Formulation and Stability Study of Omeprazole Oral Liquid Suspension for Pediatric Patients

Oriana Boscolo¹, Francesco Perra^{1,2}, Leandro Salvo¹,
Fabián Buontempo^{1,3}, and Silvia Lucangioli^{1,4}

Abstract

Objectives: To develop and to study the physicochemical and microbiological stability of omeprazole liquid oral formulations used as therapeutic agent in many acid-related disorders, for pediatric use. Furthermore, to optimize and validate a stability-indicating high-performance liquid chromatography (HPLC) method for the analysis of omeprazole in the studied formulations. **Method:** Oral liquid suspensions of omeprazole were prepared at 2 mg/mL using crushed omeprazole pellets (formulation A) and pure omeprazole (formulation B) with a complete vehicle including humectant, suspending, sweetening, antioxidant, and flavoring agents. Samples were stored at 4°C and 25°C. Omeprazole content of each formulation was analyzed in triplicate using micro-HPLC at 0, 3, 7, 14, 30, 60, 90, 120, and 150 days. Other parameters were also determined, such as appearance, pH, resuspendibility, and viscosity. Microbiological studies were conducted according to the United States Pharmacopeia (USP) guidelines for non-sterile products. **Results:** Formulation A stayed physicochemical and microbiologically stable at refrigerated (4°C) conditions during at least 150 days and it only stayed stable during 14 days at 25°C. Formulation B was stayed physicochemical and microbiologically stable at refrigerated (4°C) conditions at least 90 days, but it is not recommended to store at 25°C for more than 1 day. **Conclusions:** Formulation A and formulation B can be stored for at least 150 and 90 days, respectively, at refrigerated conditions. Formulation A can be stored at room temperature for 14 days. Both formulations are perfectly suitable for pediatric patients who are usually notable to swallow solid oral formulations. The proposed analytical method was suitable for the study of stability of different formulations.

Keywords

omeprazole, formulation, stability study, pediatric, acid-related diseases

Introduction

Omeprazole (OMZ) is a substituted benzimidazole (5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole) (Figure 1), which inhibits gastric acid secretion.¹ OMZ is indicated for the treatment of acid-related diseases, such as peptic ulcer, gastroesophageal reflux diseases, and Zollinger-Ellison syndrome.²

Omeprazole is a weak basic, hydrophobic compound, and it is a prodrug that is converted at low pH levels to a cyclic reactive sulfonamide, the pharmacologically active form of OMZ.³

It is well known that the chemical stability of OMZ is a function of pH. OMZ is rapidly degraded at pH value below 7.4, but it is stable at alkaline condition (pH 9.5).⁴ For this reason, OMZ is commercialized as oral dosage form like enteric-coated tablets or extended-release capsules containing enteric-coated granules or pellets. The enteric coating protects OMZ from acid degradation in the stomach.⁵

Omeprazole is extensively used to treat a wide range of patients, between them pediatric or geriatric ones. In particular, these 2 groups may have difficulties in swallowing entire capsules or tablets; moreover, adjusting the correct doses is not possible. Therefore, in this kind of patients, it is convenient to administer oral liquid dosage form like solution or suspensions.^{6,7}

Previous studies have investigated the chemical stability of OMZ in extemporaneous formulations. Most of them, OMZ

¹Universidad de Buenos Aires, Argentina

²Università degli Studi di Cagliari, Italy

³Hospital de Pediatría J. P. Garrahan, Buenos Aires, Argentina

⁴Consejo Nacional de Investigaciones Científicas y Técnicas, Buenos Aires, Argentina

Corresponding Author:

Silvia Lucangioli, Pharmaceutical Technology Department, Faculty of Pharmacy and Biochemistry, Universidad de Buenos Aires, Junín 956, Capital Federal, 1113 CABA, Argentina.
Email: slucangi@ffyb.uba.ar

Figure 1. (a) Omeprazole chemical structure. (b) Sulfone chemical structure.

Table 1. Excipients Used in Omeprazole Formulations.

Pharmaceutical excipient	Functional category	Formulation	
		(% w/v)	
		A	B
Sorbitol 70% solution	Humectant-sweetening agent	20.0	20.0
Glycerin	Humectant	5.00	5.00
Sodium carboxymethyl cellulose	Suspending agent	0.70	0.70
Sodium saccharin	Sweetening agent	0.25	0.25
Sodium bisulfite	Antioxidant	0.10	0.10
Mint essence	Flavoring agent	0.01	0.01
Sodium bicarbonate solution 8.4%	pH regulator/vehicle	qs	qs

Note. Qs = sufficient quantity.

from pellets or granules was suspended in bicarbonate solutions, or powder for reconstitution in the same vehicle.⁸⁻¹² Moreover, Whaley et al¹³ have presented the chemical stability study of OMZ in a SyrSpend SF Alca, a sorbitol, alcohol free alkaline commercially suspending agent for reconstitution. Recently, Milic et al¹⁴ have been presented a formulation for pediatric use based on a bicarbonate solution and xanthan gum, prepared from OMZ capsules and it was stable for 30 days in refrigerator, at temperature 2°C to 8°C, but not at room temperature. Moreover, Gautam¹⁵ has recently published a stability study of OMZ oral suspension in a Humco Flavor Sweet Sugar Free vehicle, and these formulations were stable for at least 90 days and cool temperature. On the contrary, an available OMZ suspension commercial kit was presented, which is stable for 30 days in refrigerator.¹⁶

The aim of this study was to develop 2 OMZ liquid oral formulations using crushed OMZ pellets and pure OMZ. A complete vehicle was designed as well, including humectant, suspending, sweetening, antioxidant, and flavoring agents. Moreover, a stability-indicating micro-high-performance liquid chromatography (HPLC) method for the OMZ analysis has been optimized and validated, and next, the physicochemical and microbiological stability of OMZ in the proposed formulations stored at 2 different temperatures were studied.

As far as we know, oral liquid formulations of OMZ with a complete vehicle and their evaluation have not been

published before. Moreover, an oral liquid formulation of OMZ prepared from the pure active form has not been reported.

Methods

Chemical and Reagent

Omeprazole pellets (Parafarm, batch 481) and sodium omeprazole (Parafarm, batch 482) were obtained from Saporiti (Buenos Aires, Argentina). Sodium carboxymethyl cellulose of high viscosity (V. Rossum, batch 04051), glycerin (Prest, batch 130520), sodium saccharin (Magel S.A., batch L201 30403), 70% sorbitol solution (Prest, batch E968E), sodium bicarbonate (Parafarm batch 022909), mint essence (Givaudan, batch X64191), sodium bisulfite (Prest, batch 46239), all excipients were USP (United States Pharmacopeia) quality. Methanol (HPLC grade) and disodium phosphate were purchased from Merck (Darmstadt, Germany). Water was purified in a EASYpure RF equipment (Barnstead, Dubuque, IA, USA).

Formulations Preparation

Omeprazole suspensions (2 mg/mL) were prepared using OMZ 8.31% pellets (formulation A) and using pure OMZ (formulation B). Table 1 shows the other excipients used for

each formulation. All trial formulations were stored in amber glass vials and kept at 25°C and refrigerated (4°C) during the stability study.

Preparation of sodium bicarbonate vehicle. A sodium bicarbonate solution was prepared by solubilizing with the aid of a magnetic stirrer during 1 hour. the desired amount of sodium bicarbonate was dissolved in 80% of purified water of the final volume of solution, in order to achieve a final concentration of 8.4% w/v. pH of the solution was adjusted to 9.5 with 0.1 M sodium hydroxide. Final volume was achieved by adding distilled water.

Preparation of formulation A. The correct amount of OMZ pellets (concentration of 8.31% w/w) was weighed in order to achieve a concentration of 2 mg/mL of OMZ and grinded in a mortar with a pestle. Sodium carboxymethyl cellulose was moistened with 90% of the total volume of glycerin for a minute, mixing until full dispersion and placed inside the mortar with the OMZ powder. 70% sorbitol was placed and grinded with the previous step inside the mortar to form the suspension. In another container, sodium saccharin and sodium bisulfate were solubilized in 50% of the final volume of the sodium bicarbonate vehicle and added to the OMZ preliminary suspension. A 0.01% of mint essence was solubilized in 10% of the glycerin, added to the suspension, and mixed. Finally, the suspension was transferred into a graduate and final volume was achieved by adding 8.4% of sodium bicarbonate solution. Final pH (9.5) of the suspension and density (1.109 g/mL) was carefully monitored.

Preparation of formulation B. Suspension B was prepared in the same manner as the preparation described for suspension A with the difference that in suspension B the correct amount of OMZ active pharmaceutical ingredient was weighed in order to achieve a concentration of 2 mg/mL.

Physicochemical Characterization of Formulations

Three aliquots of 30 mL of the formulations A and B for each study point (0, 7, 14, 30, 60, 90, 120, and 150 days) were stored in amber glass containers at 2 different temperatures (4°C and 25°C). Measures were performed at different times and comprised testing of parameters, which could possibly change during storage period, such as appearance, pH, resuspendibility, viscosity, and OMZ concentration.

Preparations were considered stable if physical properties had not changed, drug concentration has remained between 90% and 110% of the original concentration, and microbiological specification is suitable.

Appearance Test

The physical appearance properties were studied during a visual examination method of the samples stored at each

temperature. Parameters such as odor and color were monitored during the whole study.

Taste Test

In the first instance, healthy adult volunteers (n = 11) are trained with a caffeine curve of ascending concentrations (3, 6, 12, and 24 mM), as control solutions, to perceive the different degrees of bitterness.¹⁷ The different caffeine concentrations and suspensions were found at room temperature before tasting. At the beginning of the same, during the intervals of the different concentrations of caffeine and between the samples the volunteers had to rinse their mouth with distilled water to neutralize the previous tastes. A small amount (2-5 mL) of caffeine solutions and suspensions were dispensed with disposable pipettes. The volunteers tested the caffeine solutions by keeping them for an appropriate time in the mouth (10-15 seconds), then expectorated and rinsed the mouth, to cover the entire range of concentrations of caffeine solutions. Once this was done, the volunteers rinsed their mouths with distilled water and tested the suspensions and then compared them with the points of the caffeine curve.¹⁸ Bitterness levels were recorded after 2 minutes. The results were expressed in a score scale of 0 to 3, indicating the values of increasing intensity a bitterness, with 3 being strong bitterness (24 mM caffeine solution), 2 being moderate bitterness (12 mM caffeine), 1 being slight bitterness (6 mM caffeine), and 0 being threshold (3 mM caffeine).¹⁹

pH Measurements

pH values were measured with a digital pH/mV-meter IQ 140 (IQScientific Instruments, CA, USA). Measurements were determined at 0, 7, 14, 30, 60, 90, 120, and 150 days by triplicate and the results were averaged.

Resuspendibility

The time taken for the suspension to redisperse completely was determined after the samples were vigorously shaken to redistribute the sediment and the result was expressed in seconds.

Rheological Study

The viscosity measurements were carried out using a Brookfield Rotational Viscometer RVT (Massachusetts, USA). The developed suspensions were placed in a sampler tube using spindle number 1 at 10 rpm and 22°C. The results were expressed in mPA s.

Analytical Method

The chromatographic system consisted of an isocratic solvent delivery pump (Thermo Scientific Spectra System P4000,

Thermo Scientific, Waltham, MA, USA) with a 50 mm $\times$ 2.1 mm reverse phase microcolumn C18 particle diameter 3.5 μ m (XTerra C18 Waters Corp., Milford, MA, USA). Chromatograms were processed using Breeze Software (Waters, MI, USA). The mobile phase consisted of a mixture of methanol and 0.030M disodium phosphate pH = 7.6 (40:60) with a flow rate of 0.3 mL/min. The column temperature was set at 25°C. Ten microliters of each sample were introduced into the column using an automatic injector (Thermo Scientific Spectra System AS3000). The column effluent was monitored with a wavelength ultraviolet detector set at 280 nm (Thermo Scientific Spectra System UV2000). According to the stability study design, 2 aliquots were collected from each of the 3 containers for each temperature on 0, 7, 14, 30, 60, 90, 120, and 150 days.

Preparation of Standard Solutions

Standard solution of OMZ. A stock standard solution of OMZ containing 6 mg/mL was prepared in methanol and appropriately diluted in mobile phase to render a 8 μ g/mL standard solution.

Sample preparation. The content of OMZ in the suspensions was assayed. An OMZ suspension (2 mg/mL) was shaken vigorously by hand immediately before use. One gram was accurately weighed in a 10-mL volumetric flask and dissolved in methanol, sonicated for 5 minutes, and centrifuged to 14 000 rpm for 5 minutes. A final dilution was performed from the supernatant obtained in the previous centrifugation step, with mobile phase to make a concentration of 7 μ g/mL of OMZ.

Stress Conditions

Oxidation: 25 mL of a 3% v/v hydrogen peroxide solution was added to 25 mg of OMZ accurately weighed. Acidic: 20 mg of OMZ and 100 mL of 0.5 M hydrochloric acid solution were refluxed during 1 hour. Alkaline: similar condition to the method described under "acid," using 0.5 M sodium hydroxide solution. Light: 1 mg/mL of OMZ solution was exposed to white light during 1 week. All samples were diluted with diluent to obtain a final concentration of 8 μ g/mL of OMZ.

Validation of the Analytical Method

Validation of the method was performed by studying specificity, linearity, limits of detection (LOD) and limits of quantification (LOQ), precision, and accuracy. First, specificity was mainly evaluated by subjecting OMZ standard solution to different possible degradation routes with acid, alkaline, oxidation, and light, which were then analyzed by micro-HPLC. In addition, blank samples with all the excipients involved were prepared and analyzed to check for interferences. The linearity

of the method was evaluated by establishing a relationship between the concentrations of OMZ and areas on the standard chromatogram. This is shown by linear regression models obtained for each of the 2 standard preparations. Linearity was verified at different concentration levels (5.0, 10.0, 25.0, 50.0, 75.0, and 100.0 μ g/mL) of OMZ, prepared in blank of excipients for each formulation and these were analyzed in duplicate in 3 separate runs. LOD and LOQ were determined. Precision was evaluated for intra-day (n = 6) and inter-day assays (n = 18), and it was expressed as relative standard deviation (RSD) for retention times and areas. Accuracy was evaluated from recovery studies. Placebo samples containing all excipients present in the suspension were supplemented with OMZ at 80%, 100%, and 120% concentration levels of the nominal values, and 3 replicates of each level were assayed.

Microbiological Studies

Microbiological tests of formulations were performed at 0 and 150 days according to the USP monograph of non-sterile products.²⁰ The microbial count was considered to be the average number of colony forming units (cfu) found in agar. Liquid oral formulations would meet microbial requirements. If the total aerobic microbial count was less than 102 cfu/mL, the total combined yeast/mold count less than 101 cfu/mL and confirmed the absence of *Escherichia coli*.

Results

Two different suspensions as oral liquid formulation have been developed. One prepared from OMZ pellets (formulation A) and the other from OMZ active (formulation B), both of them at the same concentration 2 mg/mL. Results from different physical, chemical, and microbiological studies are presented.

In the appearance test, after preparation ($t = 0$), both formulations resulted to be white suspensions, with characteristic odor of mint. For formulation A, there were no detectable changes in color or odor in any sample during 150 days at 4°C and for 2 weeks at 25°C; formulation B remained stable for 90 days at 4°C. In this sense, at 25°C, the color of the suspension B after 1 day and suspension A after 14 days changed from yellow to brown and finally violet.

In the taste test, the flavor of formulation A was similar to point 3 of the scoring scale, corresponding to strong bitterness, for 60% of the volunteers and 80% for the formulation B. Therefore, 80% of the volunteers preferred the formulation A prepared from the pellets.

Resuspendibility parameter can be observed for all formulations, because the sediments were easily redispersed after 10 seconds of vigorous and manual agitation, resulting in a homogeneous system for all temperatures and times.

The results of pH monitoring for both suspensions were formulation A, 9.4 to 10.1 and formulation B, 9.5 to 10.1 during the study.

Figure 2. Chromatogram of (a) blank excipients, (b) omeprazole standard solution (8 µg/mL), (c) omeprazole in suspension A, and (d) omeprazole in suspension B.

The viscosity values for formulation A (155-173 cps) and B (240-267 cps) presented a little variation during the 150 days and 90 days of the storage at 4°C, respectively.

The chromatograms corresponding to the standard solution of OMZ, formulation A, formulation B, and blank of excipients are presented in Figure 2. Omeprazole retention time is 6.8 minutes. No degradation products were observed under the established conditions in all cases. Moreover, results of the analytical method validation are presented in Table 2.

Table 3 shows the chemical stability results for each formulation, all of them stored at refrigerated conditions (4°C) and room temperature (25°C) expressed as mean percentage of initial OMZ concentration.

In formulations A and B at both temperatures, no contamination was observed by *E coli* in 1 g and the fungal and yeast count was below 10 cfu/g on days 0 and 150. The total viable aerobic count complied with specifications (not more than 10 cfu/g) for the formulation A at both temperatures and formulation B at 4°C during the stability study. Total viable aerobic count of 170 cfu/g at 30 days was found for formulation B at 25°C.

Discussion

Development of the Formulations

The development of pharmaceutical formulations for pediatric patients is a unique challenge. The proper design and

Table 2. Parameters of Validation of Method of Analysis of Omeprazole.

Parameter	Omeprazole
Linear range (µg/mL)	5–100
R^2	.9992
LOD (µg/mL)	0.4
LOQ (µg/mL)	1.3
Precision RSD	
Intra-day (n = 6)	
Migration time	1.2
Peak area	0.9
Inter-day (n = 6)	
Migration time	1.5
Peak area	1.5
Accuracy	Formulation A Formulation B
Spiked levels ^a	
80%	101.3 (1.3) 102.0 (1.5)
100%	100.3 (1.3) 101.2 (1.6)
120%	100.4 (1.7) 102.0 (0.8)

Note. RSD = relative standard deviation; LOD = limits of detection; LOQ = limits of quantification.

^aRSD values in parentheses (n = 3).

formulation of dosage form requires consideration of the physical, chemical, and biological characteristics of the active drugs and pharmaceutical excipients. Pharmaceutical actives and excipients must be compatible with one another

Table 3. Stability of Omeprazole Suspensions Stored at 4°C and 25°C.

Time (days)	Suspension A		Suspension B	
	25°C (%)	4°C (%)	25°C (%)	4°C (%)
0	100.0 (0.9)	100.0 (0.9, 0.9)	100.0 (0.9)	100.0 (0.9)
7	103.7 (1.2)	102.1 (0.7, 0.7)	NQ	100.2 (0.8)
14	99.6 (1.1)	99.2 (0.8, 0.8)	NQ	100.8 (0.9)
30	1, 10.3 (1.3)	102.0 (0.9, 0.9)	NQ	101.2 (1.0)
60	NQ	101.0 (0.7, 0.7)	—	99.3 (1.1)
90	—	103.0 (1.0, 1.0)	—	92.8 (1.4)
120	—	105.0 (1.2, 1.3)	—	NQ
150	—	109.1 (1.1, 1.2)	—	—

Note. RSD, SD in parentheses (n = 3). RSD = relative standard deviation; NQ = not quantifiable.

to produce formulations effective, stable, well tolerated, easy to administer, and with good palatability. Thus, liquid formulations rather than solid dosage form are preferred for oral administration to children.^{21,22}

The development of OMZ liquid formulation is a difficult task, due to its potential degradation in aqueous solutions, especially at pH values below 7. In this sense, the stability of OMZ is increased at alkaline pH, especially pH values more than 9.⁴ Previous studies have demonstrated that OMZ powder from packet for immediate-release, pellet or capsules, suspended in 8.4% sodium bicarbonate, has presented a chemical stability from 1 week to 30 days at refrigerator temperature.^{8-12,14} One of them used a commercial vehicle to resuspending the powder, presenting this formulation a stability at least 60 days at 2°C to 8°C¹³ but no one of the reported formulation, the pH value was higher than 9 and no reported usage of OMZ pure drug for the preparation of the suspension.

Suspensions are useful dosage forms for administering poorly water-soluble drugs. Moreover, a suspension can mask drug unpleasant taste improving pediatric formulation acceptance and treatment adherence. Therefore, we developed and studied 2 different suspensions, one of them prepared from commercial pellets of OMZ, and the other from OMZ pure drug, using sodium bicarbonate as vehicle and including humectant, suspending, sweetening, antioxidant, and flavoring agents. In addition, our study adds more information, like microbiological studies, plus other types of important characterization aspects such as color, odor, resuspendibility, rheological study, pH, and chemical stability.

In this regard, the suspension design was aimed at developing a simple dosage form, using a single suspending agent like sodium carboxymethyl cellulose. Sodium carboxymethyl cellulose is a cellulose derivative which is a beta-(1,4)-D-glucopyranose polymer, widely used in oral and topical pharmaceutical formulations, primarily for its viscosity-increasing properties. Viscous aqueous solutions are used to suspend powders intended for either topical application or oral and parenteral administration.²³ Different concentration levels (0.3%-1.0% w/v) of sodium carboxymethyl cellulose were studied; therefore, an adequate viscosity was allowed at 0.7%

w/v of sodium carboxymethyl cellulose in the final formulation. Along with sodium carboxymethyl cellulose, sorbitol was used as a sweetening agent at concentration level according to Pharmacopeias recommendation.^{23,24} Higher content of sorbitol in a dosage form can produce diuretic effect.²⁴ Together with sorbitol, glycerin was applied as humectant agents. The OMZ commercial pellets have a very bitter taste. Therefore, besides sorbitol, saccharin is an intense sweetener used in beverages, food products, tabletop sweeteners, and oral hygiene products such as toothpastes and mouthwashes. Oral formulation is used at a concentration of 0.25% w/v. Saccharin can be used to mask unpleasant tastes or improve the taste of different systems. Its sweetening power is approximately 500 times greater than sucrose.²⁵ Although the fact that the OMZ is formulated as a suspension reducing the perception of bitter taste, it is not sufficient and other excipients need to be added. The addition of sweetening agents, essences, and coatings are some of the most common used strategies, but in most cases are not efficient. Mint essence, due to its refreshing effects, contribute to distract the organoleptic senses from the unpleasant bitter taste added to the inherent flavor and odor of mint essence which has some anesthetic effect on sensory receptor organs associated, provides a good alternative, to improve palatability and mask bitter taste.^{26,27}

Finally, sodium bisulfite was used like antioxidant agent. Antioxidants are used to reduce the oxidation of active substances and excipients in the medicinal product.²⁸ Sodium metabisulfite is used in acidic preparations, sodium bisulfate at intermediate pH, and sodium sulfite at higher pH values. That was the case of the 2 formulations (pH 9.5).

Sodium sulfite is used in cosmetics, food products, and pharmaceutical applications such as parenteral formulations, inhalations, oral formulations, and topical preparations at concentrations of 0.01% to 1.0% w/v.²⁹

Stability Study

In the appearance test, color is an important attribute in pharmaceutical products, because the consumer immediately perceives it. It can also be a measurement of reactions extension

Figure 3. Chromatogram of (a) omeprazole (OMZ) standard solution in alkaline hydrolysis, (b) omeprazole standard solution in hydrogen peroxide, (c) omeprazole standard solution (25 $\mu\text{g/mL}$), and (d) omeprazole standard solution in acidic hydrolysis. Note. Peak at 4.3 min correspond to sulfone derivative and 5.5 min correspond to OMZ.

in medicine since formed and/or degraded compounds may contribute to a specific coloration. In the developed formulations, no changes in color and odor were observed stored at 4°C, while suspensions A and B at 25°C showed a violet color at 14 days and 1 day, respectively, due to the formation of its main degradation product, the sulfone derivative.

Suspension A at both temperatures and suspension B at 25°C present sediment easily resuspendable, while suspension B at 4°C was homogeneous at each time interval.

Compared to the study of viscosity, both suspensions presented a pseudoplastic behavior. This finding is in concordance with the content of carboxymethyl cellulose in the formula.³⁰

The pH monitoring is an important aspect of a stability study, because non-buffered vehicles may experience changes in their pH values through time. In some cases, these changes may increase the rate in which degradation products are formed or modify the formulation appearance. In this case, only slight changes in the pH values were observed.

Another aspect of this work was to investigate OMZ chemical stability under different storage conditions. In general, oral formulations such as suspension should contain not less than 90% and not more than 110% of the labeled amount of drug. Formulation A demonstrated an acceptable drug chemical stability remained above 90% at

room controlled temperature for 14 days and refrigerator temperature for a period of 150 days. Formulation B demonstrated an acceptable drug chemical stability at 4°C for 90 days. The analytical method applied for this stability study was based on a previous work.³¹ Briefly, we have developed a micro-HPLC-UV method using a hybrid column. The proposed method was validated according to international guidelines.³² The proposed method proved to be specific without interference from excipients and degradation products demonstrated by stress study. The principal degradation product of OMZ is the sulfone derivative (Figure 1). The development of micro-HPLC method with the use of a hybrid column particle allows the complete separation of OMZ from the sulfone derivative. The stability indicating capability of the method was studied by accelerated stress conditions (acid, alkaline, oxidation, and light) and specificity was also examined by comparing chromatograms of excipient blanks of the pharmaceutical formulation developed. Degradation was observed when OMZ was exposed to acidic, alkaline, and oxidation and the presence of omeprazole sulfone derivative and unknown peaks were detected in the chromatograms. As a result of acidic degradation, omeprazole sulfone derivative was observed along with unknown peaks. Exposure to light stress resulted in minimal degradation of OMZ (Figure 3).

These experiments indicate that the proposed micro-HPLC method is suitable in screening test of OMZ-related substances in drug and pharmaceutical formulations in stability studies.

Linearity was evaluated from 5.0 to 100 µg/mL with adequate R^2 as well as LOD and LOQ values. Precision was evaluated intra-day (n = 6) and inter-day (n = 18) and expressed as RSD for retention time and peak area. The RSD values obtained were less than 2.0%. Method accuracy was determined by a recovery study at 3 levels. Percentages of recovery were obtained in the range of 100.3 to 102.0 with low RSD (Table 2). Microbiological stability is a matter of great importance, and these formulations proved to be safe to prevent diseases related to bacterial and fungal contamination, which is a critical aspect when treating pediatric and neonatal patients. Moreover, microbial contamination in non-sterile liquid formulations may cause foul odor, turbidity, and adversely affect the palatability and appearance. This is especially important for immuno-compromised patients. Formulation A at both temperatures and formulation B at 4°C comply with the specifications of USP and European Pharmacopoeia (EP) on the microbial examination of non-sterile products over 150 days. Formulation B to 25°C complies with the specifications for 1 month.²⁰

Conclusions

Pediatric oral liquid OMZ suspensions presented an adequate physical, chemical, and microbiological stability. Omeprazole particles were homogeneously distributed, and this guaranteed the correct dose when administered to pediatric patients. Formulations A and B can be stored at a hospital or pharmacy refrigerator conditions for at least 150 and 90 days, respectively, or 2 weeks at room temperature (formulation A). The formulations enable pediatricians and pharmacists to administer a variable dose, which adapts to every patient, and gives the possibility of treatment when swallowing tablets or other solid forms is not possible.

However, an analytical methodology was developed for the quality control and stability study of the formulations. In this sense, a simple, fast, highly sensitive, and resolute micro-HPLC-UV method was optimized and validated for the quantitation of OMZ in pharmaceutical formulations as well as in OMZ drug. Moreover, the present method allowed the complete separation of major OMZ-related substances. In conclusion, all these features make this method suitable to be used in a routine laboratory, for quality control of OMZ in pharmaceutical formulation as well as the stability studies.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The

authors acknowledge the financial support by University of Buenos Aires and CONICET.

ORCID iD

Silvia Lucangiolli <https://orcid.org/0000-0002-9844-7331>

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