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COMMUNICATION

Physicochemical Characterization of YJA20379-8, a New Proton Pump Inhibitor

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ABSTRACT

The physicochemical properties of the potent reversible proton pump inhibitor YJA20379-8, 3-butyryl-4-[(R)-1-methylbenzylamino]-8-ethoxy-1,7-naphthyridine, were studied. YJA20379-8 is essentially nonhygroscopic pale yellowish crystalline powder. It is practically insoluble in water, and its lipid solubility is high. The pH solubility profile exhibits an L-shaped curve, indicating YJA20379-8 is a basic substance having a soluble ionized form in acidic conditions. This is consistent with the result of an experiment to determine pK_a. *The solid-state stability study shows that YJA20379-8 is stable at various temperatures and humidities, but is decomposed by light.*

INTRODUCTION

Acid appears to be a mediator common to most forms of peptic ulcer, and the gastric H^+/K^+-ATPase (proton pump) has been shown to be the primary pump for acid secretion in the stomach. Therefore, the inhibition of H^+/K^+-ATPase, which mediates the terminal step of acid secretion, would be the most effective way of controlling gastric acid secretion. Recently, many agents have been developed as inhibitors of gastric H^+/K^+-ATPase (1).

YJA20379-8, 3-butyryl-4-[(R)-1-methylbenzylamino]-8-ethoxy-1,7-naphthyridine (Fig. 1), is a newly synthesized compound that has potent antiulcerative activity as a proton pump inhibitor. To design and develop appropriate dosage forms for this drug, we have to generate the physicochemical properties of this drug. In the present study, because the quantity of the drug substance is limited, we investigated some essential properties that could affect drug performance and development of an effective dosage form (2). Solubility, lipid-water

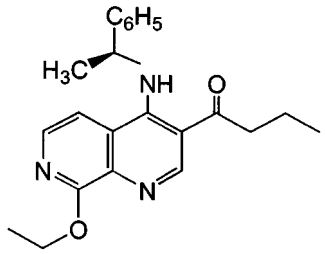

Figure 1. Chemical structure of YJA20379-8, 3-butyryl-4-[(R)-1-methylbenzylamino]-8-ethoxy-1,7-naphthyridine.

partition, ionization, and stability parameters were studied (3,4).

MATERIALS AND METHODS

Materials and Apparatus

YJA20379-8 was used as received from the synthetic laboratory of Yungjin Pharmaceutical Company, Limited (Kyunggi-do, Korea). All other substances and solvents were reagent or high-performance liquid chromatography (HPLC) grade.

The apparatus used in the experiment were as follows: differential scanning calorimeter (DSC) (V4.0B Dupont 2000, Wilmington, DE), shaking incubator (SI-900R, Jeio Tech, Korea), HPLC system (Waters pump and tunable absorbance detector, MA; Youngin integrator, Korea), centrifuge (Brushless DC motor centrifuge, Vison Sci., Korea), pH meter (SA720, Orion, Beverly, MA), and a pK_a measuring instrument (PCA101, Sirius, UK).

Thermal Analysis

The thermal properties were characterized with by DSC. A heating rate of 10°C/min was employed for the technique over a temperature range 25°C–155°C.

Hygroscopicity

On a polystyrene dish, 100–200 mg of YJA20379-8 was spread out and dried over phosphorus pentoxide in a desiccator to constant weight. Then, the dish was transferred to hygrostats containing saturated salt solutions (Table 1). Weighing was performed twice a day until equilibrium was reached. The dish was transferred consecutively from lower to higher relative humidities (RHs) (5–7).

Table 1

Saturated Salt Solution for Maintaining Constant Relative Humidity (RH) Conditions in Desiccators

Saturated Salt Solution	% RH at 25°C
Potassium acetate	23
Potassium carbonate	43
Sodium nitrite	64
Potassium bromide	83
Potassium nitrate	93

Solubility

An excess amount of YJA20379-8 was introduced into 3 ml of purified water in a screw-capped glass tube. The suspension was placed in a shaking incubator (25°C, 100 rpm) for 2 days to allow the solution to reach equilibrium (6,8). Preliminary solubility studies indicated that shaking for 2 days was adequate to attain equilibrium solubility. The aliquot was filtered through a 0.45-μm membrane filter (polyvinylidene fluoride [PVDF], Whatman, UK). To prevent error due to possible filter-adsorption losses, the first few drops were discarded. An additional aliquot was collected and assayed by HPLC.

Solubility as a function of pH was determined also. The solution pH was adjusted with 0.1 N NaOH or HCl solution, and the pH was measured before filtration (9).

Ionization Constant

The pK_a of YJA20379-8 was determined by a computerized titration instrument following Avdeef, Comer, and Thomson's method (10). YJA20379-8 is practically insoluble in water, and it was necessary to use methanol as a cosolvent.

Partition Coefficient

Mutual saturated water or buffer solution and *n*-octanol were used. Methanolic solution (100 μl) containing 150 μg of YJA20379-8 was evaporated in a glass tube, and 3 ml of each saturated solvent were added to the tube (11). Then, the tube was capped and placed in a shaking incubator (25°C, 100 rpm) for 2 days to allow the solution to reach equilibrium. The phases were separated by centrifugation at 3000 rpm for 5 min. The concentration of YJA20379-8 in the aqueous phase was determined by HPLC. The concentration of the substance in *n*-octanol

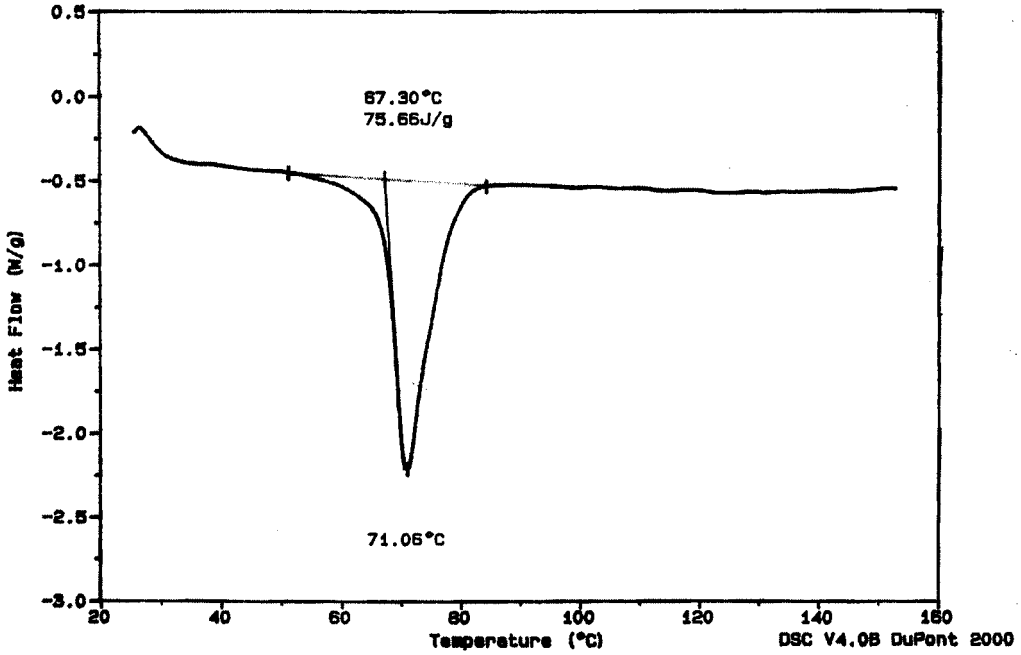

Figure 2. DSC pattern of YJA20379-8.

phase was calculated from the difference between the initial and final concentrations of the aqueous solution (4,12).

Stability

Exactly weighed YJA20379-8 (10–20 mg) was put in a transparent vial, and it was stored in a chamber with controlled temperature and humidity (40°C, 75% RH), a 40°C oven, near a south-facing window, or in a dark place. The vials were sealed except one, which was exposed in humidity (13).

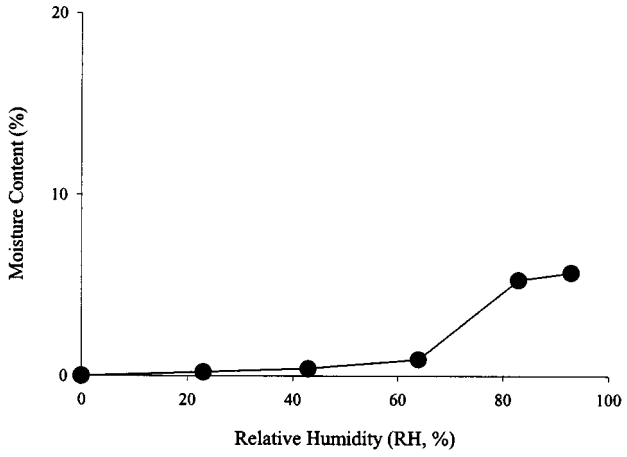

Figure 3. Hygroscopicity of YJA20379-8 at room temperature.

Analytical Method

Quantitative analysis of YJA20379-8 was accomplished by HPLC using a μBondapak C18 column (3.9 × 300 mm, 10 μm) with a mobile phase of methanol:water:pH 7.0 phosphate buffer (KP, monobasic) = 380:50:10 at a flow rate of 1.0 ml/min with UV detection at 245 nm. Under these conditions, YJA20379-8 elutes with a retention time of 4–5 min.

Table 2

Solubility of YJA20379-8 in Various Solvents at Room Temperature

Solvent	Solubility (mg/ml)
Ethanol	>1000
DMSO	180
Soybean oil	47
Water	0.0014

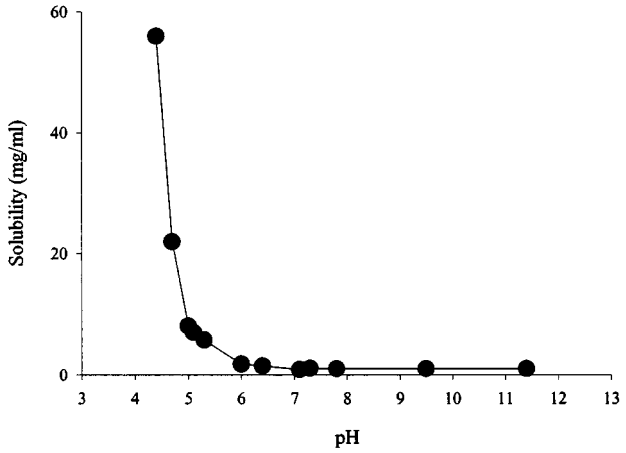

Figure 4. The pH solubility diagram of YJA20379-8 at room temperature.

RESULTS AND DISCUSSION

Physical Properties

The DSC thermogram of YJA20379-8 produced a single-melt transition near 71°C (Fig. 2).

The changes in the moisture content of YJA20379-8 at various relative humidity conditions (% RH) were determined. YJA20379-8 was found to be almost non-hygroscopic (Fig. 3).

Solubility Study

YJA20379-8 is very soluble in ethanol, freely soluble in dimethylsulfoxide (DMSO), soluble in soybean oil, and practically insoluble in water (Table 2).

The pH-dependent solubility profile of YJA20379-8 is shown in Fig. 4. The graph exhibits two distinct regions that arise as a consequence of the states of ionization of this compound. In an acidic condition, YJA20379-8 exists as a cation or as a neutral molecule, and this is reflected in the steep decrease in solubility. As the pH nears neutrality, the free base is the predominant species, and the solubility is minimized. This is consistent with the acidity constant. The pK_a of YJA20379-8 is about 5.3 at 20°C ± 1°C by sirius PCA101.

YJA20379-8 is very lipophilic. The molecule was partitioned to the aqueous phase only in an acidic condition (Table 3).

Table 3

Partition Coefficient (Log P) of YJA20379-8 at Room Temperature

Aqueous Phase	Log P[a]
Water	∞
pH 1.2 buffer	1.4
pH 6.8 buffer	∞

[a] $\log P = \log \frac{[n\text{-Octanol phase}]}{[\text{Aqueous phase}]}$.

Table 4

Stability of YJA20379-8 in Solid State

Storage Condition	Appearance	Remaining (%)
Initial	Pale yellowish crystalline powder	100
Room temperature, 7 months	Pale yellowish crystalline powder	99.8
40°C, 75% RH, 6 months	Pale yellowish crystalline powder	99.0
Sunlight, 1 month	Deep yellowish crystalline powder	95.0

Stability Study

The result of the solid-state stability test for YJA20379-8 is shown in Table 4. It is revealed that YJA20379-8 is stable over the range of temperature and humidity, but is somewhat decomposed by light.

ACKNOWLEDGMENT

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