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Development and UV-VIS Spectrophotometric analysis of an ease-of-use pediatric oral solution of dexamethasone for personalized therapies

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ABSTRACT: The usage of dexamethasone for pediatric applications is a well-known issue. In the present study, we developed an oral dexamethasone solution formulation especially aimed for dose-dependent personalized therapies and having excipients known as not harmful to be safely used in pediatrics. The aim of this study was to prepare an easy-of-use pediatric oral solution of dexamethasone and develop an UV/VIS Spectrophotometric method for the evaluation of the stability and quality control of the developed formulation. The primary source of dexamethasone for preparation of the oral pediatric solution was the dexamethasone one-time injectable solutions. This allowed the formulation to be easily prepared in basic laboratory conditions. Dexamethasone content and stability of the formulation were ensured by quantification using the developed UV/VIS Spectrophotometric method validated based on ICH Q2 (R1) guidelines. Simple, fast, reliable, and validated spectrophotometric analysis of dexamethasone was carried out at 269 nm wavelength and the method was linear in a range of 1.00 to 50.00 µg mL^{-1}.The developed formulation was stable at 4 °C at least for three weeks when protected from daylight. The other stability conditions (ambient temperature and -20 °C) were also evaluated for the assays. Although the methodology used in this study contains simple processes which can be easily adapted to basic laboratory conditions, the results were satisfactory to prepare an ease-of-use pediatric oral solution of dexamethasone for personalized medicine. The validated UV/VIS Spectrophotometric method was selective for the formulation and easily applied for the quality control and stability studies of the samples. Such formulations could be helpful for health professionals in managing real-life corticosteroid treatment application problems especially for pediatrics in hospital pharmacy.

KEYWORDS: Dexamethasone; pediatrics; personalized medicine; UV-VIS spectroptrophotometry; oral solution

1. INTRODUCTION

Corticosteroids are called steroid hormones secreted by the adrenal cortex. Corticosteroids are divided into two groups as glucocorticoids and mineralocorticoids [1]. Dexamethasone (DEX) is a synthetic adrenocortical steroid [2] and a glucocorticoid. It shows its effect by binding to the glucocorticoid receptor, which is a nuclear receptor [3]. DEX is used in pediatrics for the treatment of croup and bronchopulmonary dysplasia [4]. It is white, odorless, crystalline powder and practically insoluble in water.The molecular formula is $C_{22}H_{29}FO_5$ and chemical designation is 9-fluoro-11β, 17, 21-trihydroxy-16α-methylpregna-1, 4-diene, 3, 20-dione.

DEX formulations in the market are in injectable form and they are administered intravenously (I.V.) and intramuscularly (I.M.). There is not any available DEX oral pediatric formulation even though its usage in pediatrics is stated in literature [5-8] especially for croup and bronchopulmonary dysplasia [9-12]. McCallister et al. reported that Injectable dexamethasone administered orally may be an efficacious treatment for asthma exacerbation in pediatric patients [13]. In previous studies, Ensom and Décarie prepared a DEX 1 mg mL^{-1} oral suspension prepared from crushed tablets [14]. Binson et al reported a 5 mg mL^{-1} DEX oral suspension to be used on oncological disorders [15]. Chou et al prepared an oral suspension of DEX found to be stable (at least 90%) for 91 days [16]. Such studies encouragedus to prepare a stable ease-of-use pediatric oral solution of dexamethasone for personalized medicine. However, none of the reported studies used the common excipients to prepare the formulation easily in hospital pharmacy applications. In

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our study, the excipients known as not harmful to be used in pediatrics were carefully evaluated based on well-known reference textbooks [17]. The primary source of the DEX in the developed oral pediatric formulation was the dexamethasone 21-phosphate (DEXP) I.M./I.V. injection solutions containing 9.26mg of dexamethasone 21-phosphate disodium salt equivalent to 8.0 mg of DEXP. The aim of the usage of injectable solution instead of DEX bulk for the development of the oral pediatric formulation was to offer an easy to prepare formulation ready to be used on hospital pharmacy applications for personalized therapies. Thus, an oral solution formulation containing dexamethasone 21-phosphate disodium salt (Figure 1) was prepared and its content and stability were evaluated using a developed UV/VIS Spectrophotometric method validated based on ICH Q2 (R1) guidelines [18].

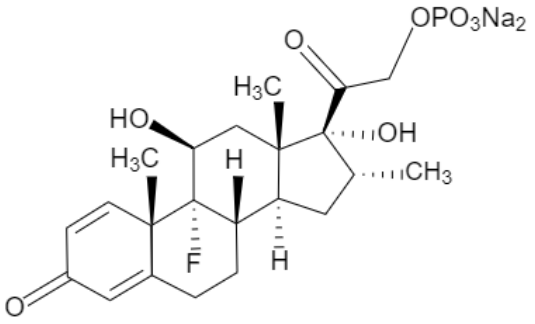

Figure 1. Structural formula of DEXP sodium salt.

Such a formulation could be useful where it is not always possible to reach I.M./I.V. applications for pediatrics during treatment period or for some health professionals who would like to prepare an ease-of-use oral pediatric formulation of DEXP for personalized therapies.

2. RESULTS AND DISCUSSION

2.1. Development of pediatric oral solution formulation of dexamethasone

The main objective of the present study was to prepare an ease-of-use, non-harmful pediatric oral solution of DEXP to be used in pediatrics. Therefore, the excipients in the formulation were tried to be limited since more excipients may cause allergic or toxic situations in pediatric use. Neither any color agent nor any extra aroma was added. Only citric acid and glycerin were used for the preparation. The aim of the glycerin and citric acid usage in the formulation was to take advantage of its usage as a thickening and sweetening agent. The main source of the DEXP was DEXP8 mg/2 mL I.M./I.V. injection solution which is easy to be find to be used in hospital pharmacy applications. The final pH was adjusted to 8.0 to be used for pediatrics. The dosage evaluation of the developed formulation is given inTable 1 [17, 19].

Table 1. Evaluation of the dosage of the prepared formulation.

1x1	1x1	3x1 (divided and taken 3 times a day)
Coch. Amp.: 15.0 mL	**Coch. Med.: 10.0 mL**	**Coch.parv.: 5.0 mL**
If there is 7.5 mg of DEXP in 25.0 mL, there is 4.5 mg of DEXP in 15.0 mL.	If there is 7.5 mg of DEXP in 25.0 mL, there is 3.0 mg of DEXP in 10.0 mL.	If there is 7.5 mg of DEXP in 25.0 mL, there is 1.5 mg of DEXP in 5.0 mL.
If 1.1 mg of DEXP is equivalent to 1 mg of DEX, 4.5 mg of DEXP is equivalent to 4.09 mg of DEX.	If 1.1 mg of DEXP is equivalent to 1 mg of DEX, 3.0 mg of DEXP is equivalent to 2.73 mg of DEX.	If 1.1 mg of DEXP is equivalent to 1 mg of DEX, 1.5 mg of DEXP is equivalent to 1.36 mg of DEX. The total daily dose of DEX is 4.08 mg.
If the 1 kg body weight dose is 0.02 - 0.3 mg, the 15 kg body weight dose is 0.3 mg - 4.50 mg.	If the 1 kg body weight dose is 0.02 - 0.3 mg, the 15 kg body weight dose is 0.3 mg - 4.50 mg.	If the 1 kg body weight dose is 0.02 - 0.3 mg, the 15 kg body weight dose is 0.3 mg - 4.50 mg.
There is no overdose in a total daily dose (4.09 mg).	There is no overdose in a total daily dose (2.73 mg).	There is no overdose in a total daily dose (4.08 mg).

1.1 mg of dexamethasone sodium phosphate is equivalent to approximately 1 mg of dexamethasone.

2.2. Development of the UV/VIS spectrophotometric method

The second aim of the study was to develop and validate an UV/VIS spectrophotometric method to determine the amount and to evaluate the stability of DEXP in the prepared formulation. To analyze the samples, the wavelength was scanned in the range of 200-400 nm in different conditions where some organic solvents and buffer systems were being employed. In our initial experiments we used methanol-water mixture to perform the analysis and the λmax of DEXP was observed at 241 nm as previously reported in literature [21, 22]. Since the ionization of sodium salt of DEXP in the formulation depends on pH of the medium, the maximum absorption wavelength (λmax) of DEXP was shifted to 269 nm when pH 3.0 20 mM phosphate buffer was used. To avoid the interference coming from matrix components in the developed formulation, the measurements were performed at 269 nm while 20 mM pH 3.0 phosphate buffer was being used (Figure 2). The UV Spectrophotometric method was developed and validated according to the ICH Q2 (R1) guidelines [18].

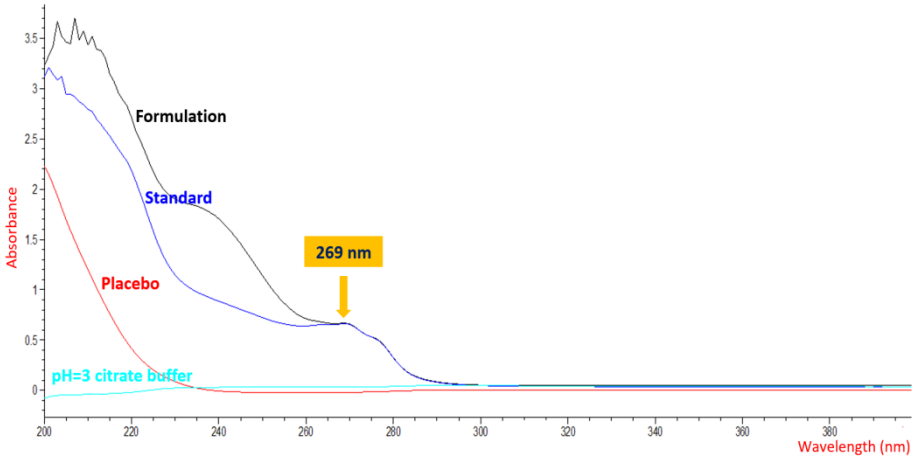

Figure 2.UV-VIS spectrum (200-400nm) of standard solution, formulation, placeboand buffer. (DEXP concentration is 20 µg mL^{-1} for standard and oral formulation).

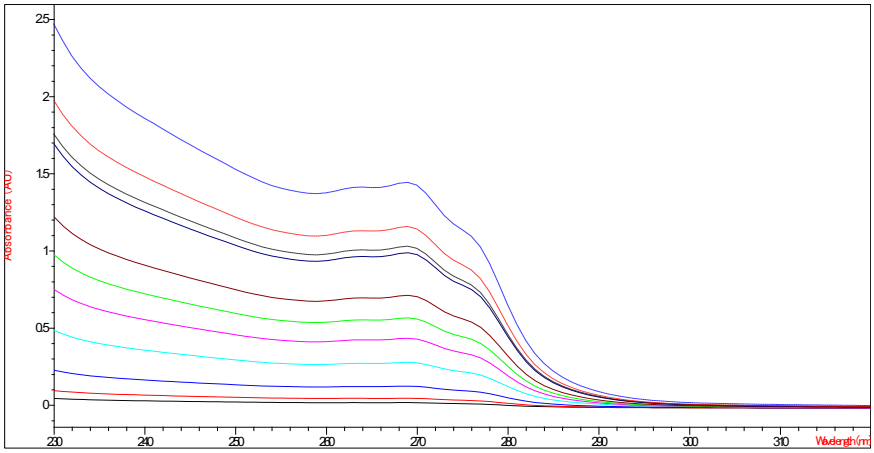

Figure 3. The spectrum in increasing concentrations of DEXP at 269 nm.

2.3. Validation

2.3.1. Selectivity

The selectivity of the developed method was proved by the comparison of standard solution, formulation, placebo and buffer solution at 269 nm wavelength. Placebo contains citric acid and glycerin. Spectra in Figure 2 shows that there was no interference coming from matrix components at the measured wavelength which can affect DEXP analysis. Therefore, the method was found to be selective at 269 nm.

2.3.2. Linearity and sensitivity

The calibration curve of DEXP standard stock solutions was prepared between 1.00 and 50.00 µg mL^{-1} as six replicates with 11 data points at 269 nm. Regression equation, correlation coefficient of the calibration curve, linearity range and sensitivity values were calculated (Table 2). Limit of detection (LOD) and Limit of quantification (LOQ) were calculated by using following equations. LOD = 3.3xσ/S and LOQ = 10xσ/S; S indicates the slope of the calibration curve and σ indicates the standard deviation of y intercepts of regression lines. The LOD and LOQ values for DEXP were found to be 0.35 µg mL^{-1} and 1.00 µg mL^{-1}, respectively.

Table 2. Characteristics of the calibration curve of the UV-VIS Spectrophotometric method (n=6).

Regression equation*	y = 0.0324 (± 0.0004) x – 0.0085 (±0.0015)
Number of data points	11
Correlation coefficient (r)	0.9996
Coefficient of determination (R^2)	0.9991
Linearity range (µg mL^{-1})	1.00 – 50.00
Limit of detection (LOD, µg mL^{-1})	0.38
Limit of quantification (LOQ, µg mL^{-1})	1.00

*y = a (±SE) x + b (±SE); x: concentration (µg mL^{-1}), y: absorbance.

2.3.3. Precision and accuracy

Precision and accuracy studies were performed as intraday and interday studies. In the precision study of DEXP, 3 different concentrations (5.00, 20.00, 35.00 µg mL^{-1}) were analyzed on the same day and on consecutive days. Precision results were found by calculating the %RSD (relative standard deviation) values (n = 6) of the answers obtained from the analyzes of the prepared solutions. Accuracy of the results was evaluated using Bias% of the results. The results are summarized in Table 3. As it is seen from the results, both RSD% and Bias% were less than 2.0% and it indicated that the method is successfully adapted to analyze DEXP concentration.

Table 3. Precision and accuracy values of the developed methods for DEXP (n=6).

	DEXP		
Added (µg mL^{-1})	**5.00**	**20.00**	**35.00**
	Intra-day		
$\overline{X}$ ± SE	5.01 ± 0.02	19.93 ± 0.10	35.09 ± 0.15
SD	0.06	0.24	0.37
RSD (%)	1.21	1.22	1.06
Bias (%)	0.22	-0.35	0.26
	Inter-day		
$\overline{X}$ ±SE	4.96 ± 0.02	20.08 ± -0.08	35.04 ± 0.13
SD	0.05	0.22	0.33
RSD (%)	1.09	1.08	0.94
Bias (%)	-0.88	0.41	0.11

$\overline{X}$ ± SE: Mean ±Standard Error; SD: Standard Deviation, RSD: Relative Standard Deviation, Bias (%) : [(Found - Added) / Added] x 100.

2.3.4. Intermediate precision

In intermediate precision study, the influence of different analysts was examined. DEXP active substance at a concentration of 20.00 µg mL^{-1}, prepared by two different analysts, was analyzed with the same instrument(n=6). The results were statistically evaluated with the Wilcoxon test (paired samples). Since $T_{Calculated} > T_{Theoretical}$, there is no difference between the two analysts and the method was found to be intermediated precision (Table 4).

Table 4. Intermediate precision results of tablet analysis.

	Analyst 1	**Analyst 2**
Added (µg mL^{-1}n=6)	20.00	20.00
$\overline{X}$ ± SE	20.22 ± 0.04	19.88 ± 0.07
SD	0.10	0.18
% RSD	0.48	0.88

$\overline{X}$: Mean ± SE; SD: Standard Deviation, RSD: Relative Standard Deviation, Wilcoxon Paired Test, p> 0.05).

2.3.5. Robustness

The robustness of a method is its capacity to remain unaffected by small but deliberate changes to method parameters. In robustness studies, small changes are made in the optimum test conditions determined for the developed method, and the effect on the analysis results is examined. Since the method used in the analysis of DEXP formulation is spectrophotometric, the robustness of the analysis method was controlled by changes in wavelength, buffer concentration and buffer pH (Table 5). As is seen, the small modification did not affect the final results statistically. RSD values for the results in different conditions were less than 1.0%. The method can be considered as robust.

Table 5. Results of robustness study of DEXP.

Parameter	**Optimum analysis conditions**	**1. Changed value**	**2. Changed value**	**DEXP %RSD**
Wavelength	269 nm	267 nm	271nm	0.12
Buffer Concentration	20 mM	19 mM	21 mM	0.24
Buffer pH	3.0	2.9	3.1	0.18

DEX amount: The results were compared with the results obtained under optimum conditions (p > 0.05). (Added DEXP: 20 µg mL^{-1}, n=3).

2.4. Stability of the DEXP oral pediatric formulation

The stability of the developed DEX oral pediatric solution and DEXP 8 mg/2 mL I.M./I.V. injection solution were evaluated using the developed UV/VIS Spectrophotometric analytical method. In our initial experiments, DEXP 8 mg/2 mL I.M./I.V. injection solution was observed to be stable at least two weeks in ambient temperature and the results were in a correlation with the reported data [23]. This situation encouraged us to use DEXP 8 mg/2 mL I.M./I.V. as the main source of DEXP in the ease-of-use oral pediatric formulation. Since the stability of DEXP alone could not confirm the stability of the developed formulation, we planned a stability study for our samples. Based on the results of the UV/VIS Spectrophotometric determinations, the developed DEXP oral pediatric solution was found to be stable at +4 °C for at least three weeks. These results presented that the developed pediatric oral solution of DEXP could be administrated to be used while it is being protected from daylight in an ordinary refrigerator (+4 °C) for at least three weeks and this period is enough for any personalized dose depended on therapy. Unfortunately, the formulation did not achieve stable till 50th day and it degraded. The disadvantage of the developed oral pediatric formulation was that it was not stable at room temperature even for 24 hours. The results were given in Table 6.When the developed oral pediatric formulation was frozen at -20 °C and a freeze-thaw cycle applied for three times, the results showed that the first freeze-thaw cycle prevent the stability of the formulation (99.85 % ± 0.34, $p>0.050$), but the second (95.11% ±0.05, $p<0.050$) and third cycle (87.64 % ± 0.27, $p<0.050$) did not allow DEXP to be stable in the formulation.

In order to confirm the stability results and to check if any other impurity peak occurred and interfered the spectrum to cause false-positive result, an HPLC analysis using an ACE 5 C18 (150x4.6mm, 5 µm) when the mobile phase was MeOH:Water (50:50 v/v) in an isocratic flow (1 mL min^{-1}) was performed and the fresh DEXP 8 mg/2 mL I.M./I.V. injection solution chromatograms were compared with DEX oral pediatric solution kept at +4 °C for 3 weeks at 269 nm detection wavelength. The results showed that peak area of the DEXP peak in the formulation was 99.4 % of the one observed for the fresh DEXP 8 mg/2 mL I.M./I.V. injection solution in identical concentrations (n=3).

Table 6.% Stability values of DEXP oral pediatric solution at different conditions (n=3).

		% Stability Values				
		24 hours	**24 hours**	**2 weeks**	**3 weeks**	**50 days**
Fresh Solution (expected)	**Fresh Solution (measured)**	**Room Temperature**	**+4 °C**	**+4 °C**	**+4 °C**	**+4 °C**
100.00	98.76	91.14	99.70	99.41	99.63	41.44
100.00	100.17	92.09	100.28	99.23	99.90	63.94
100.00	101.45	94.63	100.27	98.45	99.97	57.70
$\overline{X}$ **± SE**	100.13±0.78	92.62±1.04	100.08±0.19	99.03±0.30	99.83±0.10	54.36±6.71
p-value		0.0209 (<0.050)	**0.8985 (>0.050)**	**0.3527 (>0.050)**	**0.7954 (>0.050)**	0.0170 (<0.050)

$\overline{X}$: Mean ± Standard Error.

2.5. HPLC analysis of the formulation

Based on the results obtained from UV-VIS spectrophotometric method, the developed DEX oral pediatric solution was found to be stable at +4 °C up to 3rd week when it was protected from daylight in a glass volumetric flask. In order to confirm the stability results and to check if any other impurity peak occurred and interfered the spectrum to cause false-positive result, an HPLC analysis was performed and

the fresh DEXP 8 mg/2 mL I.M./I.V. injection solution chromatograms were compared with DEX oral pediatric solution kept at +4 °C for 3 weeks (Figure 4). The results showed that peak area of the DEXP peak in the formulation was 99.4 % of the one observed for the fresh DEXP 8 mg/2 mL I.M./I.V. injection solution in identical concentrations (n=3).

3. CONCLUSION

Personalized medicine or precision medicine is a medicinal therapy model that divides patients into different groups based on their predicted response or risk of disease. For pediatrics, it is always a discussion or a hard consideration to find the optimum dosage for corticosteroids on treatment and the best way to apply them to patients. In this study, we developed an oral pediatric solution formulation of DEXP having excipients known as not harmful for pediatric usage. The developed oral pediatric solution is designed to be easily prepared in basic laboratory conditions and found to be stable for 3 weeks at +4 °C when it is protected from daylight. The main source of DEXP in the formulation was especially selected as the one-time injectable solutions which are easily reachable from local pharmacies and hospital pharmacies. The developed UV/VIS Spectrophotometric method in the scope of the present manuscript allows the researchers/clinicians/pharmacist to perform the "in-house" quality control of the prepared formulations regularly in hospital usage since the methodology is relatively simple in comparison to high performance liquid chromatography or other advanced analytical techniques. Although the developed formulation was found to be stable and contains non-harmful excipients, such formulations must be validated with further toxicological and pharmacokinetic studies to prove their safely use in regular.

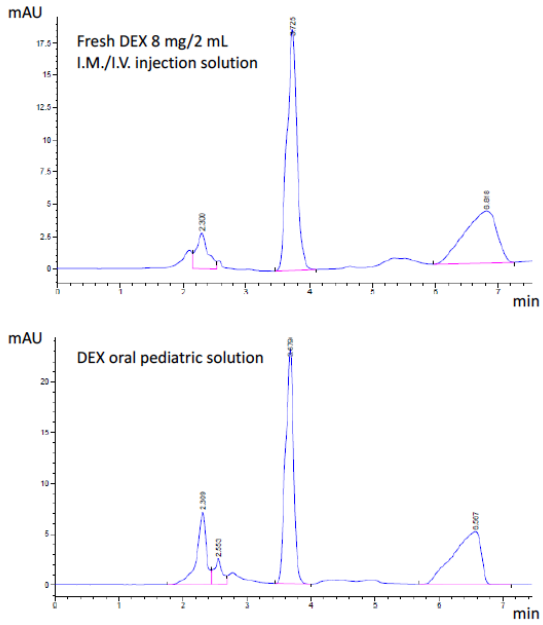

Figure 4. Chromatograms of the fresh DEXP 8 mg/2 mL I.M./I.V. injection solution and DEXP oral pediatric solution kept at +4 °C for 3 weeks. Final concentrations 10 µg mL^{-1}.

4. MATERIALS AND METHODS

4.1. Chemicals

Citric acid monohydrate (pharmaceutical grade), sodium hydroxide (NaOH, pharmaceutical grade), disodium hydrogen phosphate (Na_2HPO_4, pharmaceutical grade), and phosphoric acid were supplied from Merck (Darmstadt, Germany). Ultrapure water was obtained from Barnstead NanoPure Diamond System. Glycerin and DEXP 8 mg/2 mL I.M./I.V. injection solutions containing 9.26mg of dexamethasone 21-phosphate disodium salt equivalent to 8.0 mg dexamethasone 21-phosphate (DEXP) were provided commercially from a local pharmacy.

4.2. Instrumentation

Spectrophotometric determinations were performed by an Agilent 8453 combined with DAD UV–Vis spectrophotometer at 269 nm using 1 cm quartz cells.

4.3. Preparation of stock and standard solutions

A standard stock solution of DEXP (1000.0 µg mL^{-1}) was prepared in dilution solution. Dilution solution was consisted of 20 mM disodium hydrogen phosphate (Na_2HPO_4) which is prepared by dissolving 0.71 g of Na_2HPO_4 in 250 mL of water. pH of the dilution solution was adjusted to 3.0 with addition of phosphoric acid.

The standard working solutions were prepared from DEXP stock solution in the range of 1.00 to 50.00 µg mL^{-1} (1.0, 2.0, 5.0, 10.0, 15.0, 20.0, 25.0, 30.0, 35.0, 40.0, 50.0 µg mL^{-1}) in 10.0 mL volumetric flasks using dilution solution.

4.4. Preparation of the formulation

A total volume of 25 mL formulation containing 1.875 mL of DEXP 8 mg/2 mL I.M./I.V. injection solution to obtain 7.5mg DEXP (active ingredient), 1.25 mL glycerin (antimicrobial preservative), 0.25 grams citric acid monohydrate (buffering agent) [17, 19] and 20 mL water was mixed in a 25 mL beaker. The mixture was stirred with a magnetic stirrer. The pH of the mixture was adjusted to 8.0 with 1.0 M NaOH and the total volume was filled up to 25 mL with water. The final solution was a clear homogenous solution. The developed formulation was analyzed using UV/VIS Spectrophotometric method after appropriate dilution of the formulation to final concentration of DEXP to 20.00 µg mL^{-1} with 20 mM pH 3.0 phosphate buffer.

4.5. Stability studies

To evaluate the stability of oral pediatric solution some storage conditions were visualized. These were ambient temperature, +4 °C, and -20 °C while the assays were being protected from daylight. Oral pediatric solutions were stored in a colored volumetric flask as three replicates, and the DEXP concentrations were determined on 24th hour, 1st week, 2nd week, 3 weeks, and 50th day. Freeze-thaw cycle (3 times at -20 °C) stability was also evaluated. Before the measurements of DEXP concentrations, the solutions were diluted to 20.00 µg mL^{-1} with 20 mM pH 3.0 phosphate buffer. The determined DEXP concentration (as triplicated) of the pediatric oral solution was compared with the fresh ones (n=3) and if the results were >%95 and statistically identical ($p>0.05$) upon t test, the assays were accepted as stable during storage conditions (20).

4.6.HPLC analysis

An HPLC column, ACE 5 C18 (150x4.6mm, 5 µm) was used for injections. The mobile phase was MeOH:Water (50:50 v/v) when the flow rate was 1 mL min^{-1}. Detection wavelength was 269 nm. Calibration standards were freshly prepared from DEXP stock solution (1000.0 µg/mL) and the range was between 1.0 and 15.0 µg mL^{-1} (1.0, 2.0, 5.0, 10.0, and 15.0 µg mL^{-1}). Oral pediatric solution's final concentration was diluted to 10.0 µg mL–1 before injections and freshly prepared one and the one kept at +4 °C for 3 weeks were injected triplicate.

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