Development of an oral formulation of omeprazole

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Omeprazole has a low water solubility and is chemically labile in an acid environment. In the formulation of an oral dosage form of omeprazole the possibilities of dissolution rate limited absorption and preabsorption degradation must be kept in mind. A water suspension of omeprazole was tested in a pilot bioavailability study. The suspension was given to six healthy, fasting volunteers on two occasions – together with sodium bicarbonate solution and together with the same volume of water. When the suspension was given with water the bioavailability was reduced by about 50 % owing to preabsorption degradation. In another bioavailability study the slowest of three granule formulations with differing *in vitro* dissolution rates showed a reduced extent of absorption.

A controlled-release pellet formulation (enteric-coated) was formulated and tested in a series of bioavailability studies. A single dose given with food resulted in a delayed absorption and possibly lower bioavailability than under fasting conditions. When the granules were given on an empty stomach before the morning meal the length of time between dosage and meal was of no importance. Concomitant administration of a liquid antacid had no influence on the bioavailability of omeprazole.

Key-words: Bioavailability; controlled release; dosage form; enteric coating; omeprazole; stability

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Introduction

Omeprazole (Figure 1) is a substituted benzimidazole which selectively inhibits the proton pump in the gastric mucosa (1, 2). Omeprazole is very slightly soluble in water, but is very soluble in alkaline solutions as the negatively charged ion. It is an ampholyte with $pK_a \sim 4$ (pyridinium) and 8.8 (benzimidazole).

Omeprazole degrades very rapidly in water solutions at low pH-values. Figure 2 shows a plot of the logarithm of the observed rate constant for degradation as a function of pH. In each experiment, the initial, pseudo-first-order rate of degradation was calculated from the amount of unchanged omeprazole in buffer solutions (3). The rate of degradation proceeds with a half-life of less than 10 minutes at pH-values below 4. At pH 6.5 the half-life of degradation is 18 hours; at pH 11 about 300 days.

Preformulation studies have shown that moisture, solvents and acidic substances have a deleterious effect on the stability of omeprazole and should be avoided in pharmaceutical formulations.

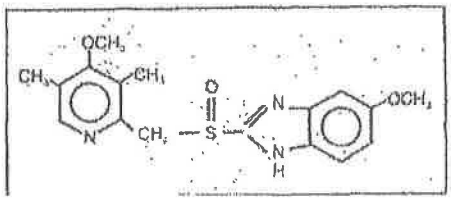


Figure 1. Omeprazole, H 168/68, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl] -1H-benzimidazole.

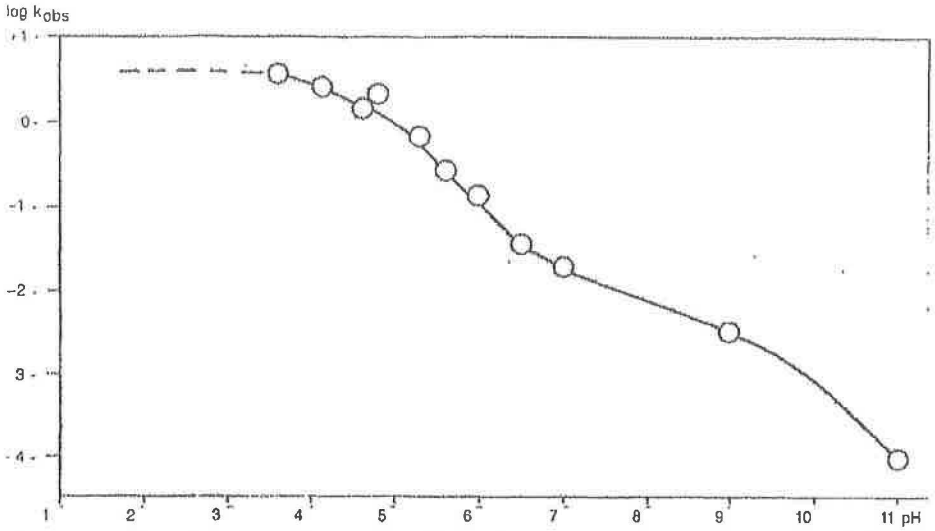


Figure 2. Logarithm of the observed rate constant (k_{obs}, h^{-1}) for the initial, pseudo-first-order degradation of omeprazole in water solution at constant pH, plotted as a function of pH.

The aim was to develop a stable, oral, pharmaceutical formulation of omeprazole in doses of 20–60 mg, with acceptable bioavailability characteristics.

Pharmaceutical considerations

For a substance which is very slightly soluble in water and which rapidly degrades in the acid environment of the stomach, there is a limited number of options as far as pharmaceutical development is concerned.

Solutions

In animal experiments and in initial studies in man it is highly preferable to use water solutions of the drug in order to avoid influences of the dosage form on the pharmacokinetics and pharmacodynamics of the drug. Omeprazole is, however, only soluble in alkaline water solutions with physiologically unacceptable, high pH-values.

Suspensions

In toxicological and phase I clinical studies, suspensions of omeprazole in water were used. Micronised omeprazole - particle surface area larger than 2.5 m^2/g – was suspended in a 0.25 % water solution of methylcellulose also containing sodium bicarbonate as pH buffer. The suspensions can be stored at refrigerator temperature for a week, or stored deep frozen for more than a year, and still retain 99 % of their initial potency. To avoid acidic degradation of omeprazole, the suspensions must be administered orally together with large amounts of pH buffering substances.

Solid dosage forms

There are two principle options for the formulation of an oral, solid dosage form of omeprazole:

- A conventional oral dosage form from which omeprazole is released and absorbed rapidly enough to avoid degradation in the stomach.
- An enteric-coated dosage form, which releases omeprazole for absorption in the small intestine.

The first option was ruled out in a pilot bioavailability study (see below), where it was shown that more than half of the omeprazole in a rapidly dissolving dosage form degrades in the stomach.

An enteric-coated dosage form, which does not release the active ingredient for dissolution and absorption until it has been transported down to the neutral reacting part of the small intestine, offers the best possibilities. The dosage form – a tablet, a capsule or granules – is coated with a polymer, which is insoluble in acid media but soluble in neutral to alkaline media. Depending on the choice of polymer and on the thickness of the coated layer, the pH-solubility profile of the enteric-coating can be controlled.

An enteric-coated dosage form of omeprazole must be perfectly coated and acid resistant, since, if any drug leaks out of the dosage form in the stomach, it is almost immediately degraded. The same is the case if an acidic medium can diffuse into the dosage form through pin-holes or damage in the enteric-coating.

Solid particles of a size exceeding 2–4 mm, such as enteric-coated tablets or capsules, are known to remain in the stomach for a long time before they are emptied into the small intestine (4–6). Non-disintegrating, coated tablets administered together with food were found to stay in the stomach for more than 14 hours (7). Enteric-coated aspirin tablets showed a prolonged and erratic gastric emptying, while enteric-coated granules of a size of about 1 mm dispensed in hard gelatine capsules dispersed in the content of the stomach and gradually emptied in to the small intestine in a reproducible way (5).

In the pharmaceutical manufacture of coated dosage forms, it is impossible to coat every single unit in a batch perfectly. A small fraction of units will have imperfect coating, or else be damaged during further handling and transport. For a single unit, enteric-coated dosage form of omeprazole, e.g, a tablet, there is always a small risk that all omeprazole contained in the dose can be degraded in the stomach. For a multiple unit, enteric-coated dosage form, e.g, enteric-coated granules dispensed in a hard gelatine capsule, only the omeprazole contained in a few pellets out of a total of hundreds is lost. Our efforts were, therefore, concentrated on developing an enteric-coated granule formulation.

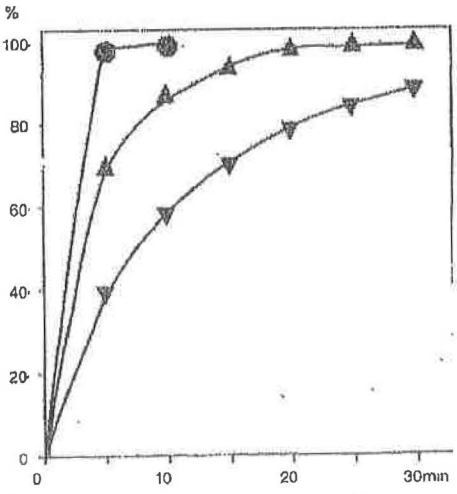


Figure 3. Dissolution of omeprazole from three granule formulations *in vitro* in phosphate buffer, pH= 6.5. The cumulative amount dissolved (%) is plotted as a function of time.
● granules, batch H 370-9-1
▲ granules, batch H 370-8-1
▼ granules, batch H 370-1-1

Formulation and *in vitro* testing

In the formulation of a solid dosage form of omeprazole, having a low water solubility of 0.1 mg/ml, there is always the risk of dissolution rate limited absorption. Three spherical granule formulations containing 10 % of omeprazole were manufactured and classified. The fraction with a diameter between 0.7 - 1.0 mm was used for further studies.

The dissolution rate *in vitro* was determined using a slightly modified beaker method according to Levy and Hayes (8). 500 ml of deaerated phosphate buffer pH 6.5, ionic strength 0.1, was kept at +37 °C and stirred at a rate of 100 rpm. An amount of granules corresponding to 10 mg of omeprazole was added and the amount dissolved determined from the continuous recording of the absorbance at 300 nm in a spectrophotometer using 1 cm flow cells. The cumulative amount dissolved is plotted as a function of time in Figure 3. All three formulations released most of their content of omeprazole within 30 minutes.

A pilot bioavailability study showed that the two faster dissolving granules were absorbed to the same extent, while the extent of absorption of the more slowly dissolving granules was reduced.

Rapidly dissolving, spherical granules containing 10 % of omeprazole were enteric-coated with approximately 15 % by weight of polymer. The coating was sprayed onto the granules from an organic solvent solution in a fluidised bed apparatus. After drying, the coated granules were analysed and dispensed in hard gelatine capsules.

The granules were tested for acid resistance *in vitro* in the following way: An amount of granules corresponding to 10 mg of omeprazole was dispersed in 500 ml of 0.1 molar hydrochloric acid at a temperature of +37 °C. Stirring was done with a paddle at a rate of 100 rpm. After two hours the granules were removed from the vessel, rinsed with water, dried and analysed for omeprazole by liquid chromatography. After two hours exposure to acid more than 85 % of the initial amount of omeprazole was recovered. When tested for dissolution rate *in vitro* in a medium of pH 6.5, more than 90 % dissolved within 15 minutes.

Omeprazole capsules have an acceptable storage stability when stored in a proper package. The stability characteristics of omeprazole – the substance is sensitive to moisture – necessitate the presence of a desiccant in the package.

Bioavailability evaluation of dosage forms

Omeprazole suspension given with and without pH-buffers

The solubility and stability properties of omeprazole prevent the use of water solutions as the reference formulation in animal and human studies. A rapidly dissolving suspension of micronised omeprazole is the second best choice as the reference formulation. However, since omeprazole degrades rapidly in an acid environment, it is essential to know the magnitude of the degradation occurring prior to the absorption of an oral dose. A pilot bioavailability study was therefore performed using six healthy, male volunteers.

A suspension of micronised omeprazole, 60 mg, in water, 50 ml, also containing 8 mmoles of sodium bicarbonate (pH=9) was administered in the following way: In the morning, after fasting for at least ten hours, the volunteers were given a solution of 8 mmoles of sodium bicarbonate in 50 ml of water. Five minutes later the volunteers took the omeprazole suspension and rinsed it down with another 50 ml of sodium bicarbonate solution. 10, 20, and 30 minutes later, a further 50 ml of sodium bicarbonate solution was taken. The amount of sodium bicarbonate is sufficient to buffer the pH of the gastric content to neutral values for at least 45 minutes.

In another experiment, a suspension of omeprazole in water (pH adjusted to 9 by sodium hydroxide) was administered according to the same protocol as above but with the sodium bicarbonate solutions replaced by water. Doses were given in random order with a week's interval between doses. Venous blood was sampled frequently over a period of four hours and blood plasma was analysed for omeprazole by liquid chromatography (9).

The results of the plasma analyses are shown in Figure 4. The absorption of omeprazole proceeds rapidly and peak plasma concentrations were

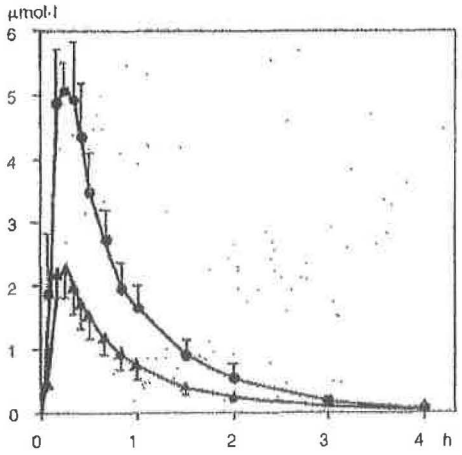


Figure 4. Plasma concentration of omeprazole in six healthy, fasting volunteers, mean + or – SEM after oral administration of omeprazole, 60 mg, given as:
● buffered suspension
▲ suspension without buffer

reached after a mean of 13 minutes in both experiments. The area under the plasma concentration time curve (AUC) was calculated by the trapezoidal method up to four hours after administration and extrapolated to infinity by dividing the last plasma concentration by the negative slope of the terminal, linear part of the log/linear plasma concentration time curve.

When the omeprazole suspension was given together with sodium bicarbonate buffer, the mean AUC was 4.8 μmol x h/l (range 2.8 – 8.8). Without the buffer protection the AUC was reduced to a mean of 2.1 μmol x h/l (44 %), indicating that more than half of the dose was lost due to degradation in the acidic stomach.

A straight-forward pharmacokinetic analysis of the data showed that the absorption of omeprazole was rapid and completed within the period during which the stomach was neutral. The results clearly show that a conventional, non-buffered, oral dosage form of omeprazole will have a low systemic bioavailability owing to preabsorption degradation of omeprazole in the stomach.

Bioavailability of granules – influence of dissolution rate

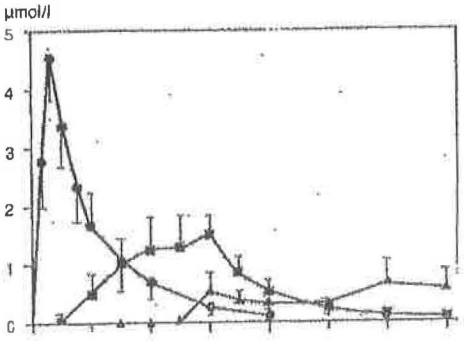
A pilot bioavailability study in six, healthy volunteers was performed in order to clarify the influence of the dissolution rate on the absorption of omeprazole. Three granule formulations – the dissolution curves are shown in Figure 3 – were tested using buffered suspension as the reference formulation. In order to avoid problems with the degradation of omeprazole, doses of 60 mg were given together with sodium bicarbonate, as described above. Venous blood was frequently sampled and blood plasma analysed for omeprazole (9). The AUC for the two faster dissolving granules (H 370-9-1 and H 370-8-1) relative to that of the reference formulation was 95 and 92 %, respectively. The granules with the lowest *in vitro* dissolution rate (H 370-1-1) were absorbed to a lower extent and had a mean relative AUC of 73 % only. The granules for the other two granule formulations and for the suspension, also indicating a lower rate of absorption.

From this experiment, it can be concluded that the *in vitro* dissolution rate method used can discriminate between acceptable and non-acceptable batches. In order to be fully absorbed, the *in vitro* dissolution rate should be as high as, or higher than, that of granules H 370-8-1.

Bioavailability of enteric-coated granules

Six, healthy, male volunteers participated in a three-way, cross-over bioavailability study. They received, in random order, 60 mg single, oral doses of omeprazole either as a buffered suspension given together with sodium bicarbonate solution, or as enteric-coated granules dispensed in hard gelatine capsules given together with 300 ml of water on an empty stomach or as enteric-coated granules in capsules together with a meal. In each experiment, standardised meals were served 2.5 and 6 hours after administration of the dose. Venous blood was sampled frequently for four hours (suspension) or seven hours (granules). Blood plasma was analysed for omeprazole by liquid chromatography according to Persson et al (9).

The results of the plasma analyses are shown in Figure 5. The absorption of omeprazole after the suspension was given was rapid, and peak plasma concentrations were reached within 10 – 20 minutes. After administration of the enteric-coated



oral doses of omeprazole as:
● buffered suspension
■ enteric-coated granules before breakfast
▲ enteric-coated granules with breakfast

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