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PREFORMULATION CHARACTERIZATION OF TOPICAL IBUPROFEN PICONOL

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ABSTRACT

Development of a topical pharmaceutical is facilitated by generation of a different type of preformulation profile than needed prior to tablet or parenteral product development. Ibuprofen piconol is a non-steroidal, anti-inflammatory (NSAID) drug marketed in Japan for the topical relief of primary thermal burns and sunburns. A complete preformation characterization was completed for this compound and is reported here to serve as a template for development of future topical drug products. The physical properties compiled include melting properties, specific gravity, viscosity, hygroscopicity, moisture content, acid-base properties, surface tension, solubility and partitioning. Chemical stability results are given for the bulk drug, the drug in solution, and the drug after formulation in both a cream and an ointment. These studies indicate that ibuprofen piconol is a chemically stable, slightly hygroscopic liquid that strongly partitions into the oil phase and shows no indication of surface activity. This drug has very limited solubility in water (16.5 ppm), modest solubility in glycerol (16.4 mg/ml), and is miscible with less polar organics except for silicone fluids.

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INTRODUCTION

Ibuprofen piconol is the 2-pyridylmethyl ester of iburpofen, and is the non-steroidal anti-inflammatory topical marketed in Japan by Hisamitsu for treatment of primary thermal burns. The potential for development of a 5% topical cream, 5% topical ointment and 10% topical spray for the U.S. market prompted preformulation evaluation of this active. Unlike most crystalline drugs that will be formulated primarily for parenteral or oral delivery, this compound was an oily liquid at room temperature and considered only for topical administration. Since the three types of topical vehicles targeted for development have widely differing physical properties and since the active was an oil, a different series of preformation tests has to be completed to best determine the likelihood of successful cream, ointment and spray formulations. While this compilation of physical and chemical properties of ibuprofen piconol may be of particular usefulness in the future research of this drug, the greater significance of this work is to serve as a template for preformulation characterization of actives that are specifically targeted for topical administration. It is expected that the physical properties necessary for determination in a preformulation profile will vary slightly from compound to compound, especially when evaluating an oily liquid rather than a crystalline solid. However, many of the solubility, partitioning, stability and delivery tests detailed below will be applicable to all topical product development efforts.

EXPERIMENTAL PROCEDURES AND RESULTS

PHYSICAL PROPERTIES

Melting Point:

Ibuprofen piconol was cooled in an isopropanol-dry ice bath and in liquid nitrogen. It was rewarmed partially and cooled again several times in each bath. A differential scanning calorimeter trace from -70°C to 0°C was also obtained. No crystalline appearance was noted in either liquid nitrogen or isopropanol-dry ice; the appearance and fracture surfaces were characteristic of a glass. There was no evidence of a solid-liquid transition in the DSC trace.

Boiling Point:

The boiling point was reported in reference (1) as 178°C at 1 mm Hg. RL Johnson (3) reports the boiling point as 165°C at 0.07 mm Hg and 196°C at 0.1 mm Hg.

Specific gravity and Viscosity:

The specific gravity was reported in reference (1) to be 1.0483 using the methods given in the Japanese Pharmacopoeia. These methods include both the use of a pycnometer and a hygrometer. Because of the number of significant figures reported, it is likely that a pycnometer was used. The viscosity was measured to be 43.3 cS in reference (1), also following the methods given in the Japanese Pharmacopoeia, which specifies using a Ubbelohde type capillary viscometer with a flow time between 200 and 1000 seconds.

Hygroscopicity:

Ibuprofen piconol was stored at 30°C and relative humidities from 32.4% to 100% for 200 hours (8 1/3 days) and analyzed for water content (1). No container size, amount of liquid, or depth of sample was given. Extrapolation of the graph gives the following estimated values:

50% RH: 0.6%
75% RH: 0.8%
100% RH: 1.1%

Moisture content:

Three lots of drug were analyzed using a Karl-Fischer analysis for water content. The values reported were 0.3% for drug stored at 30°C and 45% RH for 3 months, and lower for all other samples analyzed. Drug stored at room temperature in glass or metal containers for a year and more show 0.1% or less water content (2).

Acid-Base properties:

Since ibuprofen piconol contains a pyridine nitrogen, it acts as a weak base. The corresponding acid equilibrium constant is for the acid salt form of the drug. The pKa was determined to be 3.8 (1) using the variation of the UV spectrum with pH. Because of the low solubility of ibuprofen piconol in aqueous solutions, buffers containing various amounts of methanol were used, and the pKa extrapolated to zero percent methanol concentration.

Surface Tension of Saturated Aqueous Solution:

Surface tension was determined using a SensaDyne tensiometer calibrated with Milli-Q water having a specific resistance above 10 megohm-cm and Burdick and Jackson high purity 2-propanol. All glassware was cleaned using chromic acid and rinsed with copious amounts of Milli-Q water before using.

Table 1

pH vs Solubility of Ibuprofen Piconol in Buffer

pH	Solubility (ppm)
2.0	440
3.0	76.8
4.0	21.3
6.0	13.6
H_2O	16.5
8.0	17.2

A saturated solution in Milli-Q water was prepared an shaken for at least three days at 25°C. The surface tension was determined to be 71.0 ± 0.5 dynes/cm at 25°C.

Solubility Profile:

The miscibility of ibuprofen piconol in various solvents was determined by the addition dropwise of drug to a small amount of solvent and shaking until approximately equal amounts of drug and solvent had been added. If no phase separation was observed, the test was repeated adding solvent to a small amount of drug. This test indicated that ibuprofen piconol is miscible with squalane, mineral oil, petrolatum (at 60°C), vegetable oils, isopropyl myristate, 1-tetradecanol (at 40°C), 1-octanol, 2-propanol, ethanol, and propylene glycol. Dow Corning 344 silicone fluid (cyclomethicone) was miscible above room temperature, but clouded below room temperature. In addition, reference (1) indicates that ibuprofen piconol is miscible with hexane and diethyl ether. For glycerol, two phases were observed, and the actual solubility was determined to 16.4 ± 0.1 mg/ml using the HPLC technique described below. The Dow corning 200 silicone fluid (dimethicone) was not miscible with the HPLC mobile phase or any compatible solvent, so the solubility of drug in this solvent was determined to be 3.04 ± 0.02 wt% by titration of a small sample of ibuprofen piconol to a clear end point. Because of the extreme temperature sensitivity of the Dow Corning 344 system, no attempt was made to analyze the solubility in this solvent.

Table 2

Partition Coefficients of Ibuprofen Piconol
in Various Solvents as a Function of pH

pH	Octanol/Buffer	Hexan/Buffer	Chloroform/Buffer
1.0		20	infinite
2.0	20.2		
3.0	129	155	infinite
4.0	23,000		
6.0	48,500		
H_2O	18,750		

Britton-Robinson buffers were used for the pH solubility and partitioning studies. They were prepared as given in reference (4). Results are shown in table 1. Above pH 8.0 there is a large ibuprofen peak, which shows base catalyzed ester hydrolysis of the ibuprofen piconol.

The HPLC assay used to determine concentrations employs the column and mobile phase used in the analysis of sheep plasma and lymph fluid (5). These are: a 25-cm Zorbax C_8 column and a mobile phase of 550 ml acetonitrile, 410 ml Milli-Q water, 45 ml. 0.5 N. sodium hydroxide and 5.0 ml glacial acetic acid. A flow rate of 1.5 ml/min and a detection wavelength of 22 nm were used. Butylparaben was used as an internal standard. The concentrations of internal standard and calibration standards of ibuprofen piconol, and the injection volume, were adjusted to give adequate response while remaining within the linear range of the detector. Concentrations as low as 0.2 ppm could be assayed by taking a 3 ml sample adding, 0.2 ml 0.01% butylparaben in mobile phase, and injecting 150 μl.

Partition Coefficients:

The partitioning of ibuprofen piconol between octanol and buffer was determined by equilibrating equal volumes of buffer and 1% drug in octanol in a 25°C shaking water bath for at least 24 hours, separating the two phases using a separatory funnel and analyzing the drug concentration in each phase using the HPLC analysis given above. The buffer samples were run using the low concentration sample preparation given above. The octanol samples were prepared by taking 0.5 ml with mobile phase. An aliquot was then transferred to an HPLC vial for analysis. Results shown in table 2 are reported on a

wt%/wt% basis. Hexane/buffer and chloroform/buffer partition coefficients were taken form reference (1). Values for the octanol/aqueous partition coefficient was also calculated using the method of Chou and Jurs (5). The value of loge $P_{calculated}$ was 4.72 which was in excellent agreement with our P_{exp} value of 4.68 at pH 6.0.

STABILITY

Bulk Drug:

Bulk drug stability data is available from stability studies initiated on three lots of drug manufactured by The Upjohn Company Fine Chemicals Division. The three lots of drug on stability show a slight rise in the total amount of impurities for one lot, to 0.7%, when stored at 40°C for three months. All other test show 0.2% impurities or less. Ibuprofen is seen at the 0.1%-0.2% level and does not appear to increase. Some darkening in color has been noted at higher temperatures. Reference (1) reports that ibuprofen piconol in amber containers was stable at room temperature for 36 months. The drug turned brown after 12 months at 40°C and 3 months at 50°C. Exposure to humidity did not appear to increase the rate of degradation or yellowing. The drug also browned on exposure to sunlight and high-intensity UV light. Bubbling air through the drug gave no change in color or in impurities, although the water content increased.

In Solution

Reference (1) gives plots of the observed pseudo first order kinetic degradation of ibuprofen piconol as a function of pH. Because the drug is not soluble in aqueous solutions, 30% dioxane was added. 80 μg/ml solutions were stored at 37 ± 0.2°C, sampled at specific time intervals, analyzed by HPLC. The degradation occurs at low and high pH and is, presumably, ester hydrolysis. The pseudo first order rate constants decrease from approximately 10^{-1}/day to 10^{-2}/day from pH 1 to pH 2.5, then remain below 10^{-2}/day until pH 8. The rate constant then rises rapidly again.

Stability data was obtained in < 1mM solutions of ibuprofen piconol in 10 mM solutions of the acetate salts of various metal ions in 0.05 M pH 5 acetate buffer (2). A degradation scheme of 4 weeks at room temperature followed by 11 days at 70°C was used. After four weeks at room temperature, the Cu(II) solution of drug had degraded such that only 25.4% of its original value remained. When this

solution was heated for 22 days at 70°C, no drug was detected. Zn(II) solutions, under the same conditions, assayed at 81.6% of the drug remaining after 4 weeks, and no drug was detected after the heating cycle. The ions Cr(III), Al(III), Fe(III) and 0.1% H_2O_2 degraded drug to a smaller degree, with between 92 and 96% of their original values at room temperature, and to 30%-33% of the drug remaining after heating.

In Ointment:

Ointments containing the following components were prepared by heating the ingredients to 80°C, stirring, cooling to 40°C, and packaging.

Ibuprofen piconol	0-75 mg/g
White petrolatum	800-875 mg/g
Lexemul 515	50 mg/g
Anhydrous Lanolin-USP	75 mg/g

The ibuprofen piconol concentrations used were 0, 10, 30, 50, and 75 mg/g. The white petrolatum amount was decreased accordingly.

Stability data is available on the 5% ointment for 6 months at 8°C, 30°C and 40°C, and on the 0, 3, and 7.5% ointment for 3 months. These ointments show a maximum degradation of less than 3% after 6 months. The assay has approximately a 1% variation from sample to sample run on the same day, and seems to vary by approximately 2% from day to day. Therefore, the scatter in the data points prevents an accurate degradation rate to be determined at this time.

In Cream

Creams containing the following ingredients were prepared.

Ibuprofen Piconol	0-75 mg/g
White Petrolatum USP	125-200 mg/g
Light Mineral Oil NF	30 mg/g
Cetyl Alcohol NF	45 mg/g
Stearyl Alcohol NF	45 mg/g
Brij 58	20 mg/g
Methylparaben	2 mg/g

Phenoxyethanol	0 or 7.5 mg/g
Purified water	q.s.

Approximately 80% of the water, and the methylparaben were heated to 80°C; the other ingredients, except phenoxyethanol, were heated in a separate container to 80°C, then the aqueous and organic phases were combined and stirred vigorously. The emulsion was then q.s'd with 80°C water to the final weight (minus that of the phenoxyethanol if added), and the emulsion cooled to 50°C. The phenoxyethanol was then added, if appropriate, and the emulsion cooled further, to the congealing point, approximately 40°C. Creams containing 0, 1, 3, 5 and 7.5% ibuprofen piconol and no phenoxyethanel were prepared, and between 3 and 6 months of stability has been collected. Later, 0, 1, 3, 5 and 7.5% creams containing phenoxyethanol were prepared. One month stability data is available on these creams. All the creams appear physically stable, and only a slight, non-significant degradation is observed after up to 6 months at 8°C, 30°C, and 40°C.

DISCUSSION

The physical characterization of ibuprofen piconol has shown it to be a liquid that forms a glass on cooling much more readily than it does a true solid. It is slightly hygroscopic, but at humidities below 50% the uptake of moisture should be minimal. Higher humidities should not be a problem as long as the drug is in a tightly closed container. Surface tension measurements do not suggest that this molecule is surface active. Since the piconol ester of ibuprofen will be less polar than ibuprofen (aqueous solubility at pH 4.32 is 0.073 mg/ml), the low values of aqueous solubility for ibuprofen piconol are not surprising. The increase in water solubility below pH 4.0 can readily be explained in terms of the acid-base properties of a drug with a corresponding pK_a of 3.8. The expected increase in solubility of the acid salt is seen at the lower pH values. It should be noted that the ester hydrolyzes at a greatly increased rate at pH values less than 2.5. Thus, the increased solubility at low pH is of little value to the formulator.

A useful method for ranking the polarity of a liquid is to determine its solubility parameter. The solubility parameter is the sum of the intermolecular attractive forces, and can be empirically related to the extent of mutual solubility of different materials. Vaughan (8) recently reviewed the relevance of the solubility parameter to the formulation of cosmetics. By determining the solubility of ibuprofen piconol

in a series of solvents having a range of solubility parameters, it becomes possible to estimate how soluble ibuprofen piconol will be in any material or solvent, and the ibuprofen piconol solubility is given in Appendix A. Substances whose solubility parameters fall within two units of one another should be mutually soluble. As noted earlier, ibuprofen piconol is miscible with materials having solubility parameters ranging from 6.03 to 14.00. While systems miscible with ibuprofen piconol span an eight unit range in solubility parameters, it can be seen that immiscible combinations do occur at both extremes of the parameter range. From this solubility data, a very approximate solubility parameter of 10 can be assigned to iburpofen piconol.

The partition coefficient values indicate that ibuprofen piconol will highly favor the oil phase. Since the drug shows no indication of surface activity, ibuprofen piconol should remain in the oil phase of an emulsion, and should be readily formulated. Knowledge of the partition coefficient (52,500) in addition to the drug's aqueous solubility (0.0165 mg/ml) provides the informaiton necessary to predict the transdermal flux of ibuprofen piconol across intact skin. Use of the computational techniques described previously (9,10) results in a predicted percutaneous flux value of 35 ug/cm^2-hr for ibuprofen piconol from a saturated aqueous solution. A preliminary in-vitro percutaneous absorption study using the techniques described in reference (11) did not confirm the predicted flux values. Both a 5% ibuprofen piconol cream applied to viable nude mouse skin, and neat drug applied to human cadaver skin resulted in undetectable levels of either ibuprofen piconol or ibuprofen in the receiving media. Lack of detectable quantities of drug in the receiving media was attributed to the low aqueous solubility of the drug. it is recommended that further in-vitro transdermal studies use a 15/15/70 or similar sodium cholate/lecithin/water micellar solution as the receiving media.

Ibuprofen piconol is a very stable drug. It undergoes ester hydrolysis at pH values below 2.5 and above 8, but is stable between these two. It also degrades in the presence of metal ions, with Cu(II) and Zn(II) causing most the degradation. Therefore, the primary packaging chosen should exclude at least these two metals. Light and heat cause some darkening of the bulk drug, but does not significantly change the potency and only slowly causes an increase in the impurities. Therefore, only usual precautions need to be taken in storage and handling of the drug.

The ibuprofen cream and ointment as currently formulated are stable both to chemical degradation and to physical separation. After six months, the cream shows insignificant degradation, and the ointment shows less than 3% degradation. These results are preliminary and include assay variation which obscure any actual trends. In conclusion, stability difficulties are not anticipated for ibuprofen piconol formulations. Future cream, ointment, or spray formulations should not require exceptional developmental effort. The categories given in Appendex A provide a template for future topical product preformulation characterization studies, especially if the active is an oil rather than a crystalline solid.

REFERENCES

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APPENDIX A

PREFORMULATION DRUG PROFILE-FLUIDS/OINTMENTS

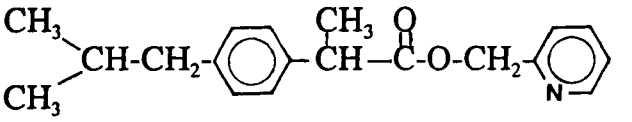
I. Compound Identification number or common name: pimeprofen

II. Chemical name: 2-pyridylmethyl-2-[p-l 2-methylpropyl)phenyl]-propionate

III. Approved Generic Name(s): Ibuprofen piconol

IV. Approved trade Name(s):

V. Chemical Structure:



VI. Molecular Formula: $C_{19}H_{23}NO_2$

VII. Therapeutic Category: Non-steroidal anti-inflammatory

VIII. Anticipated Doses: 5% Cream and Ointment; 10% spray

IX. Organoleptic Properties

A. Appearance: pale yellow, clear, slightly viscous liquid

B. Odor: Odorless

C. Taste: Bitter

D. Feel: Oily

X. Drug metabolism and Pharmacokinetics

A. Therapeutic Blood Level: N/A-ibuprofen piconol is rapidly hydrolyzed in the blood after percutaneous absorption. Thus, ibuprofen piconol could not be detected in either the blood or urine (12)

B. Biological Half-Life: N/A

C. Volume of Distribution: N/A

XI. Physical Properties

A. Melting Point < -68°C. Forms glass easily, did not crystallize on cooling to -198°C.

B. Boiling Point: 178°C at 1 mm Hg (1)
165°C at 0.07 mm Hg (3)
196°C at 0.1 mm Hg (3)

C. Specific Gravity: (at 20°C) 1.0483

D. Viscosity: 43.3 cS

E. Hygroscopicity

1. 50% RH: 0.6%
2. 75% RH: 0.8%
3. 100% RH: 1.1%

F. Moisture Content: <0.2%

G. Acid-Base properties

1. pKa: 3.8
2. pH of a 1% Solution: Not soluble
3. pH of a 10T Solution: Not soluble

H. Surface Tension of Saturated Aqueous Solution: 71.0 ± 0.5 dynes/cm at 25°C

I. Solubility Profile

1. pH vs Solubility:

pH vs	Solubility (ppm)
2.0	440
3.0	76.8
4.0	21.3
6.0	13.6
H_2O	16.5
8.0	17.2

2. Solubility Scan (Solubility parameter in parentheses)

a. Silicon Fluids: Cyclomethicone (5.99): miscible above room temperature; clouds on cooling
Dimethicone (5.92): 3.04 ± 0.02%

b. squalane (6.03): miscible

c. mineral oil (7.09): miscible

d. petrolatum (7.33): at 60°C, miscible

e. isopropyl myristate (8.02): miscible

f. 1-tetradecanol (9.16): miscible at 40°C

g. 1-octanol (10.09): miscible

h. iso-propanol (11.24): miscible

i. ethanol (12.55): miscible

j. triethanolamine (13.28): not determined

k. propylene glycol (14.00): miscible

l. glycerol (16.26): 16.4 ± 0.1 mg/ml

3. Other Solubility Data

a. hexane: miscible

b. diethyl ether: miscible

c. vegetable oils: miscible

J. Partitioning

1. Octanol/Buffer as a function of pH:

pH2	20.2
pH3	129
pH4	23,000
pH6	48,000

2. Octanol/Water as a function of drug concentration: 18,750

3. Hexane/Water

a.	Hexane/pH1	20
b.	Hexane/pH3	155
c.	Hexane/pH5-9	infinite

4. Chloroform/Water

a. All pH buffers: infinite

5. Calculated from group contribution methods: 52,500

XII. Stability

A. Bulk Drug

1. Temperature: Slight browning of oil at higher temperatures

2. Humidity: May increase rate of browning slightly

3. Light: Increases rate of browning

4. Oxygen: Air Oxidation not seen

B. In Solution

1. Temperature: Not Determined

2. pH: Basic solutions break down above pH9; stable in the pH range 3-7. Ester hydrolysis.

3. Presence of surfactants: Successfully formlated with Lexemul 515 and Brij 58.

4. Presence of preservatives: Successfully formulated with methylparaben and phenoxyethanol.

5. Presence of metal ions:

Cu(ll): extreme degradation at room temp & 70°C.
Zn(ll): moderate degradation at room temp, extreme at 70°C.
Cr(lll), Al(lll), Fe(lll) and H_2O_2: slight degradation at room temp, extreme degradation at 70°C.

C. In cream: Less than 3% loss of potency after 6 months at 40°C
D. In ointment: Less than 3% loss of potency after 6 months at 40°C