Assessment of the Pharmacopeial Analytical Methodologies in the Dissolution Test of Enteric-Coated Lansoprazole Preparations

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ABSTRACT

The performance of the analytical methodologies recommended by the *United States Pharmacopoeia* (*USP*) monograph (*1*) for dissolution testing of lansoprazole (LPZ) enteric-coated solid dosage forms (capsules/tablets) was critically evaluated. While *USP* adopts an essentially nonselective UV method, the *British Pharmacopoeia* (*2*) recommends a high-performance liquid chromatography (HPLC) method capable of separating the drug from its acid degradation products. For an acid-labile drug such as LPZ, one might think that the nonselective UV method might over- or underestimate the percentage released because the degradation product might have UV absorptivity different from that of the parent drug. We subjected six commercial products in addition to the reference product (G) to analysis according to the *USP* assay and dissolution recommendations. Products were also subjected to dissolution tests whereby a selective HPLC method was employed for quantifying the percentage release. All products passed *USP* assay tests. For dissolution, the UV method adopted by *USP* was more reliable because it indicated the actual percentage released compared with the selective HPLC method, which reflected only the percentage of released LPZ that remained intact (undegraded). Only one product (E) failed to satisfy the *USP* requirements for dissolution.

KEYWORDS: Lansoprazole; dissolution; acid labile; pharmacopeia; quality.

INTRODUCTION

Lansoprazole (LPZ, shown in Figure 1) is a proton-pump inhibitor that can be given orally and is indicated for the treatment and control of acid-related diseases such as gastro-duodenal ulcers and reflux esophagitis (*3*). LPZ is known for its chemical instability in acidic media and is, therefore, usually manufactured in the form of enteric-coated tablets or pellets in capsules (*4*). According to the data presented by Gupta et al. (*4*), a dramatic increase in the degradation rate of LPZ was observed as the pH dropped only one pH unit from 6 to 5. LPZ has been quantitatively determined in formulations using different

Figure 1. Chemical structure of lansoprazole (LPZ).

analytical methods including spectrophotometry, high-performance liquid chromatography (HPLC), and thin-layer chromatography (*5–14*).

LPZ is an official drug in both the *USP* (*1*) and the *British Pharmacopoeia* (*2*) where monographs are available for each of the raw material and delayed-release capsules. Both the *USP* and *BP* adopt chromatographic HPLC methods that share some parameters (e.g., mobile phase composition employed for assay of capsules), but they differ in others (e.g., the stationary phase chemistry and the use of internal versus external standards). Both the *USP* and *BP* require the performance of dissolution testing for the finished products over two stages (acidic and nearly neutral). Dissolution tests commonly employ a UV spectroscopic method because of simplicity of the method and absence of usual interferences from the formulation components. However, in some cases where the drug is acid labile, the degradation might be fast enough so that the resultant degradation products interfere with the simple nonselective UV procedure (*15*). Such a potentially serious effect on the overall dissolution results has been demonstrated for amoxicillin capsules (*16*). Concerning dissolution testing of LPZ; the
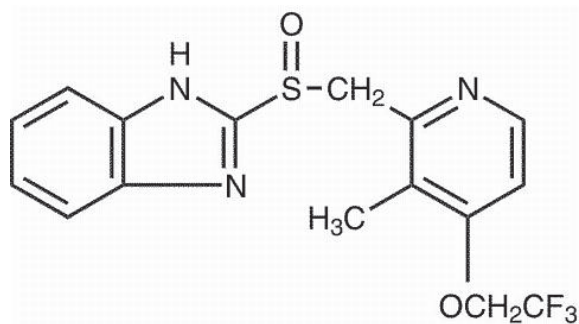
USP (*1*) adopts a UV spectroscopic method while the *BP* (*2*) adopts a more selective HPLC method. Because LPZ rapidly degrades in acidic medium, the use of a nonselective UV method could be potentially risky and may lead to inaccurate conclusions about the percentage of drug that is actually released.

This study aims to critically assess the nonselective analytical method recommended by the *USP* (UV spectroscopy) for dissolution testing of LPZ enteric-coated solid preparations in comparison to a selective HPLC method such as that recommended by the *BP*.

EXPERIMENTAL

Materials and Equipment
Working standards of LPZ were obtained from the Jordanian Pharmaceutical Manufacturing Company (JPM) with a potency of 99.8%. HPLC grade acetonitrile, trimethylamine, and methanol were obtained from TEDIA (USA). The internal standard (4-ethoxyacetophenone) and other reagents were obtained from Sigma–Aldrich (Germany). All solid dosage forms of LPZ commercially available in the Jordanian market were purchased from local pharmacies (Table 1).

Table 1. Details of the Tested Preparations of Lansoprazole

Commercial lansoprazole preparation code	Dosage Form[a]	Batch Number	Production-Expiry Dates
A	tablet	121286	12/2012–12/2015
B	capsule	0413339	06/2013–06/2016
C	capsule	679	07/2012–07/2014
D	capsule	32018	08/2013–08/2015
E	capsule	254022	08/2012–08/2014
F	capsule	130428	04/2013–04/2016
G	capsule	2D07C	05/2012–04/2014

[a] All contained 30 mg/unit

A Merck Hitachi HPLC system (model L-7400, Tokyo, Japan) consisting of a UV detector and an isocratic pump was used. Chromatograms were monitored and integrated using Clarity Light software. A typical C18 column (5 μm, 250 × 4.6 mm, Thermo Scientific, USA) as recommended by the *USP* was employed. All spectroscopic measurements were made using 1-cm quartz cells on a Spectroscan 80D, UV–vis spectrophotometer (Biotech Engineering Management Co. Ltd, UK).

Analytical Procedures
USP Assay Procedure
The commercial preparations were subjected to the official *USP* assay test to verify their content before performing dissolution tests. The *USP* procedure was strictly followed, and a highlight of the major points is described below. The wavelength of detection was 285 nm, and the mobile phase consisted of 1:40:60 triethylamine/acetonitrile/pH 10.5 orthophosphoric acid in water adjusted to pH 7 and pumped at a rate of 1 mL/min. Test solutions (known as assay preparations) were prepared three times for each commercial product and injected five times onto the HPLC. Standard preparations were made by mixing 25 mL of standard LPZ solution (3 mg/mL in 0.1 M NaOH/acetonitrile in a ratio of 3:2) with 5 mL of internal standard solution (7.5 mg/mL), diluting to a volume of 50 mL, and further diluting 3 mL of the mixture to 50 mL. Thus, the final standard preparation mixture contained 90 and 45 μg/mL of LPZ and internal standard, respectively, which are the same concentrations expected for the assay preparations.

Details of Dissolution Tests
Dissolution tests were performed per the *USP* monograph using Apparatus 2 with a paddle rotation speed set at 75 rpm. Six units from each product were subjected to the dissolution test. Dissolution was performed at two stages for all products, the acid stage followed by the buffer stage. The first acid stage medium consisted of 500 mL of 0.1 M hydrochloric acid (HCl). Sampling at this stage was made at 60 min by withdrawing a 25-mL aliquot then proceeding directly to the second buffer stage by adding 425 mL of buffer concentrate to the remaining 475 mL acid stage medium so that the total buffer stage volume would be 900 mL. The buffer concentrate was prepared by transferring 65.4 g of monobasic sodium phosphate, 28.2 g of sodium hydroxide, and 12 g of sodium dodecyl sulfate to a suitable container and adding enough water to dissolve, then diluting with water to 4 L. While the *USP* monograph requires one sample to be taken from the buffer stage at 60 min, in this study samples were obtained at 30, 60, and 90 min. The amount of LPZ dissolved in all tests samples was determined by employing the USP-recommended UV spectroscopic method as follows. For the acid stage sample, absorption at the wavelength of maximum absorbance (306 nm) was measured using the acid-stage medium as a blank and compared with a standard of LPZ solution (5 μg/mL) in 0.1 M HCl. For the buffer stage, the absorbance of samples was determined using the difference between absorbances at the wavelengths of 286 and 650 nm using

a blank solution composed of acid stage medium and a buffer concentrate adjusted to pH 6.8 (volume ratio 19:17) and compared with a standard solution of LPZ (23.3 µg/mL). Five calibration solutions were prepared to contain 1.5–15 µg/mL of LPZ in 0.1 M HCl for the acid stage and 6–30 µg/mL for the buffer stage to ensure linearity of the response in each case.

In addition to the above-detailed UV method, the concentrations of LPZ in dissolution samples (acid or buffer stages) were also determined using an HPLC method. The chromatographic method employed was essentially that recommended by the *USP* for the assay procedure after being adapted for the dissolution samples as follows. Each 2-mL dissolution sample was mixed with 2 mL of internal standard solution (30 µg/mL of 4-ethoxyacetophenone) and diluted to a volume of 10 mL using *USP* diluents before it was injected onto the HPLC. Calculation of the dissolved concentration of LPZ was achieved by comparing the peak area ratio of LPZ to the internal standard in the sample and a similarly prepared standard solution.

RESULTS AND DISCUSSION

Assay Values

To properly evaluate the characteristic release performance of the different products, the content of LPZ was determined according to the proper assay procedure recommended by the *USP*. As a part of a system suitability test, the *USP* requires that the resolution between LPZ and internal standard must be greater than 5 and the relative standard deviation (RSD) of multiple injections less than 2%. Therefore, before any analysis and data collection, we ensured that this essential requirement was achieved and maintained over the period of analysis. A sample chromatogram for the system suitability test resolution solution is shown in Figure 2. The obtained average percentage per label and corresponding RSD values for all tested products are listed in Table 2. Generally, the

obtained RSD values were reasonably low, and thus reproducibility could be judged as satisfactory. However, the RSD value for the product (A) was notably higher (3.8) than the rest of the preparations, which might reflect some variation within the product. Nevertheless, all products passed the *USP* assay test because the amount of LPZ per label was always within the range stated by the monograph (i.e., 90–110% of label claim).

Table 2. Average USP Assay Results for Commercial LPZ Products (n = 6)

LPZ Capsules/Tablets	USP Assay Test Results	
	Label (%)	RSD
A	100.54	3.80
B	105.94	0.17
C	107.62	1.61
D	106.65	2.30
E	97.84	1.23
F	103.26	2.16
G	104.84	1.24

Dissolution

The *USP* adoption of the rather nonselective UV method for the determination of the acid-labile drug LPZ in dissolution medium was a major motivation for this work. That is because the test result might be seriously affected by the rapid degradation of the released LPZ in the strong acidic medium. In the test, the capsule/tablet is placed in two successive media, the acid stage and the buffer stage, which are 0.1 M HCl solution and phosphate buffer (final pH of 6.8), respectively. Only one sample is withdrawn at the end of the acid stage (60 min), and the concentration of LPZ is determined by a direct measurement of absorbance at 306 nm and a comparison with a similarly prepared standard solution, where no more than 10% of LPZ should have been released. The amount of LPZ released in the buffer stage was determined in the same way as the acid stage using the proper blank solution and taking the difference in absorbance between 286 and 650 nm instead of a single absorbance value at 306 nm. The amount of LPZ released should not be less than 80% in the buffer stage at 60 min.

To ensure that all obtained absorbance values from the dissolution test were in the linear response range, two calibration curves were constructed for the acidic and buffer stages covering the concentration ranges of 1.5–15 µg/mL and 6–30 µg/mL, which represent release percentages of 2.5–25% and 20–100%, respectively. Typical linearity equations of $y = 0.017x + 0.002$ and y
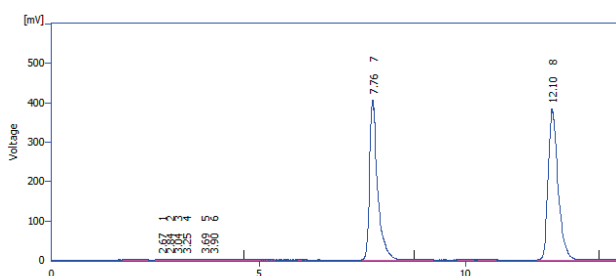

Figure 2. Sample chromatogram for the standard preparation solution containing LPZ (at 7.7 min) and the internal standard (at 12.1 min) according to the USP method.

= 0.029x + 0.042 were obtained for the acid and buffer stages, respectively, with correlation coefficients of 0.999 in both cases. It should be noted, however, that at the expected values of release of less than 10% in the acid stage, the anticipated absorbance values would be quite low (less than 0.1), which, while within the linear response range, is susceptible to variation (i.e., imprecision, which might explain the high standard deviation values for the obtained percent release of products in acidic medium, as discussed later).

Results for the dissolution test applying the recommended *USP* UV method in acidic and buffer stages are shown in Table 3. With the exception of the product (E), which exhibited a percentage release of 13% in acid stage, all other products exhibited a percentage release significantly less than the allowed limit of 10%. Therefore, it could be concluded that the product (E) is the only product that might have failed the requirements of the dissolution test. It should be noted that RSD values were significantly high for the percentage release values obtained in the acid stage unlike those for the buffer stage, which is most likely a result of the very low concentrations released and the associated low values of absorbance (0.0–0.172) in acidic medium. However, it is expected that if the percentage release for a product reached the specified limit of 10%, a high enough absorbance would be recorded and the variation, as given by RSD, would be minimized. Thus it might be argued that the high variation observed would not actually affect the final decision regarding the percentage released since it is most significant at the very low percentages released (i.e., far from the limit of 10%).

Table 3. Average Percentage LPZ Release (n = 6) Using the USP Method (UV)[a]

Product Tested	Average Percentage LPZ Released			
	Acid Stage[b]	Buffer stage		
		30 min	60 min	90 min
A	0.58 (0.96)	103.1 (10.3)	102.9 (7.4)	99.3 (3.9)
B	1.80 (1.33)	94 (8.8)	103.9 (6.1)	103.1 (2.8)
C	0.95 (0.38)	98.6 (2.6)	104.9 (1.5)	104.7 (1.7)
D	3.41 (1.49)	98.2 (9.2)	99.3 (7.4)	101.2 (6.4)
E	13.0 (2.5)	84.6 (6.6)	94.5 (5.7)	93.9 (5.0)
F	3.74 (1.16)	90.6 (6.2)	97.9 (3.9)	93.2 (3.5)
G	1.14 (1.01)	92.7 (3.2)	99.1 (4.8)	101.4 (4.9)

[a] Note that USP requires measurement at 60 min only.
[b] RSD or SD values shown in parentheses.

For the buffer stage, all products satisfied the *USP* requirements (i.e., release of greater than 80% at 60 min). Although the *USP* requirements do not include

sampling at other than 60 min, results in Table 3 show the percentage release for different products after 30, 60, and 90 min of dissolution. Differences in the performance of the products could best be seen at 30 min, while at later times (60 and 90 min), all products achieved maximum release near 100%. According to data in Table 3 and at 30 min of dissolution, while one product released as high as 103.1%, another showed only 84.6% release (i.e., 85–103%). That range became narrower when percentage release was evaluated at 60 min (95–105%). Thus it might be advisable to evaluate dissolution at 30 min instead of 60 min for the purpose of comparing release properties of different preparations.

Dissolution Test Applying HPLC Method
Dissolution samples for all products in the two stages were assayed using an HPLC method in addition to the *USP*-recommended UV method described earlier. The HPLC method was based on that recommended by the *USP* monograph for the assay of LPZ capsules/tablets. Only the sample preparation step was modified to suit the nature of the dissolution sample in terms of the analyte as well as the pH of the medium (acidic pH 1.2 or buffer pH 6.8). Exact details for sample preparation were discussed earlier. A standard solution was also prepared to contain the internal standard 4-ethoxyacetophenone, which is the same internal standard recommended by the *USP* procedure for the quantitative assay test. As part of validation of the modified HPLC method, calibration curves were prepared for each of the acid and buffer stages and linearity examined. For the acidic stage, concentrations in the range of 1–30 µg/mL were used, which correspond to 1.67–50% release of the theoretical ideal content. For the buffer stage, concentrations in the range of 1–30 µg/mL were used, which correspond to 3–100% release of the theoretical ideal content. Typical calibration equations for acidic and buffer stages were $y = 0.020x - 0.024$ ($R^2 = 0.976$) and $y = 0.032x - 0.025$ ($R^2 = 0.994$), respectively. Other validation parameters of precision and accuracy at low and high concentrations were also satisfactory.

The obtained average percentage released for all products tested using the HPLC method (Table 4) satisfied *USP* requirements for dissolution (i.e., release of not less than 80% in the buffer stage at 60 min and not more than 10% in the acid stage). However, one product (E) released the lowest percentage of LPZ as it released 75% and 87% at 30 and 60 min, respectively. That is consistent with the observation that product (E) was the only one that released greater than 10% in the initial acid stage (i.e., a larger amount of the drug was exposed for a longer time to the acidic environment with the consequent

higher percentage of degradation). The obtained percentage release for the product (E) at 60 min using the HPLC method was significantly lower (87.3%) than that obtained by the UV method (94.5%). The observed low percentage released here could not be simply attributed to a lower-than-expected content of LPZ in the preparation because it was concluded to be satisfactory according to *USP* assay results discussed earlier (97.84%). However, it could be explained in terms of degradation of the drug in the acidic medium and the selective nature of the HPLC method, which selectively determined only LPZ, while the nonselective UV method determined both LPZ and its potential degradation product. If the absorptivity of the degradation product at the measuring wavelength was significantly different from that of LPZ, then a serious error in the estimated percentage release might be anticipated when employing the UV method (*15*). To further investigate potential interferences with the UV method, the absorption characteristics of LPZ and its degradation product were investigated. A solution of LPZ was prepared at a concentration near the limit of 10% release from one capsule in the employed acidic dissolution medium, which is 15 µg/mL in 0.1 M HCl, and spectra recorded over time (Figure 3).
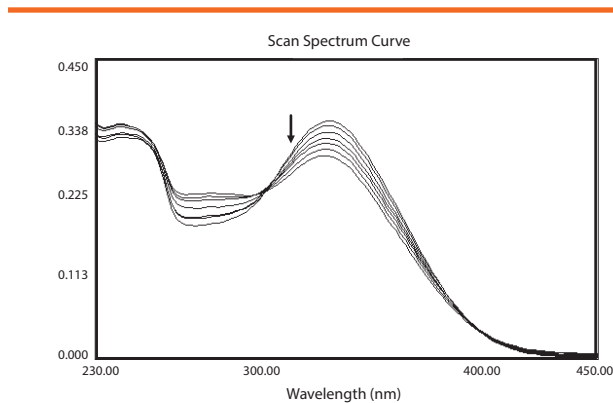

Scan Spectrum Curve

Figure 3. Overlaid UV spectra of LPZ solution (15 µg/mL) recorded at 10-min intervals (time increases according to the direction of the arrow). Note the isosbestic point at 306 nm where the absorbance does not change despite degradation.

Table 4. Average Percentage LPZ Release (n = 6) Using HPLC Method[a]

Product Tested	Acid Stage[b]	% LPZ Released		
		Buffer stage		
		30 min	60 min	90 min
A	<1	103.1 (10.3)	103.0 (7.4)	99.3 (3.9)
B	<1	105.7 (10.3)	109.2 (3.8)	103.7 (2.3)
C	<1	95.1 (3.5)	103.5 (3.9)	99.4 (6.7)
D	<1	93.5 (5.6)	94.5 (3.9)	90.2 (6.7)
E	3.7 (0.71)[b]	75.4 (7.9)	87.3 (6.5)	83.4 (4.8)
F	<1	90.6 (6.2)	97.9 (3.9)	93.2 (6.5)
G	<1	93.9 (5.3)	101.0 (6.7)	100.8 (7.7)

[a] Note that USP requires measurement at 60 min only.
[b] RSD or SD values shown in parentheses.

The overlaid UV spectra show maximum absorption (λ_{max}) at 338 nm that progressively decreased with time while the minimum absorption at about 260 nm increased, suggesting degradation was taking place. The 306 nm wavelength (which was recommended by *USP* as a λ_{max}) was an isosbestic point (but not λ_{max}) at which the absorbance remains almost constant with time, despite other clear changes in the obtained spectra (Figure 3); this reflects the occurrence of degradation. Therefore, although degradation was taking place, the absorbance

value at 306 nm did not change, and consequently, the calculated concentration of the dissolved drug would still be correct. Therefore, the *USP* method appears to be more appropriate in this context than a selective HPLC method, because in dissolution experiments, the main concern would be the overall amount of drug dissolved regardless of whether it remained chemically intact in the medium. These findings demonstrate that borderline products such as product (E) might be inappropriately rejected using a selective HPLC method like the one recommended by the *BP*, but accepted using the rather nonselective UV method recommended by the *USP*. A *T*-test was performed to check for a significant difference between the results obtained from the two methods (HPLC and UV) at both stages (acidic, 60 min; buffer, 60 min) for all products. Results for this test are listed in Table 5. For the acidic stage, the two methods produced statistically different results where only one out of the seven products tested showed similar results, with the values obtained by the HPLC method being generally less than those of the UV method. At least in part, this could be explained as a result of the low precision of the UV method at very low absorbance values encountered when only a low percentage of LPZ is released. For the buffer stage, however, where the error in the UV method was minimized due to the release of a significant amount of drug, the results obtained by both methods are almost similar with the exception of one product (E), which repeatedly showed a significant release of LPZ in the acidic stage and consequently degraded, leading to significant differences in the results obtained by the UV and HPLC methods. Thus, for products that do not release a significant percentage of the drug in the acidic stage with the consequence of no significant degradation of LPZ, no significant difference between

the results of the HPLC or UV methods is expected. Nevertheless, this work demonstrates with an actual example of a commercially available product that the analytical methodology employed might affect the final conclusion. A solid understanding of the principles of pharmacopeial analytical procedures is important. For example, an analyst who does not understand the role of the isosbestic point as a wavelength of detection in LPZ in a UV quantification method might not fully appreciate the danger of changing the wavelength of measurement.

Table 5. T-Test Values and p Values (in parentheses) for Comparing the Two Methods (HPLC and UV) at the Two Stages[a]

Product	Acidic Stage at 60 min	Buffer Stage at 60 min
A	1.8011 (0.0906)	1.2341 (0.2349)
B	3.3104 (0.0079)	1.7295 (0.1144)
C	6.1115 (0.00011)	0.663 (0.5219)
D	4.3164 (0.0015)	1.4305 (0.1831)
E	8.4876 (<0.00001)	2.3665 (0.0395)
F	5.4384 (0.0003)	0.0624 (0.9514)
G	2.7601 (0.0201)	0.5391 (0.6028)

[a] Calculated at $p < 0.05$.

CONCLUSION

All products tested satisfied the *USP* quantitative assay requirement for drug content. The selective chromatographic *USP* assay procedure was adapted and validated for the analysis of dissolution samples of LPZ in acidic and buffer media. The data obtained when applying both the nonselective UV method recommended by the *USP* together with the adapted, more selective HPLC method, leads to the conclusion that the recommended *USP* method (UV method) is more reliable and can give the actual percentage released, while the HPLC method reflects only the percentage of LPZ that remains intact. Thus, the more selective HPLC method will show a lower percentage released than what is actually released for products that release significant percentage of LPZ in the acid stage. Some of the released LPZ may degrade rapidly in the medium so that the degraded portion may not be accounted for by the HPLC method, although it is really a part of the dissolved amount. Only one commercial product (E) failed to satisfy the *USP* requirements for dissolution. The rather preliminary data presented should encourage further research to confirm our findings. Perhaps it is appropriate to recommend to other regulatory authorities who still adopt selective HPLC methods for dissolution evaluations of LPZ products (e.g., the *BP*) to revise their monographs.

CONFLICT OF INTEREST
No conflict of interest has been declared by the authors.

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