

Dissolution Stability Study of Cefadroxil Extemporaneous Suspensions

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ABSTRACT

Dissolution studies have become matter of great significance because, in most cases, drug dissolution is the rate-limiting step in the absorption process. As occurs with solid oral dosage forms, heterogeneous disperse systems (suspensions) could also have some problems with their in vitro dissolution.

The dissolution behavior of four different brands of cefadroxil extemporaneous suspensions available in the Argentinian market was evaluated. The deliverable volume, pH, visual appearance, uniformity of dosage units, and assay were also studied.

Powders for oral suspension were stored under different aging conditions. Samples at room temperature and refrigerated conditions were taken at several time points to carry out the dissolution stability study during the expiration period of the reconstituted form. Marked differences were recorded with respect to in vitro dissolution behavior between the different products under evaluation.

INTRODUCTION

Many patients, especially geriatric and pediatric patients, have difficulty swallowing whole solid oral dosage forms. An effective pharmaceutical dosage form should be considered as a dosing device to enable the accurate and repetitive dosing of drugs. Extemporaneous suspensions, like many other dosage forms, are much more than simple drug carriers, since they may affect the absorption rate and the effectiveness in the patient.

Most of the problems linked with this pharmaceutical form are associated with its physical stability and include dosing accuracy, unknown bioavailability, and lack of access to modified release preparations for pediatric patients, among others (1).

There are few stability studies undertaken on extemporaneous products (1). In this disperse type system, physical change is more important than chemical change. However, it is assumed that suspension stability is primarily governed by the decomposition of the drug dissolved in the aqueous phase (2).

In general, suspension stability determinations consider only factors like changes in chemical stability, visual appearance, pH, caking, and re-dispersability (3, 4), with no focus on *Dissolution Stability*. This term refers to the retention of the dissolution behavior of the dosage form from manufacture to the expiration date (5).

Since suspensions are similar to the disintegrated form of tablets, in vitro dissolution studies are also essential

when drug particle dissolution is a requirement for bioavailability and, in most cases, the rate-limiting step in absorption (6). In fact, the 1987 FDA Stability Guideline (7) specifically called for dissolution testing of suspensions (Section III.B.6.d). However, there are only a few compendial requirements in pharmacopeial sources for suspension dissolution studies. The *United States Pharmacopeia* (8) contains 98 monographs for oral suspensions, but only seven of them have a codified dissolution test.

Studies carried out on suspension dissolution (6, 9–15) did not consider if there were any change in this process during the administration period of the reconstituted suspension (stored at room temperature as well as under refrigeration) throughout the shelf life of the powdered product.

Dissolution stability is considered a critical parameter not only from the standpoint of quality control, but also for the impact on the bioavailability of the product, because significant changes of in vitro release profile during storage affect bioavailability. During aging, the absence of dissolution changes provides some assurance that the bioavailability remains intact (5).

Cephalosporins are widely used in suspension dosage forms and are one of the safest and most effective broad-spectrum bactericidal agents. Cefadroxil is a semisynthetic, first-generation cephalosporin antibiotic, the p-hydroxy derivative of cephalexin, with a potential activity against many moderate to mild bacterial infections including staphylococci, streptococci, and enterobacteriae (16). It is slightly soluble in water and in alcohol (16, 17). It is well absorbed from the

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gastrointestinal tract. The plasma half-life is about 1.5 h, and more than 90% of a dose may be excreted unchanged in urine within 24 h by glomerular filtration, active tubular secretion, and saturable renal tubular reabsorption (16, 18). Overall pharmacokinetics is linear only in the 250–500 mg dose range (19).

The first purpose of the present study was to establish the appropriate general conditions for performing the dissolution profiles of extemporaneous cefadroxil suspensions, and then use them as part of a comparative evaluation of commercial product quality. Our research attempted to evaluate the dissolution stability of four different formulations available in the Argentinian market over the recommended administration period of reconstituted forms, mimicking the “in use” stability. The dissolution stability of the powders for reconstitution was evaluated at different times during a year of storage in their original containers, under natural (25 °C/60% RH) and accelerated (40 °C/75% RH) aging conditions according to our ICH climatic zone (20).

MATERIALS AND METHODS

Reagents and Samples

Analytical grade potassium hydroxide and monobasic potassium phosphate, and HPLC grade acetonitrile were used (J. T. Baker, USA). Distilled water was used as dissolution medium, and HPLC grade water was used for chromatographic determinations.

Cefadroxil extemporaneous suspensions (dry powder mixture of cefadroxil and excipients for oral suspension, 250 mg/5 mL labeled amount) manufactured by four different pharmaceutical companies (A–D) were purchased from pharmacies in Buenos Aires city (Argentina). All tests were performed within product expiration dates, which were similar among brands.

Deliverable Volume

This was performed using ten containers of each brand (8).

pH

The pH (Altronix TPX-I) was measured over each reconstituted suspension at every stage of dissolution stability evaluation (8).

Visual Inspection

During the stability study, all samples were visually inspected for signs of caking, color change, and re-dispersion problems.

Uniformity of Dosage Units—Assay

HPLC System and Chromatographic Conditions

Reversed-phase HPLC was performed on a system consisting of a dual-piston reciprocating Spectra Physics pump (model ISOChrom, USA), a Rheodyne injector (model 7125) with a 20- μ L loop, a UV-vis Hewlett-Packard

detector (model 1050, Japan) set at 230 nm, and a Hewlett-Packard integrator (series 3395, China). Mobile phase consisted of a mixture of pH 5.0 buffer (13.6 g of monobasic potassium phosphate dissolved in 2000 mL water and adjusted to pH 5.0 with 10 N potassium hydroxide) and acetonitrile (960:40). Fresh mobile phase was prepared daily, filtered through a 47-mm nylon membrane (0.45- μ m pore size, μ clar, Argentine), and vacuum-degassed before use (8). Separation was performed at room temperature on a Waters Spherisorb ODS (Hypersil) C18 reversed-phase column, 10- μ m particle size, 200 \times 4.6 mm i.d. The column was equilibrated for at least 45 min with mobile phase flowing through the chromatographic system before starting the assay. All analyses were performed under isocratic conditions at a 0.9 mL/min flow rate.

HPLC Standard and Sample Solutions

Standard solutions were prepared on a weight basis using pH 5.0 buffer as diluent, sonicated for 10 min at room temperature, and suitably diluted. An appropriate volume was filtered through a 25-mm nylon membrane disposable filter (0.45- μ m pore size, μ clar, Argentine). They were injected in triplicate (RSD < 2.0%) and the results averaged.

Sample solutions were also prepared on a weight basis using 5 mL of suspension from each bottle after mixing with a standardized manual procedure, and then treated as the standard solutions. Samples mimicked the usual product dose.

In both cases, the theoretical concentration of cefadroxil monohydrate injected was 25–30 μ g/mL, and all solutions were used on the day prepared.

The uniformity of dosage units was performed using ten containers of each brand (8).

To evaluate chemical stability of the powder under reconstituted suspension form, the assay was performed at these stages:

- At the beginning of the aging process and after 6 and 12 months under specified aging storage conditions; not only at time of reconstitution, but also during the proposed administration period of the reconstituted formulations (at room temperature as well as under refrigeration). This determination was performed on a unique container of each brand.
- Only on freshly prepared suspension, under both aging storage conditions (accelerated and natural). This determination was performed on two reconstituted forms of each brand (for storage at room temperature as well as under refrigeration) and the results averaged.

Dissolution Stability Study

Apparatus and Conditions of Dissolution Profiles

Since “Cefadroxil for oral suspension” has no compendial dissolution method, the USP cefadroxil tablets test (8) was adjusted to this purpose.

Dissolution profiles were performed on a suitably calibrated USP Apparatus 2 (Vankel VK 7010) at 50 ± 1 rpm, under sink conditions in 900 mL of deaerated distilled water at 37 ± 0.5 °C, for each test (six replicates of each brand). Samples (10 mL) were withdrawn at 7.5, 15, 30, 45, and 60 min without replacement of medium and filtered through blue ribbon filter paper.

In order to obtain accurate results, the methodology for drug dissolved quantification was changed to HPLC analysis instead of UV spectroscopy codified for cefadroxil tablets dissolution (8). The solutions obtained were suitably diluted with pH 5.0 buffer, filtered through a 25-mm nylon membrane disposable filter (0.45- μ m pore size, μ clar, Argentine), and injected in triplicate for quantification by the HPLC assay methodology. Results were averaged, and cumulative percentages of drug release calculated.

Schedule of Dissolution Stability Study

The products were analyzed at the following stages:

0:	Beginning of the stability study.
3N, 6N, 9N, 12N:	3, 6, 9, and 12 months of natural (N) aging conditions.
3A, 6A:	3 and 6 months under accelerated (A) aging conditions.

Two samples of each brand were reconstituted at every time point of the dissolution stability study and stored at room temperature or under refrigeration. Dissolution determinations were carried out at different times throughout the administration period of the suspension, according to the expiration date stated on each label for the reconstituted form:

- Immediately after reconstitution (suspension freshly prepared).
- Expiration date at room temperature: 7 days for all brands.
- Midpoint of administration period under refrigeration (2–8 °C): 5 days (brand A) or 7 days (brands B–D).
- Expiration date under refrigeration (2–8 °C): 10 days (brand A), 14 days (brand C and D), or 15 days (brand B).

Sample Preparation Procedure for Dissolution Profiles

Commercially available cefadroxil monohydrate powders for oral suspension were reconstituted with drinking water according to instructions on the label, to a theoretical concentration of 250 mg/5 mL, and mixed by a manual shaking procedure prior to sampling. A suspension sample equivalent to a typical dose (5 mL) was taken on a weight basis using a suitable syringe–cannula system, and quantitatively transferred to the dissolution vessel midway between the surface of the dissolution medium and the top of the rotating blade. To calculate the exact weight of suspension added to the vessel, syringe and cannula were weighed at three stages: empty, filled with the suspension, and after the sample was expelled

into the dissolution vessel. The specific gravity of each brand was determined to express the percentage of drug dissolved in the sampled volume (250 mg/5 mL).

RESULTS AND DISCUSSION

Requirements for deliverable volume were fulfilled by all brands. No important changes in pH values were recorded throughout the stability study under both aging conditions. Those values remained in the range of 4.0–6.0, satisfying pharmacopeial specifications (8). There were no visual signs of caking after reconstitution during the stability study, and all formulations were easily re-dispersed, even after twelve months of storage of the powders for suspension.

The uniformity of dosage units test was fulfilled by all brands according to *USP 29* specifications (8), with results between 106.7 and 110.1% of the labeled amount, and an RSD within the range of 3.3–3.8%. Duplicate standards were prepared and injected previously to determine the accuracy of the analysis.

The concentration of cefadroxil measured in the assay of each brand remained within 90% of the initial value throughout the stability study (Table 1), which indicates that the analyzed powders as well as the reconstituted forms are chemically stable during the administration period at room temperature and under refrigeration according to *USP 29* general specifications (8). Nevertheless, to establish if there are differences between the assay average results during the storage period, analysis of variance (ANOVA) was used to compare those values. Statistically significant differences were recorded for assay average values at time of reconstitution (I) only between time zero and 12N for brands A ($P = 0.015$) and B ($P = 0.003$). The ANOVA results indicate that there were no significant differences throughout the stability study for brands C ($P = 0.915$) and D ($P = 0.843$). None of the four analyzed brands showed statistical differences between I–II or I–IV stages of chemical assay at times 0, 6N, 6A, and 12N of storage (P values ranged from 0.077 to 0.945).

All of the analyzed brands except brand D showed a high dissolution rate with large percentages of drug released at early time points of the dissolution profile (Table 2). High variability was found in almost every dissolution measurement of brand D, with relative standard deviations over 20% in many cases (Table 2). For brands A and C, a few measurements with relative standard deviation greater than 10% were seen, but none exceeding 20%; whereas in all cases, these values were less than 10% for brand B (Table 2). This was the characteristic performance of each analyzed brand all over their dissolution profiles.

Brand D showed significant decreases in some dissolution percentages, with values less than 80% dissolved at 60 min and a minimum dissolved percentage of 59% (Table 2).

Analysis of variance (ANOVA) was used to compare the dissolution profiles of cefadroxil from brands A, B, and C, in

Table 1. Reconstituted Suspension HPLC Assay—Chemical Stability.

Storage ^a	Time ^b	Sample							
		A		B		C		D	
		% ^c	RSD	% ^c	RSD	% ^c	RSD	% ^c	RSD
0	I ^d	109.8	1.7	110.1	1.9	108.7	1.8	107.2	2.0
	II	107.9	0.5	109.7	1.6	107.9	1.7	106.7	0.7
	III	109.4	0.8	109.7	1.6	108.0	2.0	106.9	0.7
	IV	108.1	0.05	109.0	0.5	106.1	1.3	106.2	2.8
3N	I ^e	110.8	1.3	111.0	1.9	109.2	2.0	107.3	1.4
3A	I ^e	110.3	0.1	109.5	0.3	108.9	1.6	106.9	0.3
	I ^d	111.0	0.8	109.3	0.9	109.6	0.9	106.3	1.7
	II	110.7	0.1	108.8	0.5	108.8	0.4	105.3	0.4
	III	109.0	0.4	109.0	0.6	108.7	0.9	105.9	0.4
6N	IV	109.1	0.8	108.1	0.1	108.3	1.1	104.8	0.2
	I ^d	110.8	2.0	108.0	1.1	109.8	1.8	107.1	0.4
	II	109.0	1.3	108.0	0.7	109.3	0.6	105.3	0.4
	III	110.1	0.1	107.9	0.7	108.7	0.8	107.2	0.4
6A	IV	110.5	1.8	107.1	1.7	109.1	1.1	106.4	1.2
	I ^e	108.1	1.6	108.3	1.0	108.1	1.8	106.7	1.9
	I ^d	105.1	1.9	105.7	0.8	108.6	1.3	106.3	1.5
	II	103.8	0.8	104.9	1.2	108.3	0.5	104.3	0.3
12N	III	103.2	0.3	105.7	0.3	107.5	0.7	105.2	1.3
	IV	102.9	1.2	103.9	0.1	106.9	0.04	103.1	1.2

^a Months of storage of powder for oral suspension under aging conditions

0: At the beginning of the aging process

N: Natural aging conditions

A: Accelerated aging conditions

^b Stages of analysis of reconstituted forms:

I^d: Immediately after reconstitution. The average result of “a” and “b” assay stages is presented (HPLC Standard and Sample Solutions item, Materials and Methods)

I^e: Immediately after reconstitution. The result of “b” assay stage is presented (HPLC Standard and Sample Solutions item, Materials and Methods)

II: Expiration date at room temperature storage

III: Midpoint of caducity period under refrigeration

IV: Expiration date under refrigeration

^c Percentage of label claim.

terms of Dissolution Efficiency (D.E.). D.E. is defined as the area under the dissolution curve between two time points expressed as a percentage of the curve at maximum dissolution, 100%, over the same time period (27).

Brand D was not included in the statistical comparison, because the obtained values tended to be heteroscedastic (*P* values for Levene test between 0.001 and 0.049), which could also be seen in Table 2 as RSD values greater than 10% or 20% in many cases. D. E. average values (*n*=6) and ANOVA results are summarized in Table 3. There were no

statistical differences among D.E. for brand C at different times of powder storage with respect to time zero of the aging study (Table 3). Nevertheless, some significant differences could be observed for brands A (6N, 6A, and 9N with respect to 0; *P* = 0.012) and B (3A and 12A with respect to 0; *P* = 0.012). Over the administration period of the reconstituted suspension, there were no statistical differences between I and II for the three brands, which means that the suspensions were physically stable during storage at room temperature (Table 3, Figures 1–3). Under

Table 2. Cefadroxil Extemporaneous Suspension Dissolution Stability Study.

Storage ^a	Time ^b	Brand A		Brand B		Brand C		Brand D	
		% ^c	RSD	% ^c	RSD	% ^c	RSD	% ^c	RSD
0	I	93	12.1	98	7.9	97	9.5	88	11.4
	II	103	2.9	97	4.9	89	9.4	87	23.1
	III	105	14.7	105	5.4	93	18.1	78	21.8
	IV	108	4.1	103	3.2	96	7.9	59	20.2
3N	I	105	4.6	100	5.9	86	17.0	90	4.4
	II	102	8.4	102	6.4	85	13.5	83	17.8
	III	106	5.5	102	4.7	98	12.1	91	5.5
	IV	109	2.5	104	5.2	97	4.7	80	13.6
3A	I	97	7.3	94	4.5	104	5.4	89	7.3
	II	98	5.9	94	5.1	98	8.6	70	15.2
	III	87	6.9	100	4.5	93	9.7	66	8.3
	IV	99	2.9	101	3.9	99	3.7	60	19.7
6N	I	109	2.3	99	5.6	98	5.2	88	24.9
	II	104	6.8	95	4.4	96	11.5	77	21.9
	III	106	8.9	97	4.2	101	6.5	92	3.7
	IV	109	7.7	107	3.7	98	7.2	76	20.1
6A	I	106	4.5	100	4.7	91	11.2	96	11.6
	II	104	4.5	100	6.4	91	12.4	73	22.3
	III	106	1.6	99	4.1	98	10.3	89	11.3
	IV	106	3.6	96	5.6	103	6.5	88	11.5
9N	I	106	9.0	102	2.5	96	10.4	89	16.7
	II	102	12.8	100	5.6	99	3.9	85	11.3
	III	104	0.9	105	4.5	96	12.0	89	9.5
	IV	104	3.3	103	3.1	93	9.1	83	16.1
12N	I	101	7.1	101	3.3	96	10.8	71	14.9
	II	99	2.7	98	4.1	100	6.9	69	21.6
	III	94	6.7	97	5.6	107	7.6	80	7.7
	IV	102	2.9	99	4.2	103	3.7	77	16.5

^a Months of storage of powders for oral suspension

0: At the beginning of the aging process

N: Storage under natural aging conditions

A: Storage under accelerated aging conditions

^b Stages of analysis of reconstituted suspension

I: Immediately after reconstitution (freshly prepared suspension).

II: Expiration date at room temperature storage.

III: Midpoint of caducity period under refrigeration.

IV: Expiration date under refrigeration.

^c Percentages dissolved. The average result of six units is reported. Only the last sampling profile point is shown.

Table 3. Dissolution Stability Study of Cefadroxil Extemporaneous Suspension. ANOVA Comparisons between D. E. Average Values (n=6).

Sample	Storage ^a	I ^b	Δ0 ^c	II ^b	I vs. II ^c	III ^b	IV ^b	I vs. IV ^c
A	0	87.79	-----	92.32	n. s.	93.73	96.52	** (p=0.002)
	3N	94.01	n. s.	91.65	n. s.	95.55	97.47	n. s.
	3A	86.61	n. s.	88.17	n. s.	76.85	87.71	n. s.
	6N	97.59	* (p=0.012)	93.52	n. s.	94.31	100.40	n. s.
	6A	95.08	* (p=0.012)	93.76	n. s.	94.23	95.13	n. s.
	9N	95.29	* (p=0.012)	91.92	n. s.	93.58	93.23	n. s.
	12N	90.02	n. s.	88.66	n. s.	83.94	90.98	n. s.
	12A	89.72	n. s.	82.44	n. s.	-----	-----	-----
B	0	90.75	-----	90.02	n. s.	95.31	94.19	n. s.
	3N	89.82	n. s.	92.90	n. s.	92.46	94.22	* (p=0.039)
	3A	85.00	* (p=0.012)	84.49	n. s.	91.08	92.32	** (p=0.001)
	6N	89.08	n. s.	87.06	n. s.	88.48	96.19	** (p=0.001)
	6A	90.23	n. s.	89.83	n. s.	90.32	87.72	n. s.
	9N	91.96	n. s.	91.25	n. s.	94.40	93.79	n. s.
	12N	90.69	n. s.	89.14	n. s.	87.33	89.26	n. s.
	12A	85.58	* (p=0.012)	88.88	n. s.	-----	-----	-----
C	0	85.41	-----	79.42	n. s.	87.64	87.85	n. s.
	3N	80.54	n. s.	75.76	n. s.	84.77	86.15	n. s.
	3A	92.85	n. s.	87.32	n. s.	82.93	88.05	n. s.
	6N	86.95	n. s.	85.50	n. s.	89.41	88.39	n. s.
	6A	81.06	n. s.	79.84	n. s.	86.52	91.73	** (p=0.002)
	9N	85.53	n. s.	88.58	n. s.	86.01	83.55	n. s.
	12N	88.16	n. s.	89.40	n. s.	94.61	91.81	n. s.
	12A	88.08	n. s.	85.14	n. s.	-----	-----	-----

^a Months of storage of powders for oral suspension:
 0: Beginning of the aging process.
 N: Storage under natural aging conditions.
 A: Storage under accelerated aging conditions.
^b Stage of analysis of reconstituted suspension:
 I: Immediately after reconstitution (freshly prepared suspension).
 II: Expiration date at room temperature storage.
 III: Midpoint of caducity period under refrigeration.
 IV: Expiration date under refrigeration.
^c Statistical references:
 n.s.: There were no significant differences between the compared values.
 *: There were significant differences (P values between 0.01 and 0.05).
 **: There were high significant differences (P values less than 0.01).

refrigeration, there were almost no significant differences between I and IV for brands A and C (Table 3, Figures 1 and 3), with only a statistical increase in D. E. at time 0 for brand A (P = 0.002) and at time 6A for brand C (P = 0.002). For

brand B, the ANOVA results indicate that there were significant increases in D. E. average values from I to IV at times 3N (P = 0.039), 3A (P = 0.001), and 6N (P = 0.001) of storage (Table 3, Figure 2). There were no significant

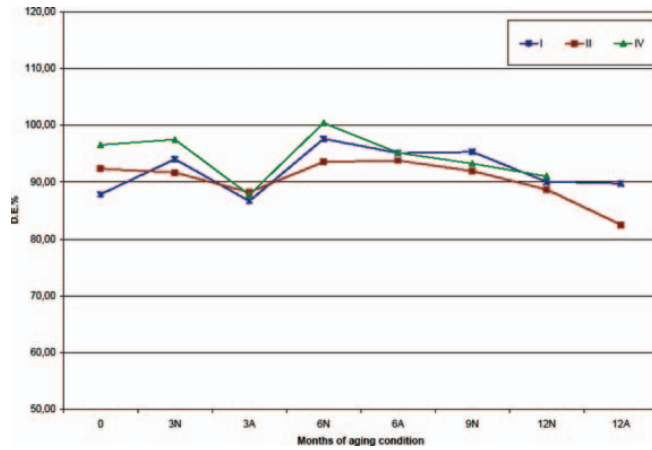


Figure 1. D.E. evolution for Sample A throughout the expiration period of cefadroxil suspension during aging study.

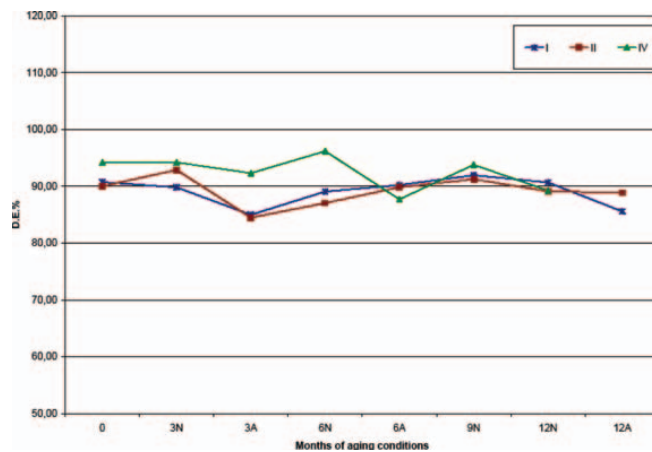


Figure 2. D.E. evolution for Sample B throughout the expiration period of cefadroxil suspension during aging study.

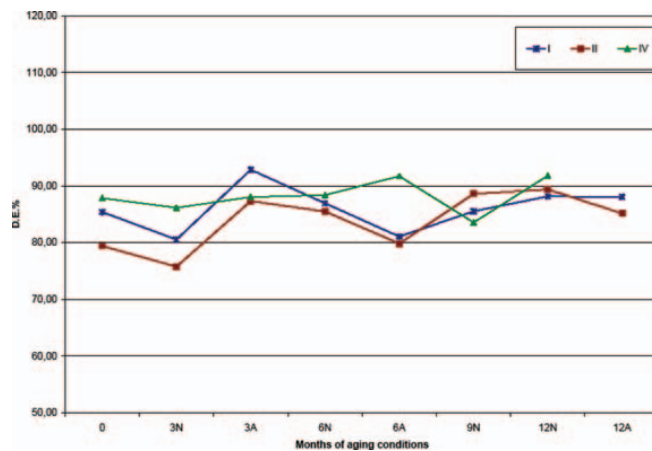


Figure 3. D.E. evolution for Sample C throughout the expiration period of cefadroxil suspension during aging study.

decreases in D.E. throughout the administration period of the reconstituted forms of the three brands under refrigeration (Table 3).

As expected, when a product is stored under the conditions specified on the label, it has to retain the initial dissolution behavior throughout its shelf life. This has been confirmed by our results for brands A, B, and C at each stage of testing. Despite some decreases in dissolution percentages, no value less than 80% significantly decreased from stage I was observed for those three brands, at any storage time.

Nevertheless, significant decreases in dissolution percentages, associated with a high variability, were observed for brand D throughout the administration period of the reconstituted form at room temperature as well as under refrigeration (Table 2, Figure 4), which could impact its bioavailability.

CONCLUSIONS

All analyzed formulations fulfilled the requirements of the assay, uniformity of dosage units, deliverable volume determination, and stability of pH values of reconstituted suspension. Visually, all samples remained homogeneous after reconstitution and did not exhibit signs of caking throughout the year of storage as powders for oral suspension.

The analyzed powders for oral suspension were chemically stable throughout the year of storage under both aging conditions and after reconstitution. Brands A, B, and C also had acceptable dissolution stability when stored at room temperature or under refrigeration throughout their expiration periods as reconstituted forms. On the other hand, the only formulation with undesirable dissolution stability was brand D, which showed high variability in the dissolution pattern during the administration period as well as over a year of storage.

The potential impact on the in vivo bioavailability and the possible factors that may be generating these

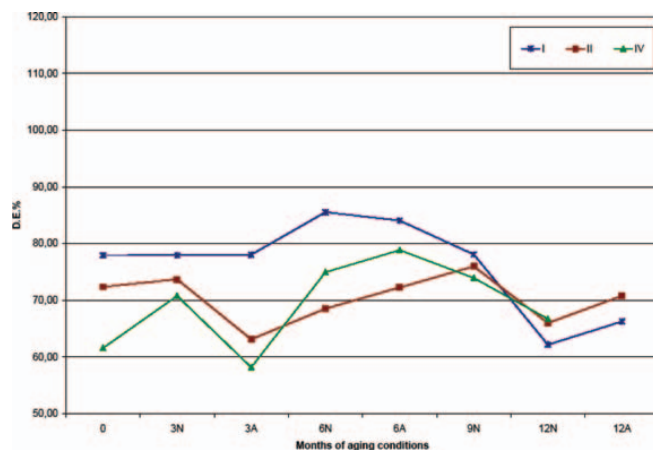


Figure 4. D.E. evolution for Sample D throughout the expiration period of cefadroxil suspension during aging study.

differences in the dissolution stability of this brand (e.g., particle-size or surface-area differences, changes in drug particle size with time, method of manufacture, composition of inactive components, and possible interactions with cefadroxil) may warrant further investigation.

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