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COMMUNICATION

Preformulation Investigation of the Novel Proton Pump Inhibitor Lansoprazole

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ABSTRACT

Some technologically important physicochemical properties of lansoprazole were investigated. This compound is very unstable, especially in aqueous solutions with low pH. It has one acidic and two basic dissociation constants. Lansoprazole has relatively high solubility in solutions with high pH and is well partitioned from aqueous to n*-octanol phase. Under conditions examined in this study, lansoprazole was not hydroscopic and did not decompose at higher relative humidities.*
Key Words: *Lansoprazole; Log* P*; Physicochemical properties; pK_a.*

INTRODUCTION

Lansoprazole is an effective acid pump inhibitor, acting at the final enzymatic step of the acid secretory pathway of the parietal cell, decreasing acid secretion regardless of the primary stimulus (1).

The main obstacle in preparing an effective lansoprazole peroral formulation is its instability, especially in the presence of acids, either in solutions or in dosage form. Therefore, lansoprazole is administered as an enteric-coated formulation (1).

In this work, we determined some technologically important properties for lansoprazole (i.e., stability/instability at different conditions and physicochemical parameters) to obtain all the necessary information for design of a peroral formulation.

RESULTS AND DISCUSSION

According to the literature data (2), lansoprazole is unstable at pH below 7. It is converted very quickly in aqueous solutions with high contents of hydronium ions to the sulfenamide form, which reacts with H^+/K^+-ATPase in parietal cells. Regarding the structural formula of lansoprazole, one can expect that it possesses at least one basic ionization constant. For its determination by the spectrophotometric method, acidic aqueous solutions

should be used. Therefore, we determined degradation first-order rate constants of lansoprazole in aqueous solutions at different pH values (in hr^{-1}): 12.4, 9.0, 8.2, 5.1, 1.2, 2.3×10^{-2}, 4.4×10^{-3}, 1.1×10^{-3}, and 2.9×10^{-4} at pH 1, 2, 3, 4, 5, 7, 9, 11, and 13, respectively. These values confirm that lansoprazole stability in aqueous solutions is pH dependent. In addition, these values for the degradation first-rate order constants are lower than those determined previously (2).

Because of the instability of lansoprazole, its pK_a values were determined by dissolving lansoprazole in methanol; this solution was then diluted with appropriate buffer (1:50, v/v); after a very short time (about 30 sec, which is still acceptable regarding the degradation rate constants), the absorbance was measured. The pK_a values determined for lansoprazole were acidic ($pK_{a1} = 8.84 \pm 0.04$) and basic ($pK_{a2} = 4.15 \pm 0.06$ and $pK_{a3} = 1.33 \pm 0.09$). From the point of stability results, in spite of very careful determinations, only acidic pK_a was determined exactly; the basic pK_a values, especially the lower one ($pK_a = 1.33$), can be considered more as estimates.

Regarding the structure of lansoprazole, which is the derivative of 2-[[(2-pyridyl) methyl]sulphinyl] benzimidazole, it can possess three dissociation constants in the range 1–14, two basic and one acidic: The pK_a of pyridine is 5.2, while the pK_a values of benzimidazole are 5.5 as a base and 12.3 as an acid (3). The comparison of literature values with those determined by the experiment for lansoprazole shows that the introduction of different substituents into the molecule significantly influenced acido-basic properties of the pyridine and benzimidazole moiety. The introduction of sulphinyl group and 2,2,2-trifluoroethoxy group is, in the case of lansoprazole, very important and increases its acidic properties (i.e., lowers its pK_a values) significantly.

The aqueous solubilities S_w were determined in the broad pH range at $T = 25°C \pm 0.1°C$ and are 7.8, 0.6, 0.8, 1.2, 35, and 908 (the values are given as $S_w \times 10^4$ mol/L) at pH 3, 5, 7, 9, 11, and in 0.1 M NaOH, respectively. The solubility experiments were performed with a large excess of the substance. It was anticipated that decomposed lansoprazole could be replaced with the intact substance during the experiment. Therefore, the samples were taken after different time intervals (1 min, 10 min, and 30 min at pH $<$ 7 and 0.5 hr, 2 hr, and 24 hr at pH $>$ 7) to determine the real thermodynamic equilibrium. However, the solubilities determined at low pH might not represent the true thermodynamic values. The results clearly show that the solubility exhibits great dependence on pH. The solubility values increased when pH increased; this was especially notable at pH values above 9, at which lansoprazole is present in dissociated form, and they are rather constant at neutral pH (pH $<$ 9, i.e., buffer pH = 7 and pH = 5), at which lansoprazole is un-ionized. Regarding the ionization studies and contrary to the literature data (2), its solubility increases again at pH 3 (lansoprazole is in protonated form at this pH because its $pK_{a2} = 4.15$). The solubility values are thus in accordance with experimentally determined acido-basic properties of lansoprazole. Our solubility results at higher pH are also in agreement with those determined previously (2,4).

Powder dissolution rate studies in water showed the influence of particle size on the dissolution kinetics. The influence of lansoprazole particle size on the dissolution rate was less than expected (the first-order rate constants for the dissolution of the particles with $d < 45$ μm and of the particles with $d > 180$ μm were 0.030 min^{-1} and 0.024 min^{-1}, respectively). This small difference was attributed to the pronounced tendency of smaller particles of lansoprazole to agglomerate after their contact with aqueous dissolution medium.

Similar to solubility results, the dissolution studies also showed the influence of the pH on the dissolution rate. However, the intrinsic dissolution rate of lansoprazole was very low. These low results were attributed to low wettability of lansoprazole (the measured value for the contact angle determined with demineralized water was $79.7° \pm 2.2°$) and to small surface area of the disk (0.5 cm^2). Calculated intrinsic dissolution rates for lansoprazole at pH 9 and at pH 6.8 were $1.2 \pm 0.033 * 10^{-2}$ mg min^{-1} cm^{-2} ($3.2 \pm 0.09 * 10^{-5}$ mol min^{-1} cm^{-2}) and $7.7 \pm 0.02 * 10^{-3}$ mg min^{-1} cm^{-1} ($2.1 \pm 0.035 * 10^{-5}$ mol min^{-1} cm^{-2}), respectively.

Lansoprazole partitioning properties between *n*-octanol and water phase also are strongly dependent on pH (log *P* values were 1.9, 2.1, 2.1, 1.6, 1.3, and 1.0 at pH 6, 7, 8, 9, 10, and 11, respectively). The log *P* values were rather constant at neutral conditions ($6 <$ pH < 8), but then slowly decreased at more alkaline conditions (pH > 9), at which lansoprazole deprotonates ($pK_{a1} = 8.84$). The partition experiments were performed by a shake flask method over a broad concentration range, and log *P* was constant over the whole range. This indicates that there are no lansoprazole associates formed in any phase.

Lansoprazole was kept at different relative humidities (RH = 44%, 75%, 96%) for 3 months at room temperature. It was found that, under these conditions, lansoprazole does not bind any water, and no degradation in any sample was observed. These observations were confirmed by a dynamic water sorption study. Lansoprazole

is practically nonhydroscopic; only 0.02% moisture was sorbed at the highest relative humidity (95%).

CONCLUSIONS

Overall, lansoprazole is a very unstable compound in aqueous solutions, especially at low pH. It is relatively well partitioned from water to the octanol phase. This could indicate its good absorption properties. It is also well soluble in the aqueous solutions with higher pH; on the other hand, the intrinsic dissolution study showed that the absorption process can be limited by the dissolution rate. Water sorption studies showed that lansoprazole is not hydroscopic, and that it does not decompose at high relative humidities.

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