan Fatty Acid Esters (Boylan, Cooper and Chowlan, 1986)

1. Nonproprietary Names

NF: Polysorbates 20, 40, 60 and 80.

BP/EP: Polysorbates 20, 60 and 80.

2. Functional Category

NF: Wetting and/or solubilizing agent: emulsifying and/or solubilizing agent.

BP/EP: Non-ionic surface-active agents.

3. Synonyms

Polyethylene oxide sorbitan esters, Tweens, Sorlates, Monitans, Crillets.

4. Chemical Names and CAD Registry Number

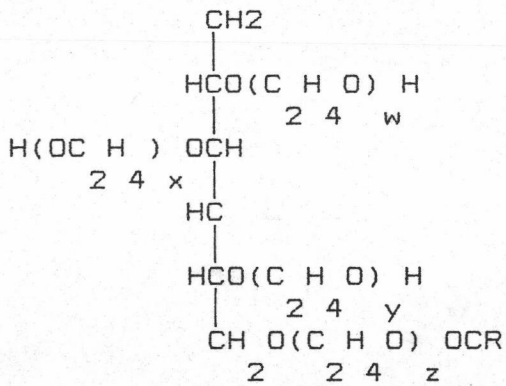
Polysorbate 80-Sorbitan, mono-9-octadecanoate, poly(oxy-1,2-ethanediyl) derivs.; (Z); polyoxyethylene 20 sorbitan monooleate [9005-65-6].

5. Empirical Formula

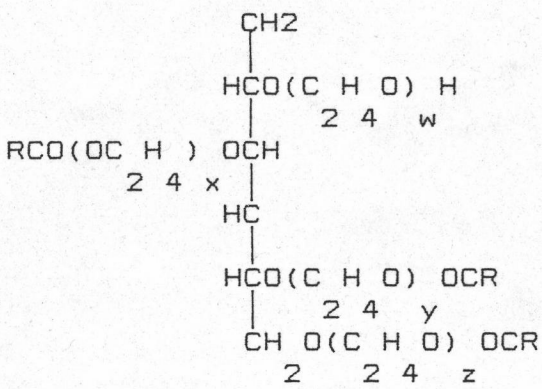
Polysorbate 80: $C_{64}H_{125}O_{26}$

Molecular weight = 1309

6. Structural Formula



Polyoxyethylene sorbitan monoester



Polyoxyethylene sorbitan triester

w+x+y+z=20

7. Description

Polysorbate 80 has a characteristic odor and a warm, somewhat bitter taste. Its color and physical form at 25 ^{0}C is yellow oily liquid.

8. Stability and Storage Conditions

Polysorbates are stable to electrolytes as well as to weak acids and bases. There is gradual saponification by strong acids and bases. The oleic acid esters are sensitive to oxidation. Preserve in a tight container protected from light and store in cool conditions.

9. Incompatibilities

Discoloration and/or precipitation occurs with various substances, especially with phenols, tannins, tars and/or tar like compounds.

10. Safety

Polysorbates are well tolerated, practically non-irritation and of very low toxicity.

11. Applications in Pharmaceutical Formulation or Technology

Use	Concentration (%)
Emulsifiers	
Used alone in water-in-oil emulsions	1-15
Used in combination with hydrophilic emulsifiers in oil-in-water emulsions	1-10
Used to increase the water-holding properties of ointments	1-10
Solubilizers	
For poorly soluble active constituents in lipophilic bases	1-10
Wetting Agents	0.1-3
For insoluble active Constituents in lipophilic bases	

Carbopol (Boylan, Cooper and Chowlan, 1986)

1. Nonproprietary Name

NF: Carbomer.

BP: Carbomer.

2. Functional Category

NF: Suspending and/or viscosity-increasing agent.

BP: Pharmaceutical aid.

3. Synonyms

Carboxypolymethylene; carboxyvinyl polymer; acrylic acid polymer; Carbopol.

4. Chemical Name and CAS Registry Number

Carboxypolymethylene[9007-20-9].

5. Typical Properties

The pH of a 1 % dispersion of carbomer in water is approximately 3.0. Carbomer is soluble in water, alcohol and glycerin. Agents that can neutralize carbomer include sodium hydroxide; potassium hydroxide; sodium bicarbonate; borax; amino acids; polar organic amines, such as triethanolamine, and lauryl and stearyl amines, which are used as gelling agents in nonpolar systems. One gram of carbomer is neutralized by approximately 400 mg of sodium hydroxide. Neutralized aqueous gels of carbomer are more viscous between pH 6 and pH 11. The viscosity is considerably reduced if the pH is less than 3 or more than 12. The viscosity is also reduced in the presence of strong electrolytes. Gels rapidly lose viscosity on exposure to sunlight, but this reaction can be minimized

by the addition of an antioxidant. Carbomer is hygroscopic.

Specific gravity: 1.4

Density, bulk: 5 g/cm^3

Density, tapped: 1.4 g/cm^3

Equilibrium moisture content(20°C and 40 % RH)

Viscosity (Brookfield, Model RVF or RVT at 20 rpm, using neutralized solutions at 25°C): 0.2 % (spindle 4): 20.5-54.5 poise; 0.5 % (spindle 6): 305-394 poise

6. Stability and Storage Conditions

Dry powder forms of carbomer do not support the growth of molds and fungi; however, microorganisms grow well in unpreserved aqueous dispersions. Dispersions maintain their viscosity on storage during prolonged periods at room temperature or at elevated temperatures when stored away from light or with the addition of an antioxidant. Certain preservatives, such as benzoic acid, sodium benzoate and benzalkonium chloride, have been shown to cause a decrease in viscosity of the dispersion. Store in an airtight or well-closed container.

7. Incompatibilities

Carbomer is incompatible with phenol, cationic polymers, strong acids and high concentrations of electrolytes, and is discolored by resorcinol. Exposure to

light causes oxidation, which is reflected in a decrease in viscosity.

8. Applications in Pharmaceutical Formulation or Technology

Use	Concentration (%)
Emulsifying agent	0.1-0.5
Suspending agent	0.5-1.0
Gelling agent	0.5-2.0

APPENDIX 2

STABILITY DATA OF PREPARED INDOMETHACIN SOLUTIONS

Stability Data of Formulation No. 1 at 70 °C

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.431	980.353
	0.433	984.938
	0.425	966.599
	0.427	971.184
13	0.429	975.768
	0.435	989.522
	0.433	984.938
	0.432	982.645
26	0.432	982.645
	0.434	987.230
	0.421	957.430
	0.421	957.430
46	0.417	948.261
	0.416	945.969
	0.412	936.800
	0.418	950.554
75	0.392	890.955
	0.393	893.247
	0.394	895.539
	0.396	900.124
90	0.392	890.955
	0.396	900.124
	0.388	881.786
	0.392	890.955
139	0.356	808.433
	0.352	799.264
	0.358	813.018
	0.357	810.726

Conc. = 995.209 − 1.278 time: R^2 = 0.952.

ln conc. = 6.906 − 0.001421 time: R^2 = 0.949.

Stability Data of Formulation No. 2 at 70°C

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.441	1003.276
	0.447	1017.029
	0.438	996.399
	0.439	998.691
13	0.426	968.892
	0.427	971.184
	0.426	968.892
	0.424	964.307
26	0.413	939.092
	0.414	941.385
	0.416	945.969
	0.414	941.385
46	0.402	913.877
	0.403	916.170
	0.404	918.462
	0.401	911.585
75	0.383	870.324
	0.371	842.817
	0.384	872.617
	0.380	863.448
90	0.375	851.986
	0.379	861.155
	0.375	851.986
	0.375	851.986
139	0.337	764.880
	0.338	767.172
	0.337	764.880
	0.337	764.880

Conc. = 992.721 - 1.640 time: R^2 = 0.985.

ln conc. = 6.904 - 0.001864 time: R^2 = 0.987.

Stability Data of Formulation No. 3 at 70 °C

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.458	1042.244
	0.454	1033.075
	0.449	1021.614
	0.452	1028.491
13	0.437	994.107
	0.437	994.107
	0.436	991.814
	0.439	998.691
26	0.435	989.522
	0.439	998.691
	0.436	991.814
	0.431	980.353
46	0.437	994.107
	0.443	1007.860
	0.430	978.061
	0.438	996.399
75	0.408	927.631
	0.410	932.215
	0.408	927.631
	0.401	911.585
90	0.394	895.539
	0.399	907.001
	0.397	902.416
	0.399	907.001
139	0.366	831.356
	0.365	829.064
	0.363	824.479
	0.363	824.479

Conc. = 1030.868 - 1.416 time: R^2 = 0.951.

ln conc. = 6.941 - 0.001528 time: R^2 = 0.949.

Stability Data of Formulation No. 4 at 70° C

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.428	973.476
	0.434	987.230
	0.436	991.814
	0.436	991.814
13	0.419	952.846
	0.419	952.846
	0.418	950.554
	0.421	957.430
26	0.413	939.092
	0.413	939.092
	0.413	939.092
	0.412	936.800
46	0.414	941.385
	0.411	934.508
	0.416	945.969
	0.413	939.092
75	0.380	863.448
	0.381	865.740
	0.382	868.032
	0.381	865.740
90	0.374	849.694
	0.374	849.694
	0.370	840.525
	0.369	838.233
139	0.333	755.711
	0.331	751.127
	0.334	758.003
	0.331	751.127

Conc. = 987.635 − 1.622 time: R^2 = 0.970.

ln conc. = 6.900 − 0.001869 time: R^2 = 0.966.

Stability Data of Formulation No. 5 at 70 °C

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.441	1003.276
	0.441	1003.276
	0.449	1021.614
	0.445	1012.445
13	0.434	987.230
	0.434	987.230
	0.431	980.353
	0.435	989.522
26	0.428	973.476
	0.429	975.768
	0.426	968.892
	0.424	964.307
46	0.406	923.046
	0.402	913.877
	0.403	916.170
	0.399	907.001
75	0.401	911.585
	0.401	911.585
	0.400	909.293
	0.402	913.877
90	0.395	897.832
	0.394	895.539
	0.392	890.955
	0.394	895.539
139	0.363	824.479
	0.365	829.064
	0.358	813.018
	0.361	819.895

Conc. = 1001.472 − 1.286 time: R^2 = 0.955.

ln conc. = 6.911 − 0.001407 time: R^2 = 0.957.

Stability Data of Formulation No. 6 at 70°C

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.442	1005.568
	0.442	1005.568
	0.443	1007.860
	0.442	1005.568
13	0.434	987.230
	0.434	987.230
	0.436	991.814
	0.436	991.814
26	0.421	957.430
	0.428	973.476
	0.426	968.892
	0.428	973.476
46	0.402	913.877
	0.407	925.339
	0.403	916.170
	0.407	925.339
75	0.392	890.955
	0.396	900.124
	0.396	900.124
	0.396	900.124
90	0.389	884.078
	0.392	890.955
	0.381	865.740
	0.385	874.909
139	0.351	796.972
	0.351	796.972
	0.353	801.556
	0.353	801.556

Conc. = 1004.349 − 1.466 time: R^2 = 0.982.

ln conc. = 6.915 − 0.001624 time: R^2 = 0.983.

Stability Data of Formulation No. 7 at 70°C

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.271	613.639
	0.270	611.347
	0.269	609.054
	0.268	606.762
4	0.261	590.716
	0.260	588.424
	0.261	590.716
	0.264	597.593
9	0.259	586.132
	0.259	586.132
	0.256	579.255
	0.259	586.132
15	0.255	576.963
	0.255	576.963
	0.255	576.963
	0.255	576.963
23	0.249	563.209
	0.247	558.625
	0.252	570.086
	0.250	565.501
32	0.249	563.209
	0.248	560.917
	0.248	560.917
	0.247	558.625
49	0.246	556.332
	0.245	554.040
	0.246	556.332
	0.245	554.040
79	0.233	526.533
	0.235	531.117
	0.236	533.410
	0.233	526.533
104	0.229	517.364
	0.228	515.072
	0.230	519.656
	0.230	519.656

Conc. = 593.161 − 0.785 time: R^2 = 0.915.

ln conc. = 6.386 − 0.001407 time: R^2 = 0.927.

Stability Data of Formulation No. 1 at 60 °C

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.456	1037.708
	0.456	1037.708
	0.457	1040.000
	0.454	1033.123
7	0.450	1023.954
	0.449	1021.662
	0.449	1021.662
	0.449	1021.662
22	0.447	1017.077
	0.449	1021.662
	0.441	1003.324
	0.446	1014.785
76	0.446	1014.785
	0.439	998.739
	0.441	1003.324
	0.445	1012.493
103	0.436	991.862
	0.442	1005.616
	0.436	991.862
	0.439	998.739

Conc. = 1028 - 0.305 time: R^2 = 0.732.

ln conc. = 6.936 - 0.000301 time: R^2 = 0.734.

Stability Data of Formulation No. 3 at 60°C

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.462	1051.461
	0.463	1053.754
	0.453	1030.831
	0.449	1021.662
7	0.454	1033.123
	0.458	1042.292
	0.455	1035.415
	0.457	1040.000
22	0.452	1028.539
	0.454	1033.123
	0.455	1035.415
	0.453	1030.831
76	0.449	1021.662
	0.447	1017.077
	0.448	1019.370
	0.447	1017.077
103	0.430	978.109
	0.429	975.817
	0.428	973.524
	0.433	984.986

Conc. = 1042.690 − 0.517 time: R^2 = 0.785.

ln conc. = 6.950 − 0.000511 time: R^2 = 0.783.

Stability Data of Formulation No. 5 at 60°C

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.457	1040.000
	0.460	1046.877
	0.462	1051.461
	0.462	1051.461
45	0.457	1040.000
	0.452	1028.539
	0.453	1030.831
	0.457	1040.000
53	0.451	1026.246
	0.457	1040.000
	0.451	1026.246
	0.451	1026.246
76	0.443	1007.908
	0.441	1003.324
	0.443	1007.908
	0.447	1017.077
103	0.442	1005.616
	0.440	1001.032
	0.440	1001.032
	0.440	1001.032

Conc. = 1050.790 - 0.472 time: R^2 = 0.866.

ln conc. = 6.957 - 0.000461 time: R^2 = 0.865.

Stability Data of Formulation No. 1 at 50 °C

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.454	1033.123
	0.455	1035.415
	0.453	1030.831
	0.455	1035.415
40	0.450	1023.954
	0.450	1023.954
	0.453	1030.831
	0.456	1037.708
79	0.456	1037.708
	0.454	1033.123
	0.451	1026.246
	0.455	1035.415
104	0.453	1030.831
	0.452	1028.539
	0.450	1023.954
	0.451	1026.246
130	0.453	1030.831
	0.451	1026.246
	0.452	1028.539
	0.450	1023.954
168	0.444	1010.201
	0.443	1007.908
	0.444	1010.201
	0.443	1007.908
217	0.447	1017.077
	0.442	1005.616
	0.440	1001.032
	0.445	1012.493

Conc. = 1037.261 − 0.125 time: R^2 = 0.659.

ln conc. = 6.944 − 0.000122 time: R^2 = 0.658.

Stability Data of Formulation No. 3 at 50°C

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.465	1058.338
	0.463	1053.754
	0.456	1037.708
	0.458	1042.292
40	0.461	1049.169
	0.463	1053.754
	0.461	1049.169
	0.459	1044.585
79	0.455	1035.415
	0.455	1035.415
	0.457	1040.000
	0.458	1042.292
104	0.452	1028.539
	0.453	1030.831
	0.456	1037.708
	0.455	1035.415
130	0.445	1012.493
	0.447	1017.077
	0.444	1010.201
	0.446	1014.785
168	0.444	1010.201
	0.443	1007.908
	0.442	1005.616
	0.442	1005.616
217	0.439	998.739
	0.440	1001.032
	0.440	1001.032
	0.440	1001.032

Conc. = 1054.230 - 0.257 time: R^2 = 0.879.

ln conc. = 6.961 - 0.000250 time: R^2 = 0.880.

Stability Data of Formulation No. 5 at 50°C

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.456	1037.708
	0.459	1044.585
	0.457	1040.000
	0.455	1035.415
40	0.455	1035.415
	0.460	1046.877
	0.455	1035.415
	0.455	1035.415
79	0.456	1037.708
	0.453	1030.831
	0.455	1035.415
	0.452	1028.539
104	0.453	1030.831
	0.452	1028.539
	0.453	1030.831
	0.452	1028.539
130	0.450	1023.954
	0.449	1021.662
	0.450	1023.954
	0.450	1023.954
168	0.442	1005.616
	0.443	1007.908
	0.440	1001.032
	0.440	1001.032
217	0.436	991.862
	0.438	996.447
	0.435	989.570
	0.432	982.693

Conc. = 1047.627 - 0.238 time: R^2 = 0.858.

ln conc. = 6.954 - 0.000234 time: R^2 = 0.855.

Stability Data of Formulation No. 1 at 40°C

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.457	1040.000
	0.454	1033.123
	0.456	1037.708
	0.456	1037.708
86	0.452	1028.539
	0.452	1028.539
	0.454	1033.123
	0.455	1035.415
109	0.451	1026.246
	0.452	1028.539
	0.451	1026.246
	0.451	1026.246
117	0.453	1030.831
	0.454	1033.123
	0.450	1023.954
	0.448	1019.370
124	0.450	1023.954
	0.450	1023.954
	0.449	1021.662
	0.449	1021.662
143	0.450	1023.954
	0.447	1017.077
	0.451	1026.246
	0.449	1021.662
181	0.447	1017.077
	0.448	1019.370
	0.451	1026.246
	0.450	1023.954
230	0.443	1007.908
	0.444	1010.201
	0.447	1017.077
	0.446	1014.785

Conc. = 1038.175 − 0.105 time: R^2 = 0.767.

ln conc. = 6.945 − 0.000103 time: R^2 =0.766.

Stability Data of Formulation No. 3 at 40°C

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.458	1042.292
	0.460	1046.877
	0.462	1051.461
	0.457	1040.000
86	0.454	1033.123
	0.457	1040.000
	0.455	1035.415
	0.455	1035.415
109	0.458	1042.292
	0.459	1044.585
	0.458	1042.292
	0.458	1042.292
117	0.458	1042.292
	0.458	1042.292
	0.457	1040.000
	0.457	1040.000
124	0.457	1040.000
	0.456	1037.708
	0.457	1040.000
	0.456	1037.708
143	0.456	1037.708
	0.453	1030.831
	0.455	1035.415
	0.454	1033.123
181	0.450	1023.954
	0.452	1028.539
	0.453	1030.831
	0.455	1035.415
230	0.451	1026.246
	0.450	1023.954
	0.451	1026.246
	0.450	1023.954

Conc. = 1047.563 − 0.088 time: R^2 = 0.659.

ln conc. = 6.954 − 0.000085 time: R^2 =0.659.

Stability Data of Formulation No. 5 at 40°C

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.457	1040.000
	0.460	1046.877
	0.462	1051.461
	0.462	1051.461
53	0.458	1042.292
	0.460	1046.877
	0.460	1046.877
	0.461	1049.169
86	0.457	1040.000
	0.457	1040.000
	0.453	1030.831
	0.452	1028.539
109	0.455	1035.415
	0.456	1037.708
	0.459	1044.585
	0.457	1040.000
117	0.451	1026.246
	0.452	1028.539
	0.456	1037.708
	0.456	1037.708
143	0.450	1023.954
	0.449	1021.662
	0.448	1019.370
	0.447	1017.077
181	0.450	1023.954
	0.449	1021.662
	0.447	1017.077
	0.448	1019.370
230	0.451	1026.246
	0.451	1026.246
	0.450	1023.954
	0.450	1023.954

Conc. = 1048.082 − 0.128 time: R^2 = 0.656.

ln conc. = 6.954 − 0.000124 time: R^2 =0.655.

Stability Data of Formulation No. 1 at Ambient Temperature

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.457	1040.000
	0.454	1033.123
	0.456	1037.708
	0.456	1037.708
46	0.452	1028.539
	0.455	1035.415
	0.447	1017.077
	0.452	1028.539
77	0.460	1046.877
	0.458	1042.292
	0.459	1044.585
	0.458	1042.292
103	0.454	1033.123
	0.453	1030.831
	0.454	1033.123
	0.454	1033.123
124	0.453	1030.831
	0.455	1035.415
	0.452	1028.539
	0.455	1035.415
181	0.453	1030.831
	0.452	1028.539
	0.451	1026.246
	0.453	1030.831
230	0.452	1028.539
	0.452	1028.539
	0.452	1028.539
	0.453	1030.831

Conc. = 1036.664 − 0.033 time: R^2 = 0.146.

ln conc. = 6.944 −0.000031 time: R^2 = 0.146

Stability Data of Formulation No. 3 at Ambient Temperature

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.462	1051.461
	0.463	1053.754
	0.453	1030.831
	0.449	1021.662
46	0.454	1033.123
	0.454	1033.123
	0.460	1046.877
	0.459	1044.585
77	0.461	1049.169
	0.462	1051.461
	0.462	1051.461
	0.461	1049.169
103	0.461	1049.169
	0.460	1046.877
	0.454	1033.123
	0.456	1037.708
124	0.457	1040.000
	0.456	1037.708
	0.458	1042.292
	0.457	1040.000
181	0.457	1040.000
	0.461	1049.169
	0.461	1049.169
	0.459	1044.585
230	0.452	1028.539
	0.453	1030.831
	0.457	1040.000
	0.455	1035.415

Conc. = 1043.206 − 0.016 time: R^2 = 0.016.

ln conc. = 6.950 − 0.000015 time: R^2 = 0.019.

Stability Data of Formulation No. 5 at Ambient Temperature

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.457	1040.000
	0.460	1046.877
	0.462	1051.461
	0.462	1051.461
46	0.460	1046.877
	0.460	1046.877
	0.461	1049.169
	0.467	1062.923
77	0.457	1040.000
	0.462	1051.461
	0.460	1046.877
	0.459	1044.585
103	0.453	1030.831
	0.453	1030.831
	0.454	1033.123
	0.455	1035.415
124	0.460	1046.877
	0.459	1044.585
	0.459	1044.585
	0.458	1042.292
181	0.455	1035.415
	0.454	1033.123
	0.455	1035.415
	0.454	1033.123
230	0.454	1033.123
	0.455	1035.415
	0.459	1044.585
	0.458	1042.292

Conc. = 1048.456 − 0.058 time: R^2 = 0.304.

ln conc. = 6.955 − 0.000056 time: R^2 = 0.304.

APPENDIX 3

STABILITY DATA OF ELMETACIN™

Stability Data of Elmetacin™ at 70°C

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.354	803.849
	0.353	801.556
	0.355	806.141
	0.353	801.556
51	0.350	794.680
	0.352	799.264
	0.352	799.264
	0.352	799.264
60	0.352	799.264
	0.350	794.680
	0.350	794.680
	0.354	803.849
76	0.354	803.849
	0.352	799.264
	0.352	799.264
	0.352	799.264
117	0.350	794.680
	0.350	794.680
	0.350	794.680
	0.350	794.680

Conc. = 802.915 − 0.066 time: R^2 = 0.467.

ln conc. = 6.688 − 0.000082 time: R^2 = 0.467.

Stability Data of Elmetacin™ at 60°C

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.350	794.728
	0.354	803.897
	0.356	808.481
	0.350	794.728
7	0.359	815.358
	0.354	803.897
	0.349	792.436
	0.349	792.436
22	0.338	767.221
	0.338	767.221
	0.339	769.513
	0.339	769.513
45	0.348	790.143
	0.349	792.436
	0.346	785.559
	0.351	797.020
53	0.355	806.189
	0.356	808.481
	0.358	813.066
	0.351	797.020
76	0.356	808.481
	0.353	801.605
	0.352	799.312
	0.350	794.728
103	0.348	790.143
	0.351	797.020
	0.353	801.605
	0.353	801.605

Conc. = 792.184 + 0.068 time: R^2 = 0.032.

ln conc. = 6.974 + 0.000087 time: R^2 = 0.033.

Stability Data of Elmetacin™ at 50°C

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.356	808.481
	0.349	792.436
	0.353	801.605
	0.353	801.605
16	0.350	794.728
	0.352	799.312
	0.348	790.143
	0.347	787.851
29	0.349	792.436
	0.347	787.851
	0.348	790.143
	0.347	787.851
40	0.354	803.897
	0.357	810.774
	0.357	810.774
	0.356	808.481
47	0.353	801.605
	0.357	810.774
	0.355	806.189
	0.356	808.481
79	0.359	815.358
	0.360	817.650
	0.353	801.605
	0.351	797.020
96	0.350	794.728
	0.350	794.728
	0.354	803.897
	0.353	801.605
104	0.349	792.436
	0.349	792.436
	0.352	799.312
	0.352	799.312
130	0.347	787.851
	0.351	797.020
	0.349	792.436
	0.350	794.728
168	0.351	797.020
	0.350	794.728
	0.354	803.897
	0.352	799.312
217	0.356	808.481
	0.352	799.312
	0.351	797.020
	0.357	810.774

Conc. = 799.186 − 0.006 time: R^2 = 0.003.

ln conc. = 6.684 − 0.000008 time: R^2 = 0.003.

Stability Data of Elmetacin™ at 40°C

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.352	799.312
	0.354	803.897
	0.354	803.897
	0.352	799.312
19	0.350	794.728
	0.352	799.312
	0.353	801.605
	0.352	799.312
46	0.353	801.605
	0.353	801.605
	0.353	801.605
	0.353	801.605
53	0.351	797.020
	0.350	794.728
	0.353	801.605
	0.353	801.605
86	0.356	808.481
	0.353	801.605
	0.353	801.605
	0.352	799.312
109	0.353	801.605
	0.353	801.605
	0.352	799.312
	0.354	803.897
117	0.354	803.897
	0.354	803.897
	0.354	803.897
	0.354	803.897
124	0.354	803.897
	0.353	801.605
	0.354	803.897
	0.352	799.312
143	0.351	797.020
	0.353	801.605
	0.352	799.312
	0.352	799.312
181	0.352	799.312
	0.353	801.605
	0.354	803.897
	0.354	803.897
230	0.355	806.189
	0.355	806.189
	0.354	803.897
	0.354	803.897

Conc. = 799.934 + 0.017 time: R^2 = 0.153.

ln conc. = 6.984 + 0.000021 time: R^2 =0.152.

Stability Data of Elmetacin™ at Ambient Temperature

Time (days)	Absorbance	Indomethacin Conc. (mg %)
0	0.351	797.020
	0.350	794.728
	0.349	792.436
	0.350	794.728
46	0.353	801.605
	0.349	792.436
	0.350	794.728
	0.350	794.728
77	0.354	803.897
	0.354	803.897
	0.351	797.020
	0.353	801.605
103	0.348	790.143
	0.347	787.851
	0.348	790.143
	0.349	792.436
124	0.353	801.605
	0.350	794.728
	0.352	799.312
	0.351	797.020
181	0.347	787.851
	0.350	794.728
	0.349	792.436
	0.351	797.020
230	0.353	801.605
	0.350	794.728
	0.350	794.728
	0.352	799.312

Conc. = 795.839 - 0.000 time: R^2 = 0.000.

ln conc. = 6.679 - 0.000000 time: R^2 = 0.000.

APPENDIX 4

STABILITY DATA OF PREPARED INDOMETHACIN GEL

Stability Data of Prepared Indomethacin Gel at Ambient Temperature

Time (days)	weight (g)	Absorbance	Indomethacin Conc. in Gel (mg %)
0	1.841	0.794	1052.391
		0.796	1055.492
		0.798	1058.823
	1.965	0.841	1056.519
		0.839	1053.506
		0.835	1047.481
	2.035	0.865	1055.038
		0.860	1047.766
		0.863	1052.129
17	1.896	0.809	1045.392
		0.812	1050.078
		0.811	1048.516
	1.995	0.849	1052.556
		0.848	1051.072
		0.846	1048.105
	2.006	0.851	1049.893
		0.844	1039.562
		0.849	1046.941
32	1.875	0.801	1044.303
		0.801	1044.303
		0.798	1039.566
	2.065	0.870	1046.880
		0.865	1039.714
		0.869	1045.447
	1.870	0.796	1039.402
		0.799	1044.152
		0.802	1048.903
65	2.104	0.863	1017.632
		0.862	1016.225
		0.859	1012.005
	2.037	0.839	1016.674
		0.836	1012.313
		0.837	1013.766
	1.956	0.813	1018.957
		0.809	1012.904
		0.811	1015.931
89	2.056	0.843	1012.593
		0.840	1008.275
		0.838	1005.396
	2.090	0.854	1012.040
		0.851	1007.791
		0.852	1009.207
	1.878	0.781	1011.106
		0.784	1015.836
		0.778	1006.377
99	1.985	0.803	989.163
		0.799	983.199
		0.807	995.127
	2.045	0.824	990.831
		0.821	986.488
		0.826	993.726
	2.136	0.852	987.147
		0.859	996.846
		0.849	982.990

Conc. = 1057.721 - 0.619 time: R^2 = 0.930.

ln conc. = 6.964 -0.000604 time: R^2 = 0.927.

VITA

Miss Saranya Tharasawaeng was born on 10th July, 1962 in Ayuthaya, Thailand. She graduated a B. Sc. in Pharm. from the Faculty of Pharmaceutical Sciences, Chulalongkorn University in 1986. She had worked in Ayuthaya hospital after she left the University for three years. At the present, she has studied for the Master Degree in Pharmaceutical Sciences at Chulalongkorn University from 1989.