Formulation of proton pump inhibitors

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Introduction

The proton pump inhibitors, or gastric acid pump inhibitors, on the market or in late stage clinical studies, have the same basic chemical structure, Figure 1. Omeprazole, the first proton pump inhibitor, has a rather low water solubility of 0.15 mg/ml. It has two pKa-values: 4.0 (pyridinium) and 8.7 (benzimidazole).
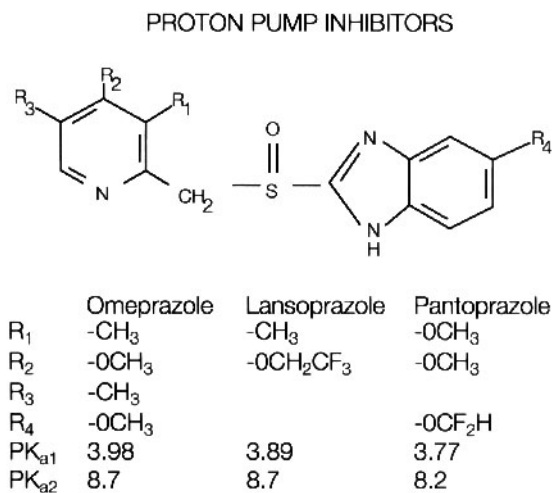
PROTON PUMP INHIBITORS

	Omeprazole	Lansoprazole	Pantoprazole
R_1	-CH$_3$	-CH$_3$	-OCH$_3$
R_2	-OCH$_3$	-OCH$_2$CF$_3$	-OCH$_3$
R_3	-CH$_3$		
R_4	-OCH$_3$		-OCF$_2$H
PK$_{a1}$	3.98	3.89	3.77
PK$_{a2}$	8.7	8.7	8.2

Figure 1. Chemical structure of proton pump inhibitors

The proton pump inhibitors are used in the treatment of gastro-intestinal disorders where a reduction of gastric acid secretion is beneficial. Omeprazole is, on most markets, indicated for treating gastric and duodenal ulcers, gastro-oesophageal reflux disease and the Zollinger-Ellison syndrome.

Omeprazole administered as a suspension given together with pH buffer solution is absorbed rapidly (1). Peak plasma concentrations are obtained within 10 to 30 minutes. Omeprazole is distributed and rather rapidly metabolised and is cleared from the body with a half-life usually less than 1 hour (2). The effect on pentagastrin stimulated gastric acid secretion is proportional to the dose (1). The proton pump inhibitors have a long duration of action. The effect of a single oral 20 mg dose of omeprazole on pentagastrin stimulated gastric acid secretion is still significantly different from control values 48 hours after dose (1). This means that the effect on gastric acid secretion is not correlated to the plasma concentration of omeprazole at any particular time, but still correlated to the dose.

The proton pump inhibitors interact with the very final step of gastric acid secretion (3). The acid is produced by parietal cells situated at the base of the oxyntic glands in the gastric mucosa. Hydrogen ions are pumped from the cytosol of the parietal cell to the secretory canal in exchange for potassium ions by an enzyme, H$^+$K$^+$-ATPase, located in the membrane between the cytosol and the secretory canal. The acid is emptied into the lumen of the gland and then further out into the stomach. The pH in the secretory canal must be very low, <pH1, since the acid produced by the parietal cell is diluted a couple of times before it reaches the stomach where pH can be as low as around pH1.

The proton pump inhibitors are pro-drugs. From the general circulation they diffuse into the parietal cells like they do into most other cells. In the parietal cells, since the proton pump inhibitors are weak bases, they partition to the acid compartment of the secretory canal, where they are trapped as positively charged ions. In the acid environment the proton pump inhibitors react to the active substance a sulphenamide, which covalently binds to sulfhydryl groups of the enzyme and inactivates it (4, 5).

The sulphenamides are very reactive. If there is no enzyme available, as is the case *in vitro*, the substances will still react and form degradation products. In acid

media the most common degradation products are two isomers (Figure 2) with fully conjugated electron systems, which make them very strong chromophores (6). The pure drug substances or pharmaceutical formulations containing them are discoloured by the degradation products when these are present in amounts of less than 1 %.
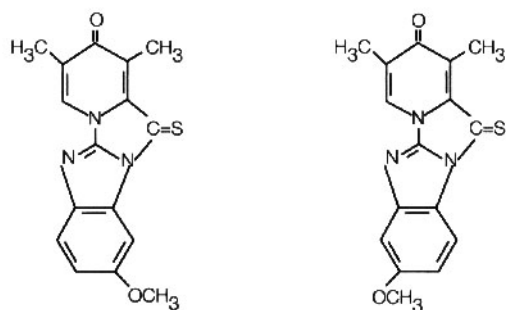
DEGRADATION PRODUCTS OF OMEPRAZOLE

Figure 2. Degradation products of omeprazole

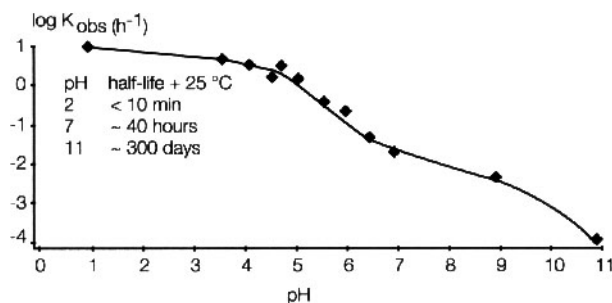OMEPRAZOLE DEGRADATION IN WATER SOLUTION

Figure 3. Degradation of omeprazole in water solution. Logarithm of the observed first-order rate constant for degradation at constant pH plotted as a function of pH

The rate of degradation of omeprazole in water solution is dependent on pH. Figure 3 shows the logarithm of the observed, initial, first order rate constant for degradation at constant pH plotted as a function of pH. In acid solution the rate is almost independent on pH and the reaction proceeds rapidly. The half-life of degradation at pH 2, room temperature, is less than 10 minutes; at pH 7 the half-life is about 40 hours, and at pH 11 around 300 days. Reaction mechanisms and rates of reactions have been studied in detail (7). A similar profile was recently published for lansoprazole (8). The rate of degradation at 37 °C of the three proton pump inhibitors is given in Table 1. Lansoprazole degrades with the highest rate followed by omeprazole and pantoprazole.

	Omeprazole	Lansoprazole	Pantoprazole
pH 2	105 sec	85 sec	195 sec
pH 7	23 hours	13 hours	39 hours

Table 1. Half-life of degradation in water solution, + 37 °C

What type of oral dosage form?

To sum up the background information.

The proton pump inhibitors:

- have rather low water solubility

- degrade rapidly in contact with acids to intensely coloured degradation products

- have better stability in neutral/alkaline media

- are absorbed rapidly and are metabolised rapidly

- have a long duration of action

There are, in principle, three options to formulate an oral dosage form of the proton pump inhibitors:

1. A dosage form which is dissolved and absorbed so rapidly that acid catalysed degradation in the stomach will be insignificant.

2. A dosage form which contains a sufficient amount of pH-buffering substances to buffer the pH of the stomach content to near neutral or alkaline values during the absorption phase.

3. An enteric coated formulation, which is insoluble in acid media but soluble in near neutral or alkaline media, such as in the small intestine.

To test the first option a pilot bioavailability study with micronised omeprazole suspended in water or in sodium bicarbonate solution was performed (9). Fasting healthy volunteers were first given 50 ml of sodium bicarbonate solution (8 mmoles = 0.67 g in 50 ml) 5 minutes prior to dose. The suspension of omeprazole in 50 ml of sodium bicarbonate solution was rinsed down with another 50 ml of sodium bicarbonate solution followed by further 50 ml portions of bicarbonate solution 10, 20 and 30 minutes after the dose; i.e. in total 300 ml of sodium bicarbonate solution. In a cross-over experiment omeprazole suspension was administered according to the same experimental procedure but the sodium bicarbonate solution was replaced by water. Frequent blood samples were taken and analysed for omeprazole, Figure 4.
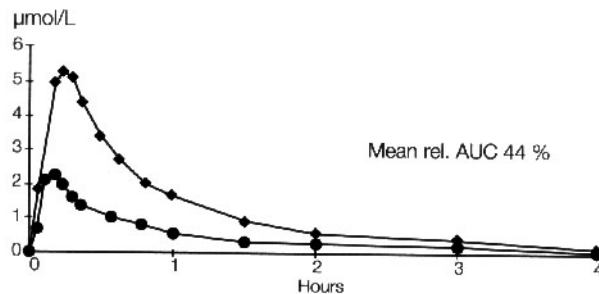
PLASMA CONCENTRATIONS OF OMEPRAZOLE

Figure 4. Mean plasma concentrations of omeprazole after administration of suspensions of micronised omeprazole to six healthy volunteers

Omeprazole was obviously rapidly emptied from the stomach to the small intestine and rapidly absorbed, distributed and eliminated. Peak plasma concentrations were found after 10 to 20 minutes in both experiments but the area under the plasma concentration versus time curve (AUC) was reduced by more than 50 % when the suspension was given without buffer protection. Without having the absolute evidences we assume that the reduced extent of bioavailability was due to acid catalysed degradation of omeprazole in the stomach.

What happens if we give omeprazole with a meal which increases the pH of the stomach content? In another cross-over pilot study we compared the micronised suspension given according to the "bicarbonate solution scheme" above with a rapidly dissolving tablet given together with an American breakfast containing eggs, toast, cheese, milk and coffee. The plasma concentration curves are given in Figure 5. We concluded that the gastric pH after breakfast was not high enough for omeprazole since more than 80 % of the dose was lost.
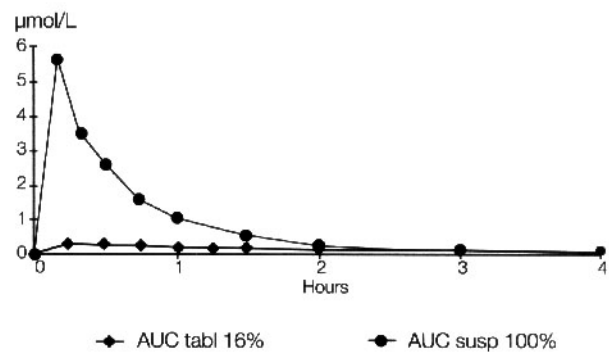
PLASMA CONCENTRATIONS OF OMEPRAZOLE

Figure 5. Mean plasma concentrations of omeprazole after administration of omeprazole suspension with buffer solution and after administration of a rapidly dissolving tablet given together with a meal to six healthy volunteers

The second option, to give omeprazole together with a sufficient amount of pH buffering substances in order to control the pH of the stomach to near neutral values during the absorption phase, would probably mean about one gram or more of sodium bicarbonate - i.e. too much for an ordinary tablet.

Remains an enteric-coated dosage form.

What is the best dosage form for proton pump inhibitors? A single unit dosage form? Or a multiple unit dosage form? Such as individually enteric-coated particles dispensed in a capsule.

Non-disintegrating, enteric-coated tablets given with food may stay in the stomach for long times, 10 to 15 hours, before they are emptied into the small intestine. Small particles, on the other hand - particle diameter less than about 3 mm -, are emptied from the stomach much more regularly, regardless of whether they are given with food or not (10).

It is not attractive to have a dosage form of an acid labile compound staying in the stomach for long periods of time, since a small damage of the enteric-coating can allow acid solution to enter into the core and destroy the active compound. A long gastric residence time will of course also delay the pharmacological effect.

Dissolution rate limited absorption

Omeprazole has a rather low water solubility, 0.15 mg/ml, which indicates that dissolution might reduce rate or extent of absorption. To test this possibility and in order to set quality limits we formulated small beads containing omeprazole by extrusion and spheronisation (9). The *in vitro* dissolution rate at pH 6.5 of three formulations is given in Figure 6.

Their absorption characteristics were tested in a small pilot bioavailability study, where the pellets were given according to the "bicarbonate solution scheme". The slower of the pellet formulations showed a somewhat slower absorption, with the peak plasma concentration occurring later, as well as a reduced AUC (73 %). The two faster dissolving formulations had their peak plasma concentration at the same time as the reference suspension and the AUC was not significantly different from the suspension, 92 and 95 % relative AUC respectively.
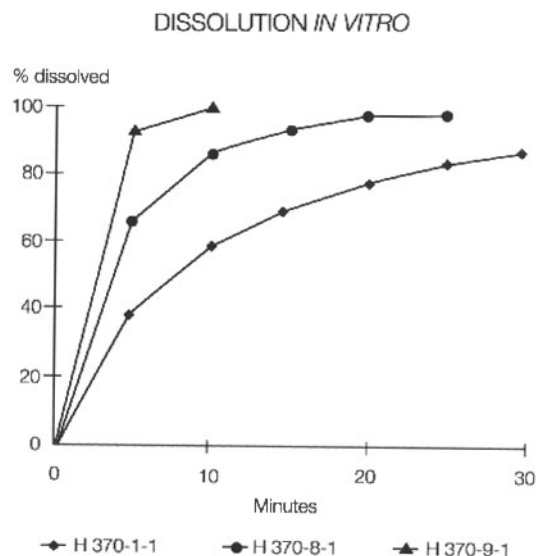

DISSOLUTION *IN VITRO*

Figure 6. Dissolution in vitro of three pellet formulations of omeprazole. USP dissolution apparatus N. 2 (paddle), 37 °C, 100 rpm, 500 ml phosphate buffer pH = 6.5

The dosage form

Omeprazole

Micronised omeprazole mixed with fillers, binders and pH-buffering substances is formulated into rounded beads, diameter 1.0-1.6 mm, by extrusion and spheronisation. After drying and sieving the beads are coated. We have used fluidized-bed technique and applied hydroxypropyl methylcellulose phthalate (HPMCP) from an organic solvent solution. For environmental reasons we are now switching to aqueous based coating with Metharylic acid copolymer (Eudragit® L3OD).

Enteric-coating polymers have free carboxyl groups. If the coating is applied directly to the omeprazole-containing cores the carboxyl groups will interact with the active substance at the surface of the core and cause discoloration during the coating process or during storage. This discoloration can be avoided by applying some type of separating layer between the core and the enteric-coating (11). Finally, the enteric-coated pellets are dispensed into hard gelatine capsules.

Lansoprazole

The dosage form used for lansoprazole on some European markets is constructed in a similar way (12). Inert cores, nonpareils 20-28 mesh, are charged into a roto-granulator. A solution of hydroxypropylcellulose (HPC) in water is sprayed onto the cores and a first powder mixture of lansoprazole, $MgCO_3$, sucrose, corn starch and low substituted HPC is added as a dusting powder, followed by a second powder mixture of sucrose, corn starch and L-HPC. Pellets are then enteric-coated with Metharylic acid copolymer and finally dispensed into hard gelatine capsules.

Pantoprazole

The pantoprazole dosage form used in clinical studies is an enteric-coated tablet.

Packaging and stability

Enteric-coated pellets of omeprazole dispensed in hard gelatine capsules are sensitive to moisture:

- capsules stored at 25 °C and 50 % r.h. are stable for one year

- capsules stored at 25 °C and 65 % r.h. are stable for three months

- capsules stored at 25 °C and 80 % r.h. are stable for two weeks, where "stable" means less than 1.5 % of degradation products

So moisture is critical for the long-term stability of omeprazole capsules and the normal moisture level of hard gelatine capsules, 15 to 17 % moisture, is too high for omeprazole and must be reduced. It is not possible to dry the empty capsules before the capsule filling operation. Dry capsules are just too brittle. At Astra we have solved the problem in the following way:

- Empty hard gelatine capsules are supplied with a moisture level of 15 ± 1 %.

- Capsules are filled and handled in an area with controlled humidity.

- Capsules are dispensed into tight bottles together with a balanced amount of a desiccant.

After 2 to 4 weeks an equilibrium moisture level is reached where the capsules have the desired water content.

Using this package configuration an expiration dating of three years at maximum 30 °C is no problem. There are, of course, other ways to reach the same moisture level and stability.

Bioavailability - influence of food

The omeprazole capsule formulation was given to healthy volunteers in a single dose, cross-over study to document the effect of food (13). The blood plasma concentrations were similar, Figure 7. The mean plasma concentration curve for fasting conditions has two peaks. Some volunteers have a short gastric emptying time when capsules are given on an empty stomach, while others empty in connection with next meal, given 2.5 hours after dose. The AUC was practically identical for the two administrations, and food has little influence on the extent of bioavailability.
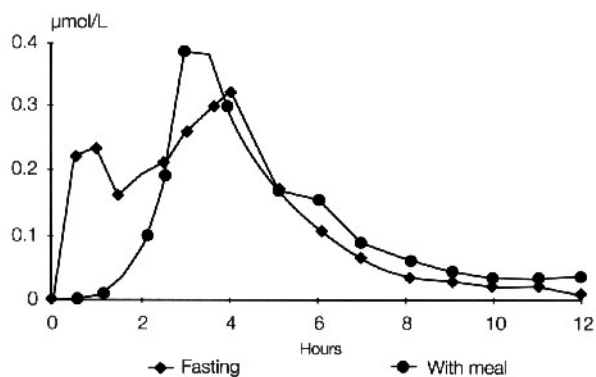
PLASMA CONCENTRATIONS OF OMEPRAZOLE

Figure 7. Mean plasma concentrations of omeprazole after administration of Losec® 20 mg capsules with and without food to 12 healthy volunteers

Enteric-coated tablets

We have also developed single-unit enteric-coated tablets of omeprazole. These are rapidly dissolving 7 mm diameter tablets cores coated first with a separating coating then with an entericcoating. The enteric coating protects tablets from dissolving in synthetic gastric juice during more than 16 hours. They still dissolve within 30 minutes when they are removed and tested in a medium of pH 6.8.

A comparative bioavailability study in 24 healthy, fasting volunteers showed that the enteric-coated tablets gave a similar mean AUC, but of course much more variation in time to reach peak plasma concentration than omeprazole capsules. According to regulatory guidelines enteric-coated single-unit tablets can never be bioequivalent with multiple-unit enteric-coated dosage forms. There will always be differences in peak plasma concentration and time to reach peak plasma concentration. A tablet is either in the stomach where it is insoluble or it is in the small intestine where it dissolves, while one part of a multiple-unit dosage form can be in the stomach and another part in the small intestine. The absorption phase for a multiple-unit dosage form will on average be longer and the plasma concentration versus time curve will be flatter.

A multiple-unit enteric-coated dosage form of a proton pump inhibitor cannot be bioequivalent with a single-unit enteric-coated dosage form (Same AUC, Cmax and tmax), but can they be considered therapeutically equivalent? The pharmacological effect of the proton pump inhibitors, which is most important for the clinical efficacy, is, of course, their ability to reduce gastric acid secretion. And so we designed a cross-over study in duodenal ulcer patients in remission. The patients, aged between 39 and 79 years, were administered omeprazole 20 mg enteric-coated tablets or enteric-coated pellets in capsules once daily with breakfast during five days. Before the study and during day six the rate of gastric acid secretion during intravenous pentagastrin stimulation was measured. Blood plasma was sampled frequently during days one and five.

The plasma concentrations after administration of capsules day one were the expected. There was a slight tendency towards a somewhat slower gastric emptying among the patients in comparison to young healthy volunteers. When tablets were administered on day one, two of twelve patients had no plasma concentrations of omeprazole during the blood sampling interval (blood was sampled every half hour during nine hours after dose), and one patient had his first measurable plasma concentration nine hours after dose. Once emptied into the small intestine the tablets were rapidly absorbed. It is quite obvious that enteric-coated tablets administered together with a meal will show a variable and prolonged gastric emptying rate in comparison with small enteric-coated pellets. During day five all patients emptied the tablets more regularly but still more variably than capsules.

The effect was measured as the maximum inhibition of pentagastrin stimulated gastric acid secretion during day 6, approximately 25 hours after the last dose. As is obvious from the data given in Table 2 there is no difference between tablets and capsules with regard to their effect on peak acid output during repeated dosing.

Still, I would like to say that a multiple-unit dosage form is the preferred dosage form for proton pump inhibitors.

Patient No	Capsule	Tablet
1	76	78
2	76	74
3	73	75
4	37	44
5	92	92
6	94	95
7	82	74
8	43	63
9	89	79
10	42	53
11	54	52
12	61	68
Average	68	71

Table 2. Inhibition of stimulated gastric acid secretion, on day 6, 25-28 hours after last dose, % inhibition of pre-study value

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