Ana Santoveña-Estévez*, Diego Dorta-Vera, Iris González-García, Javier Suárez-González, Nuria Teigell-Pérez and José B Fariña

Safe use of Dexamethasone in pediatrics: design and evaluation of a novel stable oral suspension

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Abstract

Background: Dexamethasone is used in pediatrics mainly for treatment of croup and bronchopulmonary dysplasia. Commercially available pediatric oral formulations include inadequate excipients for this population. When there are only commercially available oral dosage forms for adults, a formulation is prepared to reduce the dose by manipulation of authorized tablets or injectable dosage forms. This practice most of times is made without the quality and control that process requires. The aim of this study is to propose a formulation secure and suitable for pediatrics by the use of a Standard Operating Procedure that ensures its quality.

Methods: Design of two formulations was performed with lowest number and amount of excipients suitable for pediatrics, avoiding use of dexamethasone salts and preservatives. An accurate and precise analytical method and a methodology for analyzing uniformity of doses were developed. Physical, chemical and microbiological stability was tested.

Results: Stability of Dexamethasone was improved by acidification with citric/citrate buffer. Proposed suspension complies with quality criteria required for an oral non-sterile formulation using Dexamethasone as active pharmaceutical ingredient, and the minimum number and quantity of excipients suitable for pediatrics.

Conclusions: This formulation is physical, chemical and microbiologically stable during 15 days storage at 5 and 25 °C.

Keywords: corticosteroids, dosing, drug compounding, drug safety, hplc, pediatrics, pharmaceutic technology, quality assurance

Introduction

Dexamethasone is a glucocorticoid with high anti-inflammatory activity and a slight mineralocorticoid effect used in pediatrics in treatment of croup and bronchopulmonary dysplasia at dose of 0.6 mg/Kg and 0.5–0.6 mg/Kg/day [1]. In some countries there are commercial oral liquid formulations of Dexamethasone for pediatrics [2], but they include a combination of inadequate excipients for this population such as preservatives (benzyl alcohol, benzoic acid, benzoates), sweeteners (sucrose, fructose, sorbitol, xylitol, aspartame), solvents (lactose, ethanol, propylene glycol) or colouring agents (azo dyes, quinoline dyes, triphenylmethane dyes, xanthene dyes) [3]. Therefore, this therapeutic gap must be covered. Dexamethasone is classified as a Biopharmaceutics Classification System-Class I/III active substance [4], authorized by oral, ophthalmic, otic and parenteral routes. Dexamethasone sodium phosphate is authorized for parenteral, ophthalmic and otic routes [5]. Dexamethasone phosphate lacks sufficient data on oral bioavailability [6], so it is not marketed as an oral formulation [7, 8]. Recently Binson et al. published a study about the preparation of an oral stable suspension using the acetate salt formulated with complex excipients as Ora-Sweet® and Ora-Plus® at a dose of 5 mg/mL [9]. This salt is authorized in France for oral solid formulations [10], but it is not authorized for this route of
administration in other European countries as Spain [11] or USA [12]. When Dexamethasone needs to be administered orally at pediatric doses, a compounding preparation should be elaborated from Dexamethasone as active pharmaceutical ingredient (API) authorized for this route, rather than from an authorized dosage form not indicated for this use [13, 14]. A Standard Operating Procedure (SOP) must also be followed to ensure the quality of the final compounding. Also, if this preparation needs to be administered to a vulnerable population as pediatrics, the lowest possible number of excipients must be used and in the lowest proportions [15, 16]. When lower doses of Dexamethasone than the marketed form for adults are needed in clinical practice, what actually happens is that oral formulations are prepared by manipulation or compounding [17, 18] the authorized Dexamethasone tablets or intravenous formulations. The main disadvantage of using tablets is that excipients from this authorized dosage form are introduced into the new formulation. These excipients could be not suitable for pediatrics (sucrose, lactose, coloring, etc) [2, 5], difficult to disperse (magnesium stearate, starch, lactose, etc) [2, 5] and/or interfere with the distribution of the API, especially when it is formulated in low proportions [19]. In the case of using injectable forms, the Dexamethasone phosphate is administered orally as suspension using complex excipients (benzyl alcohol, sodium sulfite and citrate) [2, 5]. This is not necessary due to this salt being easily soluble in water [20, 21]. Toledo et al. conducted a pharmacokinetic comparison between Dexamethasone from a commercially available oral formulation and Dexamethasone phosphate from intravenous formulation administered orally to healthy volunteers. They concluded that these two formulations are not bioequivalent [22].

Strict monitoring of the SOP should ensure the quality of the final formulation. To do this, a validated chromatographic method was used to determine and quantify the Dexamethasone. It was subjected to the European Pharmacopoeia test for multi-dose containers [23], adapted for determining the declared API content in each dose. Since the stability of pediatric oral formulations of Dexamethasone is only tested on those compounded from an authorized dosage form [20, 21, 24], physical, chemical and microbiological stability was also tested following pharmacopoeia criteria.

Materials and Methods

Dexamethasone, sucrose, citric acid and sodium citrate were pharmacopoeia grade and were provided by Acofarma (Barcelona, Spain). Water was purified in our laboratory by a Milli-Q system. Acetonitrile and methanol were analytical grade (Sigma-Aldrich, Madrid, Spain).

General Standard Operating Procedure (SOP)

Two different formulations were used to prepare the Dexamethasone suspensions of 1mg/ml, see Table 1. F1 is the most frequently used formulation [25], and F2 introduces a citric/citrate buffer to ensure the stability zone of Dexamethasone at pH 4 [26]. At least three batches of each formulation were prepared.

F1 was elaborated according to the following SOP:
– Firstly, the simple syrup vehicle is prepared.

The simple syrup is prepared as a solution of 64% sucrose w/w in purified water, which is roughly equivalent to 85% w/v [27], and 36% w/w of purified water at constant shaking until getting a homogeneous solution and then it was filtered.

| Formulations | Dexamethasone (mg) | Diluent-sweetener agent (qs 100 ml) | Sucrose in simple syrup (% w/w) | Citric/citrate buffer | pH | Viscosity (mPa.s) at 20 rpm |
|--------------|--------------------|------------------------------------|-------------------------------|----------------------|----|--------------------------|
| F1           | 100                | Simple syrup                       | 64                           | –                    | 7.06 ± 0.05 | 98.3 ± 1.4               |
| F2           | 100                | Simple syrup                       | 64                           | 20 ml                | 4.43 ± 0.01 | 21.7 ± 0.4               |

qs: amount which is enough to complete 100 ml. pH and viscosity is expressed as mean value ± SD; SD: Standard Deviation.
- 100 mg of Dexamethasone are weighed and transferred to a mortar where the product is pulverized.
- Measure approximately 70 ml of simple syrup in a 100 ml graduated cylinder and then 5 ml of this volume are transferred to the mortar and mixing with a pestle until a homogeneous paste is formed with the total volume measured of simple syrup.
- The contents of the mortar are transferred to a 100 ml Erlenmeyer with constant shaking using a magnetic stirrer. Recover the total paste of the mortar with approximately 10 ml of simple syrup.
- Maintain under magnetic stirring at medium power without foaming until a suspension of homogeneous appearance forms.
- The suspension is then transferred to a 100 ml graduated cylinder and washed with approximately 20 ml of simple syrup.
- Complete the 100 ml volume with simple syrup.
- It is then packaged in a 125 ml amber bottle with dispenser closure.

F2 was elaborated according to the following SOP:
- Firstly, the simple syrup vehicle and the citric/citrate buffer are prepared.

The simple syrup is prepared with 64 % w/w of sucrose and 36 % w/w of purified water at constant shaking until getting a homogeneous solution and then it was filtered.

The citric/citrate buffer are prepared with 33 ml of 0.1 M citric acid solution and 17 ml of 0.1 M sodium citrate solution completed 100 ml with water. The pH of this buffer is adjusted to pH 4 with approximately 5 ml of sodium citrate solution.

- 100 mg of Dexamethasone are weighed and transferred to a mortar where the product is ground to powder.
- Measure 20 ml of the buffer in a 25 ml graduated cylinder.
- Add approx. 5 ml of the buffer to the mortar and mixing with a pestle.
- Transfer the contents of the mortar to a 100 ml Erlenmeyer with constant shaking using a magnetic stirrer.
- Recover the total suspension from the mortar with the rest of the buffer.

- Measure approximately 60 ml of simple syrup in a 100 ml graduated cylinder.
- Wash the mortar with this volume of simple syrup and transfer to the Erlenmeyer, recovering the total suspension of the mortar.
- Maintain under magnetic stirring at low power without foaming until a suspension of homogeneous appearance forms.
- The suspension is then transferred to a 100 ml graduated cylinder and washed with approx. 20 ml of simple syrup.
- Complete the 100 ml volume with simple syrup.
- It is then packaged in a 125 ml amber bottle with dispenser closure.

The suspensions were physically and chemically characterized as described below.

**UPLC method validation**

Dexamethasone was analyzed applying an adapted High Performance Liquid Chromatography (HPLC) method [28] to a reversed phase Ultra Performance Liquid Chromatography (UPLC) in an Acquity UPLC® H-Class System with a X-Select® C18 column 2.5 µm XP (2.1x75 mm) (Waters, Milford, MA, USA). The data acquisition software was Astra 6.0.1. (Chromatographic Manager, Waters Corporation). The mobile phase was acetonitrile/water (40/60, v/v), at a flow rate of 0.4 ml/min. The UV detection was at 240 nm. The injection volume was 10 µL. All chemicals and reagents were UPLC grade. All samples and solvents were filtered with 0.2 µm pore-size filters (Millipore, Billerica, MA) and degassed.

In order to validate the analytical method [29], six standard solutions were prepared adding 10 ml of methanol to promote the solubilization of Dexamethasone (10 mg), and then purified water was added until 100 ml. After these first solutions were prepared, they were diluted with mobile phase to a concentrations interval between 1 – 8 µg/ml. The variance analysis (ANOVA) of the linear regression confirmed the linearity of the method, through rejection of the null hypothesis of deviation from linearity for a significance level of 0.05 (α = 0.05). The coefficient of variation of the method was 2.7 %. The equation of the regression line was: Area = 53,995*C; r = 0.9992 (n = 36), with a residual standard error of 7,905.
The method precision (as repeatability) was 0.48 %, determined by a six-fold analysis of the same sample. System accuracy was expressed as percentage recovery by assay of a known added amount of drug, being the mean value 98.7 % (n = 9). The detection and quantitation limits, based on the standard deviation of the response and slope, were 0.4 and 1.2µg/ml respectively. Robustness was also tested to establish the effect of operational parameters on the analysis results. The flow-rate (0.4 ± 0.01 ml/min), injection volume (10 ± 0.3 µl), mobile phase composition (40.0 ± 1/60 ± 0.5), and column performance over time were determined to confirm the method’s robustness. To calibrate the UPLC system and monitor its performance, we analyzed a Dexamethasone solution sample daily as standard.

The estimated area for the standard concentration (5 µg/ml) was 272562 with a relative standard deviation (RSD) of 2.3 %. The upper and lower limits for the control chart were established at ±3 standard deviation (SD) of this value, taking as SD the value obtained from the variance of the analytical method. Peak’s area stays between the established limits every analysis time. The chromatographic conditions (e.g. flow-rate, relative mobile phase composition) and column performance were checked, especially the tailing factor and column efficiency. When necessary, corrective action was taken.

**Extraction yield**

To determine the efficiency of extraction of Dexamethasone from each formulation studied, six samples of 5 ml each were taken, to which had been added 5 mg of Dexamethasone and the quantities of each formulation component. After homogenization of the samples, they were dissolved in 50 ml of MilliQ water. Subsequently, they were suitably diluted with mobile phase to proceed with UPLC analysis.

**Quality Control**

**pH**

The pH was determined every 7 days for 60 days (7, 14, 21, 35, 42 and 60 days) for both formulations stored at 5, 25 and 40 °C. The samples were the same used for the chemical stability studies (see below). The pH was tested in duplicate using a Crison GLP 21 pHMeter (Barcelona, Spain).

**Viscosimetry**

The viscosity was measured in a programmable viscometer Brookfield® LVDV-II (Middleboro, MA, USA) at 25 °C. A spindle SCa-18 was used so as to determine viscosities between 1.5 and 30,000 mPa.s with 8 ml as sample volume. Data were processed with the Wingather® 32 program (Middleboro, MA, USA). All the measurements were taken with a torque between 10–90 %. Every characterization was in triplicate.

**Dose content uniformity**

The European Pharmacopoeia (EP) states that for multidose containers, 20 doses are individually weighed at random and the individual and average masses determined; no more than 2 of the individual masses may deviate from the average by more than 10 % and none may deviate 20 % [23]. This mass uniformity criterion only indicates the uniformity of mass extracted with respect to the average mass, and assumes a uniform distribution of the active ingredient in the formulation. To test this latter aspect, a modification of this test was additionally applied, the percentage of declared Dexamethasone content was determined instead of the average content in each preweighed dose, applying the same test criteria.

20 doses (5 ml) taken randomly from the elaborated formulations were weighed prior to determining each Dexamethasone content at day 0 and after stored 30 days at 5 ± 2 °C. This dose volume was taken out with an 5 ml syringe (BD Discardit™ II) for oral use after the formulations were manually shaken [30]. This device allows accurate dose measurement and controlled administration to the buccal cavity for all ages [3]. Afterwards, the samples were diluted adding 5 ml of methanol to promote the solubilization of Dexamethasone, and after purified water was added until 50 ml. Dilution to concentration 5µg/ml were made with mobile phase. A Dexamethasone mass balance was determined from the volume remaining in the containers after removal of 20 doses.

**Chemical stability studies**

An accelerated study of Dexamethasone’s stability at a temperature of 60 ± 0.1 °C (Heraeus UT 6060, Spain) and a concentration of 50µg/ml at different pH conditions (citric/citrate buffer, pH 2–8) was performed. At time 0,
1, 18, 24, 42 and 48 h, the samples were diluted with mobile phase to a concentration of 5 µg/ml and were analysed immediately by UPLC.

F1 and F2 were checked for stability at different temperatures and storage conditions following the International Conference Harmonization (ICH) guidelines [31, 32]. At 5 ± 0.1 °C (Fridge-stove P-selecta Welidow type, Spain), at 25.0 ± 1.3 °C (dark chamber, own manufacture), and at 40 ± 0.1 °C (Heraeus UT 6060, Spain). Samples (5 ml) from each Dexamethasone formulation batch were taken every 7 days in triplicate until 42 days (7, 14, 21, 35 and 42 days).

**Physical stability studies**

An additional test was performed to determine the physical stability of the dosage form and to indicate the importance of shake before removal of the dose [33]. A possible sedimentation of Dexamethasone could influence the uniformity of the dose extracted from different heights of the formulations elaborated as suspensions (F1 and F2). Each formulation in duplicate was poured into a 100 ml graduated cylinder to study the degree of flocculation and sedimentation of the suspensions and after manual shaking (10 times inverted 180°), doses were taken at heights ZI (100–80 ml) and ZIII (20–0 ml), see Figure 1.

Doses (5 ml) were taken, weighed and their Dexamethasone contents were determined. This process was done after 30 days stored at 5 ± 0.1 °C (Fridge-stove P-selecta Welidow type, Spain).

From this test two parameters were calculated: Dmax, the maximum difference between doses taken at different heights, and Dmax/t, Dmax corrected for the standing time after shaking. Both parameters were expressed as a percentage of declared dose (DV %).

**Microbiological stability studies**

Microbiological tests of formulations were done at 0, 15 and 30 days of storage at room temperature (25 °C), simulating the conditions under which daily doses are removed. Both formulations were prepared at the compounding laboratories at two pharmacies following the SOPs proposed for F1 and F2. Tests were performed according to the EP and The United States Pharmacopeia (USP) monograph of non-sterile products [34, 35] at a laboratory accredited as quality manager.

![Figure 1: Heights (Z1 and Z3) at which the doses were taken from F1 and F2 suspensions at time 0 (a), after 30 days storage at 5 °C (b), and after shaking 180° 10 times (c).](image-url)
ISO 9001. The microbial count was considered to be the average number of colony forming units (cfu) found in the appropriate medium by plate-count method. Liquid oral formulations meet microbial requirements if the total aerobic microbial count was less than 10^2 cfu/ml, the total combined yeast/mold count less than 10^1 cfu/ml, and the absence of Escherichia coli was confirmed.

**Results**

Figure 2 shows the chromatogram obtained by the UPLC method for Dexamethasone as pure pattern, after its extraction from suspension F2 and after 2 days stored at 60 °C at pH 6.14, for testing the ability of the method to separate degradation products in the elaborated formulation. A peak with an elution time of approximately 1.4 minutes was detected. The chromatographic area of this peak decreased with time at 60 °C and a new peak appeared, identified as a degradation product at approximately 1.2 min [36, 37]. As can be seen, no interference with the excipients of the suspension was detected. The average extraction yield of Dexamethasone by the UPLC method was 102.5 ± 4.3 % and 100.2 ± 3.4 %, from F1 and F2 respectively.

Table 1 shows the pH and viscosity values obtained for both suspensions. As can be seen F2 has a more acid pH and lower viscosity as expected, since F2 is F1 diluted with citric/citrate buffer.

The results of the accelerated stability test at pH 7.85 (Figure 3) reveal how rapidly Dexamethasone degraded, after 48 h leaving a remainder of less than 10%. However, at pH 7.09 the molecule degraded more slowly, showing a greater decrease in the percentage remaining between 18 and 24 h. The pH with maximum stability for Dexamethasone was the most acidic (2.13) [26], with 100% remaining at 42 h.
determine the physical stability of the dosage form and highlight the importance of shake before removal of the dose, we measured the variation in uniformity of doses taken from different heights of the same formulation. As seen in Table 4, the Dmax at 30 days gives the maximum difference between quantities of Dexamethasone in the sample dose taken from the two zones after storage of the formulations in the indicated conditions. This parameter gives us an idea of the rate of sedimentation of the solid. In our case, the highest difference between areas was clearly F1 after 30 days of storage at 5 ± 0.1 °C, taking the dose without previous shaking. F2 presented a sediment after 30 days, which was readily redispersible after shaking (Figure 1). Dmax 70 min and Dmax 90 min indicate the maximum difference between areas after 70 and 90 minutes of rest following 180° inversion 10 times. Dmax/t value was slightly smaller for F1 than

Table 2: Mass uniformity test of the doses (5 ml) of F1 and F2 at time 0 and after storage at 5 ± 0.1 °C during 30 days.

| Dw (g) | t 0 days | t 30 days | t 0 days | t 30 days |
|-------|---------|----------|---------|----------|
| F1    |         |          |         |          |
| 1     | 6.75    | 6.69     | 6.40    | 6.38     |
| 2     | 6.70    | 6.69     | 6.40    | 6.36     |
| 3     | 6.67    | 6.71     | 6.39    | 6.37     |
| 4     | 6.65    | 6.68     | 6.40    | 6.38     |
| 5     | 6.70    | 6.70     | 6.40    | 6.37     |
| 6     | 6.70    | 6.71     | 6.39    | 6.37     |
| 7     | 6.65    | 6.69     | 6.38    | 6.36     |
| 8     | 6.61    | 6.68     | 6.41    | 6.39     |
| 9     | 6.68    | 6.68     | 6.40    | 6.38     |
| 10    | 6.62    | 6.67     | 6.43    | 6.36     |
| 11    | 6.63    | 6.67     | 6.40    | 6.38     |
| 12    | 6.66    | 6.69     | 6.42    | 6.37     |
| 13    | 6.67    | 6.69     | 6.38    | 6.36     |
| 14    | 6.70    | 6.72     | 6.38    | 6.39     |
| 15    | 6.64    | 6.67     | 6.40    | 6.38     |
| 16    | 6.67    | 6.68     | 6.38    | 6.35     |
| 17    | 6.63    | 6.72     | 6.41    | 6.38     |
| 18    | 6.61    | 6.70     | 6.41    | 6.41     |
| 19    | 6.59    | 6.69     | 6.41    | 6.38     |
| 20    | 6.65    | 6.72     | 6.39    | 6.38     |
| A     | 6.66    | 6.69     | 6.40    | 6.37     |
| SD    | 0.04    | 0.01     | 0.01    | 0.01     |
| RSD   | 0.60    | 0.15     | 0.16    | 0.16     |

Dw: dose weight; A: average value; SD: standard deviation; RSD: relative standard deviation; LL: lower limit; UL: upper limit.
Table 3: Content uniformity test of the doses (5 ml) of F1 and F2 at time 0 and after storage at 5 ± 0.1°C during 30 days.

|   | F1 t 0 days | F1 t 30 days | F2 t 0 days | F2 t 30 days |
|---|-------------|-------------|-------------|-------------|
| 1 | 102         | 92.6        | 95.3        | 84.8        |
| 2 | 106         | 90.9        | 98.0        | 86.1        |
| 3 | 96.3        | 92.5        | 97.0        | 85.1        |
| 4 | 101         | 90.1        | 99.6        | 86.3        |
| 5 | 104         | 90.9        | 98.2        | 86.2        |
| 6 | 97.9        | 94.2        | 97.6        | 86.3        |
| 7 | 97.0        | 92.3        | 99.1        | 87.3        |
| 8 | 98.3        | 95.5        | 101         | 85.1        |
| 9 | 106         | 93.2        | 98.4        | 88.5        |
| 10| 95.5        | 93.7        | 102         | 86.3        |
| 11| 95.7        | 93.3        | 97.9        | 84.0        |
| 12| 93.0        | 97.5        | 98.2        | 85.8        |
| 13| 89.4        | 95.4        | 96.6        | 86.4        |
| 14| 95.0        | 99.4        | 95.6        | 86.3        |
| 15| 95.0        | 96.6        | 99.2        | 87.4        |
| 16| 88.2        | 99.6        | 97.8        | 86.0        |
| 17| 101         | 97.9        | 97.2        | 84.7        |
| 18| 96.9        | 98.0        | 98.3        | 86.6        |
| 19| 96.4        | 97.9        | 96.6        | 87.5        |
| 20| 89.3        | 100         | 96.6        | 86.5        |
| A | 97.1        | 95.1        | 98.0        | 86.1        |
| SD| 5.0         | 3.2         | 1.6         | 1.1         |
| RSD| 5.2       | 3.4         | 1.6         | 1.3         |

DV (%): declared value expressed as percentage; A: average; SD: standard deviation; RSD: relative standard deviation; LL: lower limit; UL: upper limit.

For F2. A two-factor ANOVA with two samples per group was used to analyse these data. There were no statistically significant differences (p > 0.05) between zones before and after shaking each formulation (Table 4).

After storage of the two formulations under different temperature conditions, Dexamethasone in F2 (Figure 6) was observed to maintain its average remaining percentage above 90%, regardless of temperature. In addition, at 25°C the average remaining percentage detected was higher than 95% during 21 days, see Figure 6b.

For both formulations prepared at two pharmaceutical compounding pharmacies which followed strictly the SOPs proposed, the total aerobic microorganism count was less than 10² cfu/ml and total combined yeast/molds was also less than 10³ cfu/ml at 15 days of storage. During this time, the daily dose sampling was simulated and the storage temperature was the most favorable for microbial growth (25°C). No E. coli contamination was observed during this time. Although these types of formulations usually have a 30 days period of validity, in this case is less due to mold growth.

Discussion

The UPLC method allowed us to detect and quantify Dexamethasone accurately and precisely, both as a pure pattern and after extraction from the suspensions studied (F1 and F2). In addition, this chromatographic method can be used as a stability-indicating method since it detects the degradation products of Dexamethasone.

Two 1 mg/ml suspensions of Dexamethasone as API, no using its salts, were easily prepared without preservatives as parabens, and with the least number of excipients and at their lowest possible proportions, suitable for pediatrics. Suspension F1 shows a higher viscosity and a neutral pH, in opposition to F2 that incorporates a citric/citrate buffer in order to acidify the pH to a more stability area of the API. Both formulations have a Newtonian rheological behavior, ensuring constant viscosity. Citric/citrate as buffer at formulation F2 decreased viscosity but did not change rheological behaviour. Both suspensions met the EP test for uniformity of mass, but this is insufficient information to know if drug content in each dose agrees with the declared one. If we apply the same criteria for dose uniformity with respect to the declared Dexamethasone content (1 mg/ml), F1 and F2 also met the criteria, recently prepared and after 30 days of storage at 5°C. It must be noted that the variability of the doses measured as RSD decrease with storage time for both formulations in all uniformity tests. But it was lower in F2 which leads us to conclude that in this formulation the API is more uniformly distributed after shaking.

Then, the UPLC method is valid to study the uniformity content and its evolution with storage time.
The use of certain parameters (Dmax and Dmax/t) in extracted dose determination enabled us to analyze the sedimentation of the two suspensions. High values of Dmax point to insufficient resuspension of the API after the inversion of the container. The uniformity of doses, taken from different heights of each formulation stored under the same conditions, reveals how F2 improved after shaking of the container. Analysis of the variance in dose content sampled at different heights confirms this conclusion. Considering all the above, although F2 presents a sediment in the storage conditions, it is easily redispersible after shaking and it is the formulation which Dexamethasone is more uniformly distributed.

With respect to chemical stability study, Dexamethasone average remaining percentage extracted from F2 at 21 days after storage at 25°C was above 95% of the declared content in each dose. At F2 Dexamethasone is more stable when stored at different temperatures, due to more acid environment. This was checked in the accelerated studies reported here, and in the literature [38, 39].

Microbiological stability reveals presence of mold at 30 days. F1 and F2 complies with EP and USP specifications for microbial examination of non-sterile products during 15 days period. These results indicate the validity of use of F2 during 15 days stored at 5 and 25°C although the physical and chemical stability studies indicate more time. This period could be increased if F2 is prepared with simple syrup that contains parabens dissolved in the water in which it is prepared. The addition of parabens can be done avoiding the usual use of propylene glycol as co-solvent due to its toxic effect in pediatrics [40].

**Conclusion**

F2 is a novel and suitable Dexamethasone suspension for oral pediatric administration that, if it is strictly prepared following the proposed SOP, ensures mass and content uniformity in each dose, as well as physical, chemical and microbiological stability for 15 days stored at 5 and 25°C. It is possible the safe oral administration of Dexamethasone as API in pediatrics using the minimum number and minimum proportion of excipients suitable for this population, without the use of preservatives. Avoiding the manipulation or compounding the intravenous formulations, with the sodium form not authorized for oral route, or the commercial tablets which introduces excipients not appropriated for oral liquid formulations.

**Table 4:** Results of physical stability studies at 30 days of storage at 5 ± 0.1°C and two-factor ANOVA with two samples per group.

|            | F1 | F2 |
|------------|----|----|
| 30 days DV (%) | 17.9 | 9.4 |
| 30 days Dmax (%) | 15.3 | 15.2 |
| 70 min DV (%) | 21.6 | 24.6 |
| 70 min Dmax (%) | 93.6 | 5.6 |
| 90 min DV (%) | 93.2 | 98.5 |
| 90 min Dmax (%) | 92.1 | 93.1 |
| 90 min Dmax/t (%)/min | 93.4 | 98.7 |
| 0.02 | 0.06 |

**ANOVA Probability**

| Between Z1 and Z3 | 0.3138 | 0.1271 |
| Before and after shaking | 0.7861 | 2.7801.10^-6 |
| Interaction | 0.2585 | 0.1771 |

DV (%): declared value expressed as percentage; F: formulation; Z: heights; Dmax: maximum observed difference; Dmax/t: Dmax corrected for the standing time after shaking.
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Bionotes

Ana Santoveña-Estévez

Departamento de Ingeniería Química y Tecnología Farmacéutica, Facultad de Ciencias de la Salud, Universidad de La Laguna (ULL), Campus de Anchieta 38203, La Laguna (Tenerife), Spain; Instituto Universitario de Enfermedades Tropicales y Salud Pública de Canarias (IUETSPC), Universidad de La Laguna (ULL), Campus de Anchieta 38203, La Laguna (Tenerife), Spain, ansanto@ull.edu.es

Ana Santoveña-Estévez received her PhD in 2002 and is Senior Lecturer of Pharmaceutical Technology at the Faculty of Pharmacy of University of La Laguna since 2011. She is member of the Drug Development and Pharmaceutical Technology research group, and her research is focused on three areas: compounding, preparation and adaptation of active pharmaceutical ingredients of interest in pediatrics, characterization and stability of macromolecules, and drug release systems. In the last years her research has been focused on designing better medicines for children.
Diego Dorta-Vera studied pharmacy at the University of La Laguna in Tenerife. During this time he collaborated with the research group of Drug Development and Pharmaceutical Technology, focused on development, analysis and stability control of pediatric pharmaceutical compounding; essential to ensure the production of stable, safe and effective medicines for young children. Currently, he is Hospital Pharmacy Resident in the Hospital Insular Materno Infantil of Gran Canaria.

Iris González García received her degree in Pharmacy at the University of La Laguna in 2016. During her last year of study she developed a collaboration grant at the Chemical Engineering and the Pharmaceutical Technology Department, based on the development of pharmaceutical preparations for pediatric patients and the validation of analytical methods using Ultra-High Performance Liquid chromatography. In 2017 she obtained a research grant at the same department, where she worked for 5 months on the development of pharmaceutical preparations for pediatrics.

Javier Suárez-González studied pharmacy and is today a PhD student at the University of La Laguna, Spain. He does research in the New Therapies and Medicines Development working group which belongs to the Institute of Tropical Diseases and Public Health of the Canary Island. Since 2015 he has been working on the development of child-friendly medicines with different active pharmaceutical ingredients of interest for the paediatric population. His latest research was related to the improvement of a fixed-dose combination dispersible tablet for the treatment of tuberculosis in children.

Nuria Teigell-Pérez received her PhD in 2015. She is a member of the University Institute of Tropical Diseases and Public Health of the Canary Islands. In the last year her research focused on the composition of bacterial and fungal airborne communities in the Canary Islands, and the effects different factors may have over them.

José B Fariña is Full Professor of Pharmaceutical Technology at the Faculty of Pharmacy of University of La Laguna, where he was the Dean. He is the head of the Research Group of Drug Development and New Therapies at the University Institute of Tropical Diseases and Public Health of the Canary Islands and a member of the Drug Development and Pharmaceutical Technology research group as well as of the National Commission of the Industrial Pharmacy Specialty. His research is based on compounding active pharmaceutical ingredients of interest in pediatrics, characterization and stability of macromolecules and drug release systems.