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Critical Quality Attributes and Pharmaceutical Equivalence Assessment of Allopurinol Tablets in Argentina

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ABSTRACT

Dissolution studies have evolved from a simple quality control test to an indicator of biopharmaceutical performance and alternative for in vivo equivalence and interchangeability assessment. Pharmaceutical equivalents imply products formulated with the same active pharmaceutical ingredient (API), in the same quantity and dosage form, that are intended to be administered by the same route fulfill the same quality criteria. The medicine market in Argentina is composed mostly of multisource products that are supposed to be pharmaceutical equivalents, but the generic market here is different from other parts of the world. In this scenario, the comparison of different products formulated with the same API becomes essential. Allopurinol, the drug of choice in the treatment of gout and tumor lysis syndrome, is classified as an essential medicine according to the World Health Organization. The present work aimed to compare critical quality attributes and in vitro dissolution characteristics of Allopurinol tablets purchased in Argentina to establish pharmaceutical equivalence. All evaluated products fulfilled the pharmaceutical equivalence criteria. Three of the tested products (the reference and two multisource formulations) comply with the criteria for 'very rapidly dissolving' and can be described as similar.

KEYWORDS: Allopurinol, Biopharmaceutical Classification System, dissolution profiles, pharmaceutical equivalence

INTRODUCTION

Allopurinol (ALLO) is a urate-lowering active pharmaceutical ingredient (API) that acts by decreasing the formation of uric acid through the inhibition of xanthine oxidase and is included in the World Health Organization (WHO) List of Essential Medicines (*1*). The drug was first approved by the United States Food and Drug Administration (US FDA) in 1966, and is currently used worldwide for the treatment of gout, gouty arthritis, uric acid stones, or hyperuricemia due to cancer or chemotherapy (*2*, *3*). In fact, the development of ALLO was one of the most important advances in the treatment of hyperuricemia, an effort that was awarded with the 1988 Nobel Prize in medicine (*4*, *5*).

ALLO presents a solubility value in water and 25 °C of 0.48 mg/mL. (*6*). This API is presented in the pharmaceutical market at two dosage strengths, 100 and 300 mg. The 100-mg formulation is one example of APIs now included in the class 1 of the Biopharmaceutics Classification System (BCS) (*7*). Before the change in WHO regulations, where the permeability criterion was relaxed from the FDA value of 90% to 85% to consider an API as 'highly permeable', the ALLO classification included mostly BCS class 3, and eventually a class 4 case (*8–10*). Classification of the 300-mg formulation of ALLO is not straightforward, but the FDA clearly indicates that ALLO 300 mg belongs to class IV (*11*).

In Argentina, ALLO tablets are available both as a reference and multisource product. In the Argentinean pharmaceutical market, it is a common practice for patients to replace the reference with multisource products, and even between the latter ones, based on economic reasons. Even though treatments could become more effective if patients were provided with proper knowledge to comprehend their care, it is important to point out that multisource products must have proven pharmaceutical equivalence. To establish that products containing the same API are pharmaceutical equivalents (i.e., same quantity, dosage form, and route of administration), it must be verified that they all comply with comparable critical quality standards (*12, 13*). Furthermore, in vitro dissolution studies can

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be applied to obtain useful information concerning the biopharmaceutical performance of the products. In this sense, dissolution profiles can be obtained in dissolution media of biological relevance, such as aqueous buffer solutions with pH values in the physiological range. In the case of APIs belonging to BCS class 1 and 3, this procedure corresponds to similarity studies (for biowaivers), which are used to assess interchangeability of formulations in lieu of in vivo studies, under recommendations of national and international regulatory agencies (*13–17*). In the case of APIs outside this classification, the assessment of dissolution behavior in media of physiological relevance completes the critical evaluation of pharmaceutical equivalence and assures the availability of essential drugs of proven quality, safety, and efficacy at affordable prices.

To the best of our knowledge, only one study has been published in the literature comparing different ALLO products, and there are no studies regarding products marketed in Argentina (*18*). Therefore, the aim of the present study was to assess critical quality attributes and pharmaceutical equivalence of five commercial products containing ALLO (300 mg), marketed in Argentina, with focus on their biopharmaceutical performance.

MATERIALS AND METHODS

Materials

ALLO was acquired from Saporiti (Parafarm, Argentina). Distilled water was used for assay and preparation of dissolution media. Analytical grade chemicals were used for the same purpose, namely sodium hydroxide (NaOH), hydrochloric acid (HCl), glacial acetic acid, potassium chloride, sodium acetate trihydrate and monobasic potassium phosphate (ANEDRA, Argentina). Aqueous buffer solutions (pH 1.2 HCl, pH 4.5 acetate, and pH 6.8 phosphate), used as dissolution media of physiological significance, were prepared in compliance with the United States Pharmacopeia (USP) (*19*).

Five different ALLO tablets (labeled amount: 300 mg) were purchased in local pharmacies of the Argentine market. Tablets were arbitrarily labeled from A to E, with sample D being the reference product, and the other formulations being multisource products. The composition of the evaluated formulations is presented in Table 1. All tests were performed within the shelf life of the products.

The information present in labels (primary and secondary packaging) and patient leaflets was evaluated and compared to verify compliance with local legislation (*20, 21*).

Table 1. Qualitative Composition of Excipients in Allopurinol Formulations

Excipient type	Excipient	A[b]	B	C[c]	D (Ref.)	E[c]
Filler/Diluent	Lactose		–	+	+	–
	Microcrystalline Cellulose[a]		+	–	–	+
Disintegrant	Corn Starch[a]		–	+	+	–
	Povidone[a]		+	+	+	+
	Crospovidone		–	–	–	–
	Croscarmellose sodium		–	+	+	+
	Docusate Sodium[a]		–	–	–	–
	Sodium Starch Glycolate		+	–	–	–
	Pregelatinized starch[a]		–	–	+	–
Glidant	Sodium Lauryl Sulphate[a]		–	–	–	–
	Colloidal Silicon Dioxide		+	–	+	+
	Talc[a]		–	–	–	–
Lubricant	Magnesium Stearate		+	+	+	+
	Polyethylene glycol		–	–	–	+

[a]This excipient has multiple functions.
[b]Label and/or leaflet do not inform qualitative composition of excipients.
[c]Label and/or leaflet inform qualitative and quantitative composition of excipients.
+ indicates presence and – indicates absence of excipient.

Equipment

A Varian Cary 50 Conc Spectrophotometer (Varian Instruments, Australia) was used for assay and quantification of API in dissolution studies. Hardness, friability, and disintegration of the tablets were measured using a Scout DGM02, FGMO2, and EGMO2, respectively (Scout Electronics, Argentina). In vitro dissolution studies were performed with an Erweka DT60 (Erweka GmbH, Germany). An Acculab ALC- 210.4M (Acculab, USA) electronic analytical balance was used to weigh materials and tablets.

Evaluation of Critical Quality Attributes

For weight variation analysis, 10 randomly chosen tablets from each commercial sample were individually weighed, and the mean value and corresponding standard deviation (SD) were calculated.

Friability, hardness, and disintegration tests were completed according to Argentine Pharmacopeia (*20*). Ten tablets from each sample were weighed and placed into the friability tester. After 100 revolutions (25 rpm for

4 min), the tablets were removed from the tester and weighed, and the result was compared with the initial weight value (*20*). The hardness of 10 individual tablets of each sample was measured in terms of the degree of force in kilopounds (kp) required to break each tablet across the diameter. The disintegration time of tablets (n = 6, for each sample) was assessed at 37.0 ± 2.0 °C in distilled water for 30 minutes. Unless otherwise specified in the corresponding monograph, it should be observed that all tablets completely disintegrate in the indicated testing time (*20*).

For the assay test, 20 tablets were randomly selected, weighed, and finely powdered. An exactly weighed quantity of powder, containing approximately 100 mg of ALLO, was dissolved using 0.05 M NaOH. The obtained solution was filtered through a 0.45-µm pore-size nylon membrane (Gamafil, Argentina) and suitably diluted with 0.1 M HCl. ALLO concentration was determined by UV-spectrophotometry at 250 nm (applying the standard calibration curve developed for this purpose: y = 0.0576 x – 0.0096; r^2=0.9998; concentration range 4.0–14.0 µg/mL) (*22*, *23*). This same methodology was individually applied to 10 tablets of each commercial sample for assessment of uniformity of dosage units.

Dissolution tests were performed using a calibrated USP apparatus 2 at 75 rpm with 900 mL of 0.01 N HCl at 37.0 ± 0.5 °C as dissolution medium (*19*, *20*). Six replicates (n = 6) of each product were evaluated for stage 1 (S1) of dissolution acceptance criteria. Samples were withdrawn at the time specified in the corresponding monograph (45 min), filtered through a 0.45-µm pore-size nylon membrane (Gamafil), and suitably diluted with the same medium. Drug concentration was determined by spectrophotometric analysis at 250 nm (applying the following calibration curve: y = 0.0584 x – 0.0249; r^2 = 0.9997). Argentine Pharmacopeia states that not less than 75% (Q) of the labeled amount of ALLO should be dissolved within 45 minutes (*20*).

Biopharmaceutical Performance of ALLO tablets

To evaluate the biopharmaceutical performance of the selected products, dissolution profiles (n = 12 for each sample) were performed at pH 1.2, 4.5, and 6.8, applying the same experimental conditions of the dissolution quality control test (as stated above). Samples (10 mL) were withdrawn at 5, 10, 15, 20, 30, 45, and 60 minutes (with replacement of fresh medium) and subsequently filtered, diluted, and measured by UV analysis. The concentration in each sample was calculated from calibration curves constructed in each dissolution medium (r^2 range: 0.9973–0.9994). Cumulative percentages of dissolved API were calculated for dissolution profile assessment, where each point of the dissolution profile corresponds to the mean value and its respective SD.

Statistical Analysis

Dissolution profiles were characterized in terms of the model independent parameter dissolution efficiency (DE) (*24*). DE values were statistically evaluated applying analysis of variance (ANOVA) followed by least significant difference (LSD). Mathematical comparison of dissolution profiles was carried out in terms of similarity factor, f_2 (*13–17*). Statistical analysis was performed using InfoStat software, version 2014 (http://www.infostat.com.ar).

RESULTS AND DISCUSSION

Not all the evaluated products could be considered equivalent with respect to the information provided about storage conditions (Table 2). Argentine Pharmacopeia states that the correct storage conditions should be "to preserve in well-closed containers," and this should be indicated both in the secondary packaging and patient leaflet (*20*). None of the samples indicated the requirement of "well-closed" packaging, although sample C indicated keeping the tablets in their original container. All samples referred to conditions of appropriate storage, and almost all presented an upper limit of 30 °C. Concerning the general information provided by the manufacturers, it is important to highlight that sample A did not provide information about the composition of excipients (qualitative not quantitative) (Table 1), which is a requirement of local legislation (*21*). Another issue is the important differences in the prices of evaluated ALLO products, with sample E having the highest cost, 62.5% higher than the most economic one (sample A) (Table 2). This is an important factor to be considered because interchangeability decisions by patients in Argentina are generally based on economic reasons.

Critical Quality Attributes

The results of physical tests are shown in Table 2. Large differences were detected between the weight values of different samples, with mean results ranging from 432.0 to 720.2 mg. Differences in composition, typical of each manufacturer (and presented in Table 1), and different physical dimensions of each product could explain this range of results, without necessarily involving variations in the API content or dissolution performance. With respect to hardness evaluation, the mean results ranged from 7.5 to 34.3 kp, which could be considered an acceptable range. In the case of friability tests, the pharmacopeial specification states that 'a maximum

Table 2. Information of Evaluated Products and Results of Physical Quality Control Tests for Allopurinol Formulations

Sample	Price[a]	Storage Conditions[b]	Tablet Weight (mg)[c]	Hardness (kp)[c]	Friability (% of weight loss)	Disintegration Time[d]
A	3.46	Store between 15 and 30 °C	432.0 ± 5.0	9.7 ± 0.5	0.41	51 s
B	4.86	Store at a room temperature (pref. between 15 and 30 °C).	451.3 ± 3.7	7.5 ± 0.3	0.29	2 min 36 s
C	5.30	Store at a room temperature between 15 and 30 °C, in its original case and protected from light and heat.	695.7 ± 3.0	11.6 ± 0.5	0.04	5 min 36 s
D (Ref.)	5.34	Store in original case at room temperature and dry place.	708.9 ± 7.0	15.8 ± 1.0	0.05	5 min 11 s
E	5.62	Store at room temperature be-low 30 °C.	720.2 ± 7.0	34.3 ± 0.1	0.04	5 min 42 s

[A]Price per tablet in argentine pesos at the time of analysis.
[B]Information presented in labels and leaflets.
[C]Mean value ± SD.
[D]Maximum time needed for complete disintegration of evaluated tablets.

mean weight loss of not more than 1.0% is considered acceptable' (*19*, *20*). All evaluated samples fulfilled this requirement, as shown in Table 2. For disintegration assessment, the pharmacopeial specification states that 'at the end of the time limit specified in the monograph all of the tablets have disintegrated completely' (19, 20). All evaluated products showed acceptable disintegration times, with results ranging between 51 seconds and almost 6 minutes (Table 2). Therefore, all samples met the official compendium requirement of 30-minute disintegration time (*20*). It is important to point out that the hardest formulation (sample E) also exhibits the lowest weight loss in friability determination and the longest disintegration time (Table 2). Nevertheless, no apparent relationship could be found, because the sample with the lowest hardness value (sample B) had an intermediate result for friability and disintegration time, and samples with similar friability and disintegration time (samples E and C) differed in hardness results (Table 2).

ALLO tablets should contain an amount equivalent to 93.0–107.0 % of the labeled amount of ALLO, as indicated in the respective monograph (*20*). As shown in Table 3, assay results for all evaluated products fulfilled these requirements, with results that ranged from 97.8 ± 2.6 (sample A) to 103.7 ± 2.1 (sample E). On the other hand, the specifications for uniformity indicate that API content should be between 85.0–115.0% of the labeled amount in each evaluated dosage unit, and the relative standard deviation (RSD) should not exceed 6.0% (*20*). All evaluated products fulfilled these requirements.

The ALLO tablets monograph includes specifications for in vitro dissolution testing, stating that 'not less than 75% (Q) of the labeled amount of ALLO is dissolved in 45 minutes' (*20*). According to the results shown in Table 3, all formulations complied with specification for the S1 dissolution test.

Table 3. Assay, Uniformity of Dosage Units, and Dissolution Test Results for Allopurinol Formulations

Sample	Assay[a]	Uniformity of Dosage Units[b]	Dissolution Test (S1 Stage)[c]
	93.0–107.0%	85.0–115.0%; RSD < 6.0%	75% (Q) in 45 min
A	97.8 ± 2.6	95.9–100.0 / 1.2	88–92 / 1.8
B	101.5 ± 2.9	100.5–102.8 / 0.8	89–92 / 1.7
C	99.2 ± 2.0	98.8–100.3 / 0.5	90–95 / 2.4
D (Ref.)	102.1 ± 2.8	100.3–104.2 / 1.2	101–105 / 2.0
E	103.7 ± 2.1	102.5–105.7 / 1.0	100–102 / 1.1

[A]Percentage of labeled amount. Mean value ± SD.
[B]Range of % labeled amount / RSD.
[C]Range of % labeled amount dissolved /RSD. S1 Stage corresponds to the first (of three) instance of approval for in vitro dissolution test according to the acceptance table for "Dissolution" chapter in United States Pharmacopeia.
RSD: relative standard deviation; Q: amount of dissolved active pharmaceutical ingredient, specified in the individual monograph, expressed as a percentage of labeled content of the dosage unit.

Biopharmaceutical Performance

Dissolution profiles obtained in physiologically relevant media are presented in Figures 1–3. The reference formulation (D) and the samples B and E are considered as 'very rapidly dissolving' (i.e., 85% dissolved in the first 15 minutes). On the other hand, DE results could be considered satisfactory, because values were greater than 77.0% for all samples and all media, with the highest values registered for samples D and E (Table 4).

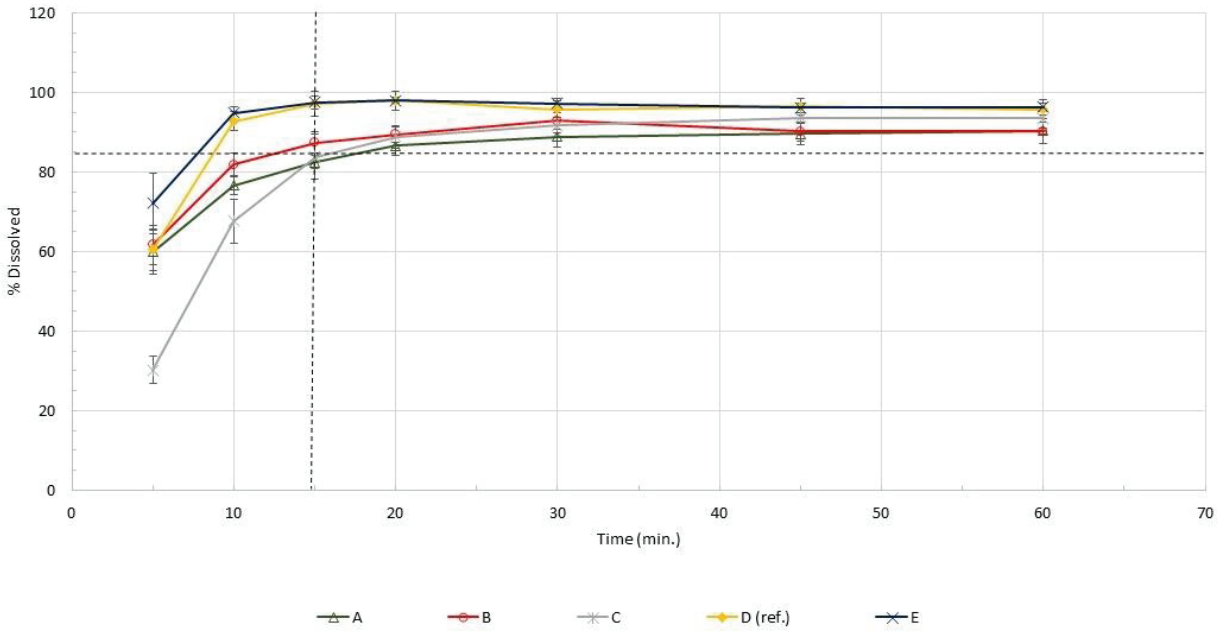

Figure 1. Dissolution profiles for Allopurinol formulations in hydrochloric buffer solution (pH 1.2). Each point of the profile represents the mean result for the percentage of ALLO labeled amount dissolved, at each sampling time, and the corresponding error bars (standard deviation). Dotted lines represent the 'very rapidly dissolving' limits (85% dissolved at 15 minutes).

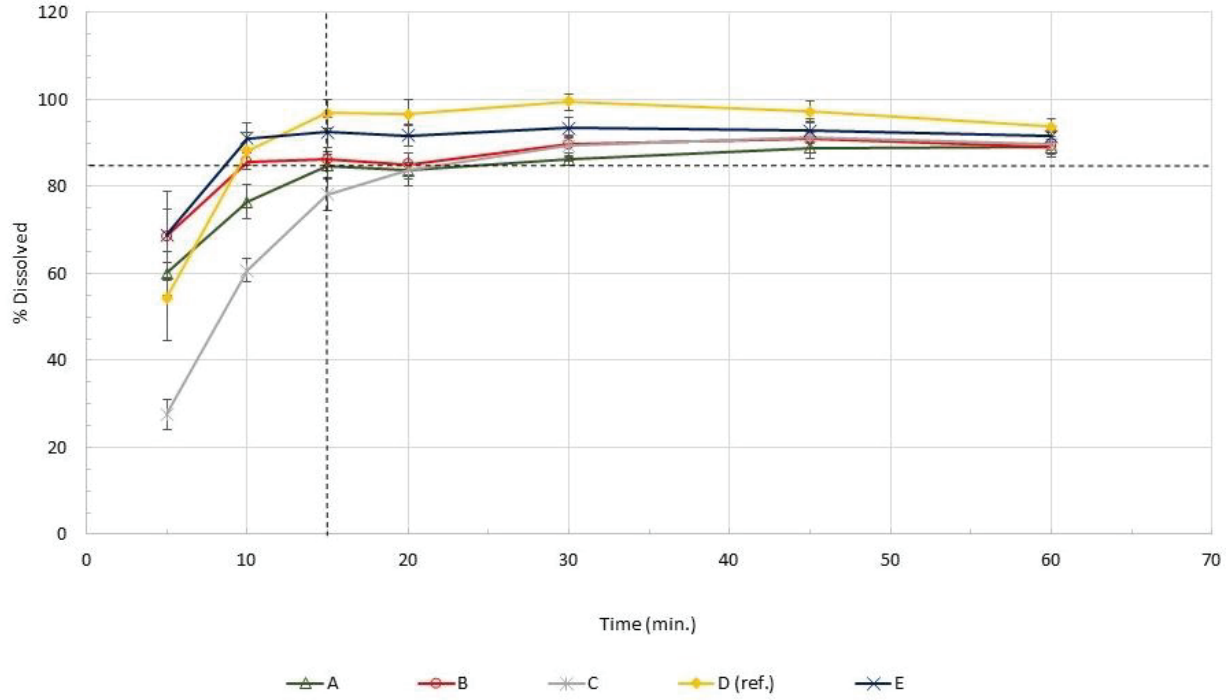

Figure 2. Dissolution profiles for Allopurinol formulations in acetic buffer solution (pH 4.5). Each point of the profile represents the mean result for the percentage of ALLO labeled amount dissolved, at each sampling time, and the corresponding error bars (standard deviation). Dotted lines represent the 'very rapidly dissolving' limits (85% dissolved at 15 minutes).

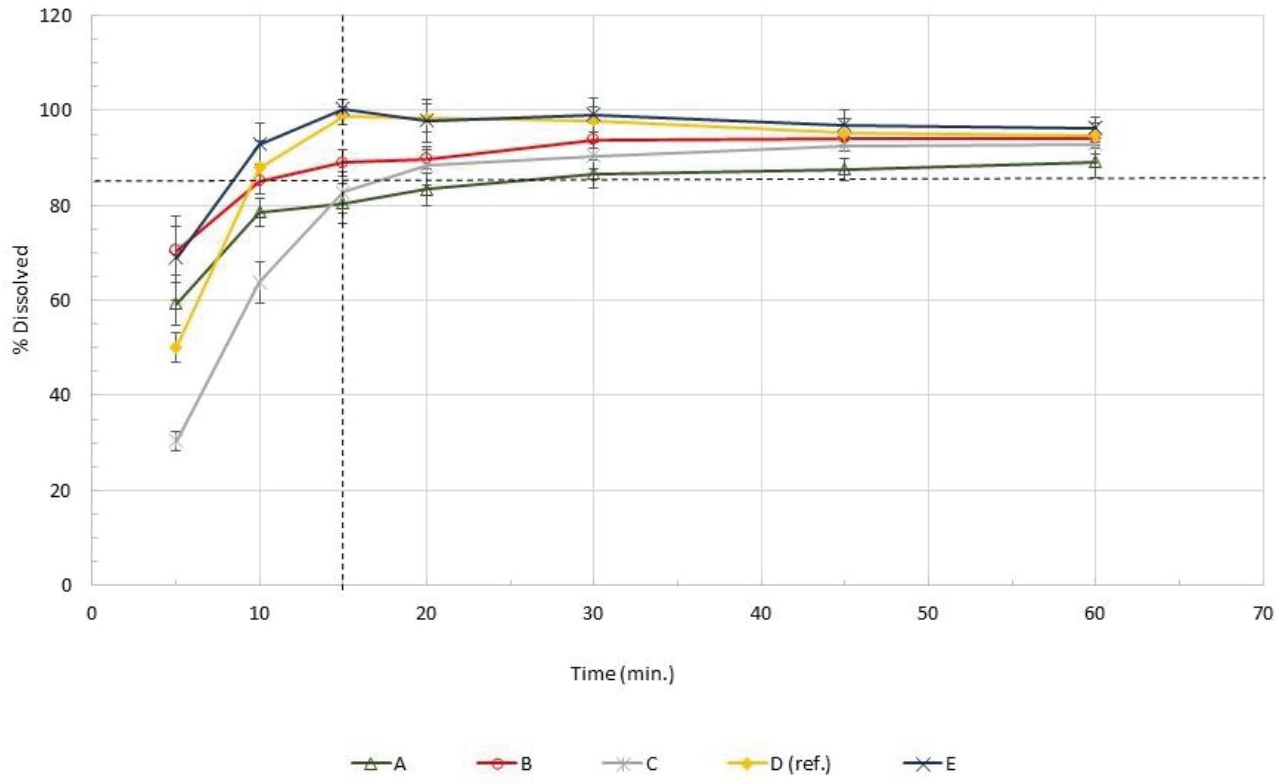

Figure 3. Dissolution profiles for Allopurinol formulations in phosphate buffer solution (pH 6.8). Each point of the profile represents the mean result for the percentage of ALLO labeled amount dissolved, at each sampling time, and the corresponding error bars (standard deviation). Dotted lines represent the 'very rapidly dissolving' limits (85% dissolved at 15 minutes).

The statistical comparison of these results (by ANOVA) revealed the existence of significant differences in DE results for samples A and C, with respect to the reference formulation, in all media (Table 4). In the case of sample B, significant differences were detected in pH 1.2 and 4.5 buffer solutions, but not in phosphate buffer (Table 4). Finally, for sample E no statistical differences were detected when compared to reference formulation, in all media (Table 4). Dissolution profiles were also compared using the similarity factor, f_2. Even though 300-mg ALLO is considered a BCS class IV drug, the application of $f2$ could be useful to completely characterize and compare dissolution profiles. In this sense, considering that both samples B and E, as well as the reference product D, are 'very rapidly dissolving' formulations, the mathematical evaluation is considered not necessary because the profiles would be essentially similar (*13–17*). In the case of samples A and C, f_2 was calculated prior to verification that all requirements for its application were fulfilled (*13–17*). In the comparison of sample A with the reference formulation, the obtained f_2 results were 45.4, 46.8, and 44.0 for buffer pH 1.2, 4.5, and 6.8, respectively. In the case of comparison of sample C with the reference product D, the results were 33.6, 34.4, and 36.9, respectively. All obtained similarity factors were lower than the limit value of 50, suggesting that these profiles could not be considered similar, which is in accordance with the ANOVA results (*13–17*).

Table 4. Dissolution Efficiency Results for Allopurinol Formulations

Medium	A	B	C	D (Ref.)	E
pH 1.2	81.3 ± 2.0*	83.6 ± 2.0*	80.5 ± 1.9*	89.1 ± 1.0	90.6 ± 0.9
pH 4.5	80.2 ± 1.9*	83.3 ± 1.0*	77.0 ± 1.5*	88.8 ± 1.4	86.6 ± 1.1
pH 6.8	79.7 ± 2.6*	86.5 ± 1.1	79.4 ± 1.6*	88.1 ± 2.1	91.0 ± 2.0

Results are expressed in % of labelled amount dissolved (mean ± SD).
** indicates significant differences ($p \leq 0.05$) detected, with respect to the reference formulation D.*

CONCLUSION

All evaluated products fulfilled Argentinean Pharmacopeial specifications for critical quality attributes

under the experimental conditions employed. These results demonstrate that the 300-mg ALLO products tested from the local market are pharmaceutical equivalents. Nevertheless, caution must be critically exerted, especially with products A and C, considering that patients may interchange multisource products for economic reasons, regardless of biopharmaceutical performance.

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DECLARATIONS OF INTEREST

The authors disclosed no conflicts of interest related to this article.

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