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COMMUNICATION

Dissolution of Omeprazole from Delayed-Release Solid Oral Dosage Forms

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ABSTRACT

The evaluation of the biopharmaceutical quality of omeprazole enteric-coated products (granules in capsules) with respect to its dissolution characteristics is not specifically regulated in any of the most common official pharmacopoeia. USP 23 includes a general monograph for enteric-coated products. This paper reports the evaluation of the medium pH effect on the dissolution rates of omeprazole from four omeprazole-containing products of different manufacturers. It is concluded that the USP 23 recommended dissolution procedure for enteric-coated products is not suitable due to the degradation of omeprazole under such conditions. Furthermore, the medium with pH 8.0 showed different dissolution rates not observed at pH 7.4, allowing discrimination between products of different manufacturers.
Key Words: *Enteric-coated products; In vitro dissolution; Omeprazole.*

INTRODUCTION

Omeprazole, 5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl] sulphinyl} 1-H-benzimidazole, is a powerful inhibitor of gastric acid secretion. Omeprazole may be considered as a prodrug because first it must be transformed into its sulfonamide form and only then is it able to react with the ATPase H^+/K^+ enzyme in the parietal cells of the stomach (1).

The knowledge of the physical and chemical properties of drugs is a major step in the development of the most appropriate pharmaceutical dosage forms. Granulation of omeprazole with gastroresistent coatings avoids the acidic degradation of the drug in the stomach and therefore is indispensable for the achievement of therapeutic levels after oral administration (2).

The USP 23 (3), Portuguese Pharmacopoeia VI (4), British Pharmacopoeia 1993 (5), and European Pharma-

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copoeia 3rd edition (6) do not include individual monographs of omeprazole pharmaceutical dosage forms.

This paper describes the dissolution studies developed at our institute for the characterization and comparison of the dissolution characteristics of omeprazole-containing, delayed-release, solid oral dosage formulations.

EXPERIMENTAL

Materials and Methods

Omeprazole (Union Quimico Farmaceutica, S.A., subsidiary of Holliday Chemical Holdings PLC) was supplied as a gift by Laboratório Medinfar, Produtos Farmacêuticos S.A., Amadora, Portugal. Acetonitrile was high-purity grade. All other reagents were analytical grade. The water used was purified through an Ultra-filtration Continental Modulab® analytical system. All dissolution tests were performed in an Erweka® DT6 dissolution apparatus (Erweka GmbH, Germany).

Omeprazole was determined in all samples by high-performance liquid chromatography (HPLC) analysis. The HPLC apparatus included a Merck-Hitachi L-6000A pump (Japan), a Waters 717 plus autosampler (Milford, MA), a Waters UV 486 detector at 280 nm, and a Merck-Hitachi D-2500 Chromato-Integrator. Separations were carried out using a Merck-Aluspher® RP-18 column (244 × 4 mm) at 5 μm (mobile phase phosphate buffer 0.05 M:acetonitrile 75:25; flow rate 1.0 ml/min). All samples were centrifuged prior to injection.

Products Studied

The products studied, granules in capsules, were from normal production batches and were bought in the Portuguese market. These were Gasec® (lot 62147, expiry date March 1998, Mepha Lda, Amadora, Portugal), Proclor® (lot 64601, expiry date June 1998, Pentafarma-Coc. Téc.-Med., S.A., Sacavem, Portugal), Proton® (lot 6247, expiry date April 1999, Lab. Medinfar, Prod. Farm., S.A.), and Losec® (lot XE6444, expiry date May 1999, Astra Portuguesa, Lda, Queluz, Portugal).

Determination of Omeprazole pH Stability

Omeprazole stability as a raw material was evaluated at different pH values in buffered solutions prepared according to USP 23. Solutions of omeprazole were prepared and kept at 20°C during the entire procedure. All solutions were analyzed at predefined times after sample preparation. The pH values, ranging from 3.0 to 8.8, included 12 different determinations.

Determination of Formulation Stability in Acidic pH

To evaluate the influence of acidic pH on the integrity of the formulations, all the products went through an initial acidic step. The amount of omeprazole eventually dissolved in the acidic media would become rapidly degraded. Thus, an adaptation of the method described in the USP 23 general monograph for delayed-release solid

Table 1

Dissolution Test Conditions for the Determination of the Dissolution Extent

	pH 6.8	pH 7.4	pH 8.0
Medium	0.05 M phosphate buffer	0.05 M phosphate buffer	0.05 M sodium borate buffer
Volume	900 ml	900 ml	900 ml
Temperature	37°C	37°C	37°C
USP dissolution apparatus	1 (basket)	1 (basket)	1 (basket)
Agitation speed	100 rpm	100 rpm	100 rpm
n	1	6	6
Sampling times	10, 20, 30, 45 min	5, 10, 20, 30, 45, 60 min.	5, 10, 20, 30, 45, 60 min.
Sampling volume	5 ml (without reposition)	5 ml (without reposition)	5 ml (without reposition)

oral dosage forms was necessary. After 2 hr in 1000 ml of the acidic medium (HCl 0.1 N or potassium biphthalate buffer solution 0.05 M, pH 4.6) at 37°C, 100 rpm with paddle, the granules in each dissolution vessel were recovered and dissolved in a solution of sodium borate 0.01 M and acetonitrile (75:25). A 1-ml aliquot was taken from each solution, centrifuged, and analyzed by HPLC for omeprazole content.

Determination of Dissolution Rates

The dissolution procedure was adapted from the general monograph, ''Drug Release,'' of the USP 23 for delayed-release solid oral dosage forms. Each dosage unit was submitted to an acidic initial step, followed by a second dissolution phase. The dissolution characteristics of the four products at pH 6.8 were evaluated without going through the first acidic step. All dissolution test conditions are described in Table 1.

In the dissolution testing procedures at pH 7.4 and 8.0, after 2 hr in the acidic medium, the content of each capsule was recovered and placed in a vessel containing the dissolution medium. All dissolution media were deaerated through a Millipore® HVLP (0.45 μm) filtration system under vacuum and equilibrated at 37°C prior to the start of the dissolution procedures. The selected agitation speed (100 rpm) is the middle value of the recommended interval (7).

RESULTS AND DISCUSSION

Omeprazole Stability

As seen in Table 2, the increasing acidity of the solvent medium is related to an increasing degradation rate of omeprazole. At pH 6.8, 1.40 hr after preparation of the standard solution, 95% of omeprazole remained in solution. These results suggest that the dissolution procedure of formulations containing omeprazole could be done at pH 6.8, in accordance with the general recommendations stated in USP 23.

Table 2

Stability of Omeprazole at Different pH Values

pH	Time (hr)	% OPZ[a]
3.0		
$t1$	0.3	38.7
4.0		
$t1$	0.3	39.9
5.0		
$t1$	0.3	66.6
6.4		
$t1$	1.0	96.0
Δt	6.3	71.6
6.8		
$t1$	1.4	95.0
Δt	6.3	82.1
7.2		
$t1$	1.7	98.0
Δt	6.3	86.3
7.5		
$t1$	2.1	99.7
Δt	6.3	89.1
7.8		
$t1$	2.4	99.9
Δt	6.3	93.4
8.0		
$t1$	15.7	95.1
Δt	9.8	86.6
8.2		
$t1$	15.3	96.2
Δt	9.8	87.5
8.4		
$t1$	15.0	97.7
Δ	9.8	93.9
8.8		
$t1$	14.6	98.3
Δt	9.8	95.5

$t1$ = time of 1st determination after preparation; Δt = time between 1st and 2nd determinations.

[a] Relative to the initially prepared concentration.

Stability of the Formulations in Acidic pH

It is well known that acrylic resins used in the pharmaceutical industry for the coating of delayed-release pharmaceutical dosage forms have solubility properties that differ according to the pH of the medium. These differences are due to structural modifications of the different chemical groups (carboxyl, amino, etc.) in the polymeric chains. The solubility of metacrilic acid is a good example of this (8).

The evaluation of the solubility behavior of the coatings at two different acidic pH values, 1.1 and 4.6, was performed because the nature of the polymeric coating used in each product was unknown. Table 3 shows the results obtained for the content of omeprazole in the capsules after 2 hr in the acidic media. At pH 1.1 and 4.6, the contents of omeprazole in the granules was above

Table 3

Remaining Omeprazole After the Acidic Stage

	Remaining Omeprazole (% of the Label) (n = 6)	
Products	pH 1.1	pH 4.6
Gasec	89.4	91.3
Proclor	95.2	95.4
Proton	92.7	96.2
Losec	90.6	95.4

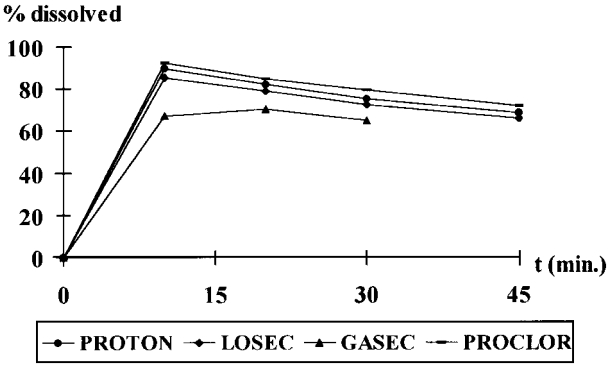

Figure 1. Dissolution profiles at pH 6.8.

89%, confirming the ability of the coatings to resist a wide range of acidic dissolution media. In both tests, Gasec showed the lowest remaining omeprazole content.

Dissolution Rates of Omeprazole

According to the USP 23, the dissolution testing procedure for gastroresistent solid oral dosage forms should be done at pH 6.8. Davidson and McCallum (9) reported 30-min dissolution testing results for delayed-release formulations containing omeprazole in such dissolution medium. Our own stability data led us, in a first approach, to use the same medium.

Results obtained (Table 4) show similar behavior for three products (with the exception of Gasec), as expressed by over 85% dissolution at 10 min. However, the point to stress is that, after the maximum dissolution has been achieved, the concentration of omeprazole in the dissolution medium does not remain at a plateau and drops continuously until the last recorded dissolution point at 45 min (Fig. 1). The experimental conditions of the dissolution test, that is, the volume of the dissolution medium, the agitation, and the temperature, might contribute to these findings. A single-point dissolution procedure would not detect this effect, leading to incorrect conclusions with respect to the extent of omeprazole dissolved.

In opposition, dissolution results at pH 7.4 and 8.0 (Table 5) seem to reflect pure dissolution, with negligible influence of degradation. Figures 2 and 3 show the dissolution profiles obtained for each of the four products in both dissolution media.

At pH 7.4, the dissolution profiles of the four products are relatively superimposable. Furthermore, the slight retardation effect on the release of omeprazole observed at pH 7.4 for Losec and Gasec becomes more evident at pH 8.0. At pH 7.4, after 5 min of dissolution, the products are gathered in two groups, with Proton and Proclor recording higher dissolution rates, with over 70% dissolved, and with Losec and Gasec with dissolved omeprazole values below 35%. Nevertheless, after 10 min, all products had released more than 85% of the labeled dose.

At pH 8.0, Proton and Proclor show a very slow dissolution rate up to 5 min from the test start. After 10 min,

Table 4

Results of the Dissolution Extent at pH 6.8

	% Dissolved			
Time (min)	Proton	Gasec	Proclor	Losec
10	90.0	67.3	92.3	85.5
20	82.4	70.2	84.7	78.9
30	75.2	64.9	79.5	72.5
45	68.6	[a]	71.8	66.3

[a] Sample lost due to operator error.

Table 5

Dissolution Extent at pH 7.4 and 8.0

Amount Dissolved (% of the label)	Sampling Times (min)					
	5	10	20	30	45	60
pH 7.4 (phosphate buffer)						
Gasec	16.9	85.3	86.3	86.5	85.2	84.3
Proclor	81.5	92.1	91.0	90.1	89.5	88.4
Proton	70.4	100.7	101.0	99.8	98.9	97.7
Losec	32.9	94.7	96.9	96.1	94.8	93.9
pH 8.0 (borate buffer)						
Gasec	0.5	2.3	57.7	87.6	89.3	86.7
Proclor	0.4	56.6	94.5	94.6	93.8	91.9
Proton	5.8	69.0	101.7	102.1	102.0	101.1
Losec	5.0	5.1	7.5	43.3	89.0	96.7

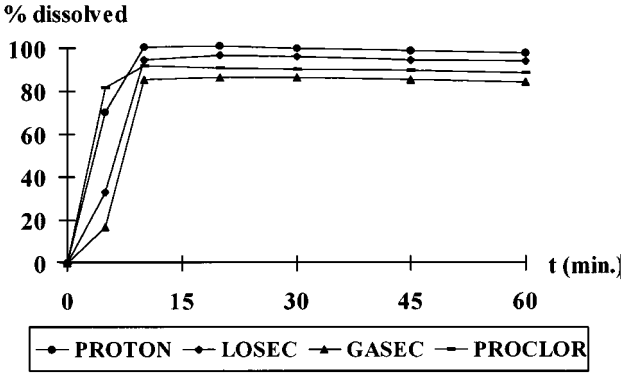

Figure 2. Dissolution profiles at pH 7.4.

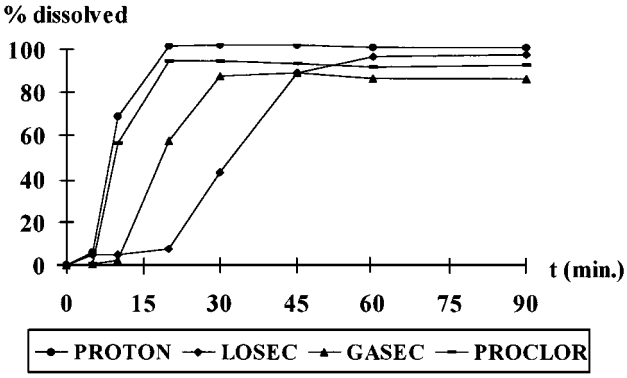

Figure 3. Dissolution profiles at pH 8.0.

the dissolved fraction was still below 70%, and after 20 min, dissolved omeprazole was over 90% for both products.

Losec and Gasec, which at pH 7.4 had already shown a slightly minor dissolution rate in the first 5 min, showed a very slow dissolution rate at pH 8.0 until 10 min. At 20 min, released omeprazole was still below 60%; however, at 30 min, 85% of the labeled omeprazole was already dissolved.

The results obtained in this study suggest that the dissolution procedure for delayed-release solid oral dosage forms recommended by the general monograph of USP 23 is not adequate for oral formulations containing omeprazole as it leads to false conclusions due to the chemical instability of the drug in a formulation of pH 6.8 buffered medium. Although pH 8.0 dissolution medium is well above physiologic conditions, it reveals different dissolution rates for the tested products that were not observed at pH 7.4. These conditions may allow the detection of differences among products from different manufacturers and different production batches of the same production site, representing an advantage over the pH 6.8 dissolution medium.

Furthermore, it would be advisable to avoid single-point dissolution procedures because in such cases degradation effects would never be detected. Therefore, when a product monograph is not yet available, we strongly recommend a design of the dissolution procedure that takes into account all the dissolution profiles with several sampling times.

REFERENCES

1. J. G. Hardman, P. B. Molinoff, and A. G. Gilman, *Goodman and Gilman's the Pharmacological Basis of Therapeutics*, McGraw-Hill Interamericana Editores, S.A., Mexico, 1996, p. 667.
2. S. V. Dighe, in *Bio-International: Bioavailability, Bioequivalence and Pharmacokinetics* (K. K. Midha and H. H. Blume, Eds.), Medpharm Scientific, Stuttgart, 1993, pp. 247–255.
3. U.S. Pharmacopeial Convention, *The United States Pharmacopeia*, 23rd rev., Author, Rockville, MD, 1995.
4. *Farmacopeia Portuguesa VI*, Imprensa Nacional Casa da Moeda, Lisbon, 1997.
5. *British Pharmacopoeia*, Her Majesty's Stationery Office, London, 1998.
6. *European Pharmacopoeia*, 3rd ed., Council of Europe, Strasbourg, 1997.
7. FIP (Féderation Internationale Pharmaceutique), *Guidelines for Dissolution Testing of Oral Products*, 1995.
8. K. Lehman, Acta Pharm., 93, 55–74 (1984).
9. A. G. Davidson and A. McCallum, Drug Dev. Ind. Pharm., 22, 1173–1185 (1996).