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Physicochemical stability evaluation of liquid extemporaneous preparation based on tretinoin for administration via enteral tube

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Abstract

Objective: The purpose of the study was to evaluate the content and physicochemical stability of a liquid oral formulation obtained from ATRA gelatin capsules in an oil/water vehicle, given the demand for this formulation for intubated patients undergoing treatment for acute promyelocytic leukemia. **Methods:** Analyzes were performed using High Performance Liquid Chromatography (HPLC) coupled to a UV detector, using a C-18 column. The run was performed with a mobile phase composed of ultrapure water with 0.5% glacial acetic acid (v/v) as solvent A and acetonitrile as solvent B, in an isocratic run (25:75) (A/B) with a flow of 1 mL/min, temperature at 30°C and detection at 355 nm. The sample injection was 10 µL and the run time was 12 min. The oral formulations were prepared from ATRA (Vesanoid, FQM) in mineral oil/ultrapure water (3:7) (v/v) by dissolution process and heating at 40°C, in oral dosers protected from light and kept under refrigeration (2 – 8°C). Analyzes were performed on days 1, 2, 3, 7, 9 and 14**. Results:** The extemporaneous preparation showed acceptable visual physical stability, with a change in appearance due to the hardening of aqueous phase, corrected by heating the formulation in water bath at 40°C. The ATRA content was considered adequate until D3 according to the Brazilian Pharmacopeia (FB) 6th edition, presenting 103.3%, 94.8% and 95.6%, on days 1, 2 and 3, respectively. The concentration of isotretinoin, a degradation product, varied from 0.16% to 1.44%, between days 1 and 14, respectively. **Conclusion:** The results suggested that the liquid oral preparation presented satisfactory content and physicochemical stability for up 48 hours after preparation, when stored protected from light and under refrigeration, as recommended by RDC 67/2007.

Key words: tretinoin; intubation; gastrointestinal; drug stability; acute promyelocytic leukemia.

Estudo de estabilidade físico-química de preparação extemporânea líquida à base de tretinoína para administração via sonda

Resumo

Objetivo: O estudo visou investigar o teor e a estabilidade físico-química da formulação oral líquida obtida a partir de cápsulas gelatinosas moles de tretinoína (ATRA) no veículo óleo/água, visto a demanda desta formulação para pacientes entubados em tratamento de leucemia promielocítica aguda. **Métodos**: As análises foram realizadas por Cromatografia Líquida de Alta Eficiência (CLAE) acoplada a detector UV, utilizando coluna C-18. A corrida foi executada com fase móvel composta por água ultrapura com ácido acético glacial 0,5% (v/v) como solvente A e acetonitrila como solvente B, em corrida isocrática (25:75) (A/B), com fluxo de 1 mL/min, temperatura de 30°C e detecção em 355 nm. A injeção da amostra foi de 10 µL e o tempo de corrida foi de 12 min. As formulações orais foram preparadas a partir de ATRA (Vesanoid, FQM) em óleo mineral/água ultrapura (3:7) (v/v), por processo de dissolução e aquecimento a 40ºC, em dosadores orais protegidos da luz e conservadas sob refrigeração (2 - 8°C). As análises foram realizadas nos dias 1, 2, 3, 7, 9 e 14. **Resultados**: A preparação extemporânea apresentou estabilidade física visual aceitável, com alteração de aspecto pelo enrijecimento da fase aquosa corrigida com aquecimento da formulação em banho-maria a 40°C. O teor de ATRA foi considerado adequado até o D3, conforme a Farmacopeia Brasileira (FB) 6ª edição, apresentando 103,3%, 94,8% e 95,6%, nos dias 1, 2 e 3, respectivamente. A concentração de isotretinoína, produto de degradação, variou de 0,16% a 1,44%, entre os dias 1 e 14, respectivamente. **Conclusão**: Os resultados sugeriram que a preparação oral líquida apresentou teor satisfatório e estabilidade físico-química por até 48 horas após o preparo, quando conservada protegida da luz e sob refrigeração, conforme preconizado pela RDC 67/2007.

Palavras-chave: tretinoina; intubação; gastrointestinal; estabilidade de medicamentos; leucemia promielocítica aguda

Introduction

Acute promyelocytic leukemia (APL) is a hematological neoplasm characterized by the aberrant proliferation of promyelocytes. Mainly caused by the translocation of chromosomes t(15,17) q(24.1;q21.2) promoting the rearrangement of the PML/RAR-α genes, it is considered a medical emergency. APL is associated with high early mortality rates due to coagulopathies, such as disseminated intravascular coagulation (DIC) and hyperfibrinolysis[1, 2].

The PML gene is an organizer of nuclear domains and exerts growth-suppressing properties, including involvement in p53 activation, encoding transcription factors that are important in inhibiting proliferation and, consequently, promoting myeloid differentiation. The RAR-α gene (retinoic acid receptor-α) is responsible for myeloid differentiation mechanisms. The PML-RAR-α gene produces protein with low affinity to retinoids, interrupting cell differentiation and leading to self-renewal mechanisms, suppressing checkpoints and apoptotic signals[3].

All-trans-retinoic acid (ATRA), known as tretinoin, is a first-generation retinoid derived from retinoic acid (vitamin A), considered a differentiation agent that should be initiated as soon as the diagnosis of APL is suspected. As a mechanism of action, ATRA induces promyelocyte differentiation into granulocytes through its binding to the RARA-RXR complex, causes degradation of the PML-RAR-α complex, allows PML activity, with subsequent activation of p53, inhibiting cell self-renewal mechanisms [3-5].

Patients with APL generally present symptoms such as anemia, thrombocytopenia, weakness, fatigue, infections, coagulopathies and, in some cases, after starting treatment with ATRA, they may present the differentiation syndrome, consisting of fever and respiratory failure[6]. In these cases, they require ventilatory support via orotracheal intubation (OTI) and the administration of medication via a tube.

ATRA, for oral use, is only available in soft capsule form[7] and is essential for the treatment of the disease. For intubated patients, it is essential to adapt the pharmaceutical form from a soft gelatin capsule to a liquid oral preparation. Handling is recommended in a controlled environment to avoid occupational exposure, since the medication has teratogenic potential[8]. There are several preparation methods published in the literature, using the following vehicles: distilled water, milk, medium-chain triglycerides (MCT), water/mineral oil and oil, as well as the recommendation to aspirate the contents of the capsule[9-11]. Of particular interest is the preparation with water/mineral oil, since the water is added to break up the soft gel capsules and the mineral oil acts as a lipophilic vehicle for the ATRA, according to the method described by Okumura *et al*[10]. However, there are no studies on the stability of the adapted pharmaceutical form, which is extremely important since ATRA is sensitive to light, heat, and oxygen, especially when it is in solution[12].

The objective of this study was to determine the content and define the physicochemical stability of the extemporaneous preparation of ATRA from the soft gelatin capsule, using the water/mineral oil vehicle, in order to ensure the dose administered to the patient, shelf life and storage recommendations for the care team.

Methods

Reagents and solutions

ATRA 10 mg soft gel capsules (Vesanoid, FQM - Catalent Germany, Germany) were used to prepare the liquid oral solution together with ultrapure water (Direct-Q 3 UV Purifier, Merck, Germany) and mineral oil (Farmax, Brazil) in 10 mL oral dispensers (Zhejiang Huafu Medical Equipament, China). A 20 mg generic brand isotretinoin suspension (Ranbaxy - Sun Pharmaceutical, India) was prepared to assess the presence of degradation compounds in the sample. The analytical grade ATRA standard (98% purity) used for method validation was purchased from Toronto Research Chemicals (Toronto, Canada). In addition, HPLC grade methanol (Honeywell, USA), 99.8% glacial acetic acid (Neon, Brazil), HPLC grade acetonitrile (Êxodo Científica, Brazil) and ultrapure water were used for analytical purposes.

Instrumentation and analytical procedures

High Performance Liquid Chromatography (HPLC) method

The analyses to determine the content and chemical stability were carried out using High Performance Liquid Chromatography (HPLC), via a Prominence model LC-20AT liquid chromatograph (Shimadzu, Japan), coupled to a SPD-20A UV-VIS detector, using an Ascentis Express C-18 column (15 cm x 4.6 mm) with a particle size of 5 µm (Supleco CO., USA). The run was carried out using a mobile phase composed of ultrapure water with 0.5% glacial acetic acid (v/v) as solvent A and acetonitrile as solvent B, in an isocratic run (25:75) (A/B), with a flow rate of 1 mL/min, a temperature of 30°C and detection at 355 nm. The sample was injected in 10 µL and the run time was 12 min. The chromatographic conditions were adapted from the ATRA determination method recommended in the United States Pharmacopeia: Pharmacopeial Forum Volume n°41- Tretinoin[13] (USP).

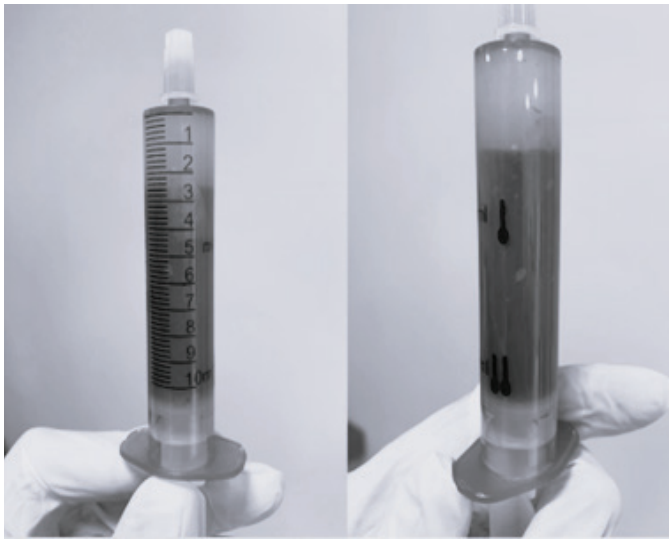
Calibration curve

An analytical grade ATRA stock solution was prepared at a concentration of 1 mg/mL in methanol and, from this, ATRA solutions at concentrations of 1, 5, 10, 20, 30 and 40 µg/mL were obtained, all diluted in the same solvent. ATRA standard solutions at a concentration of 20 µg/mL were prepared daily as an analytical control.

Handling extemporaneous preparation

Liquid oral suspensions were prepared by adding four ATRA soft gelatin capsules, totaling a 40 mg medication dose, in 7 mL of warm ultrapure water at 40°C (± 2°C) and 3 mL of mineral oil, in oral dispensers with a capacity of 10 mL, covered with aluminum foil to ensure photoprotection of the preparation. The suspension was kept in a water bath at 40°C and stirred frequently by hand until completely dissolved. The samples were then stored in a refrigerator (2°C - 8°C), protected from light. Figure 1 shows the liquid oral preparation after production.

Figure 1. Liquid oral preparation based on ATRA in a mineral oil/distilled water vehicle (3:7) in a PVC-free oral dispenser with a 10 mL capacity.



Content determination and stability study

For the stability study, aliquots of each of the prepared samples were analyzed in triplicate and evaluated on days D1, D2, D3, D7, D9 and D14 after preparation. The analysis on D1 was carried out immediately after the suspension had been prepared. The other samples were analyzed on subsequent days and went through the dissolution process again in a water bath at 40°C (± 2°C).

To determine the content, a 2 mL aliquot of the oil phase was placed in an ultrasonic bath model SSBuc 10L, frequency 40 Hz (SolidSteel, São Paulo) for about 10 minutes and then extracted. The extraction process was carried out using hexane/methanol in a 1:1 ratio, in 50 mL Falcon tubes, with the aim of separating the mineral oil, which has an affinity for hexane, from the ATRA substance, which is soluble in methanol. Subsequently, successive dilutions of the methanolic phase were carried out to obtain a solution with a final concentration of 20 µg/mL, according to the USP ATRA determination protocol[13]. For each dilution, the aliquots were vortexed at a speed of 2800 rpm for 1.5 min and then analyzed in HPLC.

Assessment of the degradation compounds presence

The presence of degradation compounds was observed over the days of the stability study analysis. It is known that isotretinoin is one of the degradation compounds of ATRA[14], so a suspension of isotretinoin prepared from its commercial presentation was used, according to the method described for extemporaneous ATRA preparation, in the absence of a standard substance, for comparative purposes with the aim of determining the retention peak corresponding to the molecule and evaluating the increase in its area during the study period.

Aspect analysis

The formulations were analyzed for their appearance, color and redispersibility by visual analysis and odor change during the study period, on days 1, 2, 3, 7, 9 and 14.

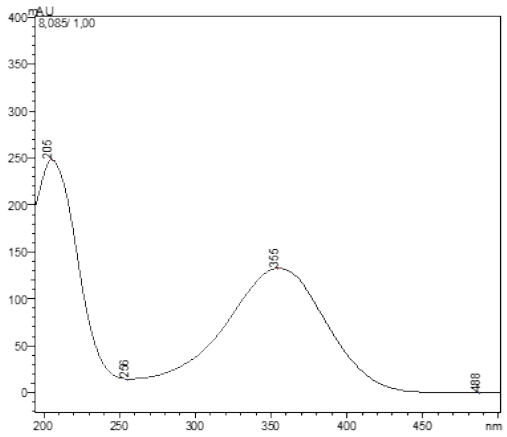
Resultados

The assay and stability of the samples over the 14-day study period were carried out under chromatographic conditions based on the USP[13] determination method, and the ATRA retention time was approximately 8.0 min at 355 nm, as shown in Figure 2. Adaptations made resulted in a well-defined peak with satisfactory chromatographic resolution and good separation of ATRA from its degradation compounds.

The analytical method was linear between the concentrations of 1 and 40 µg/mL (r^2> 0.9997). The content of the samples was calculated based on the calibration curve, and the assay results, standard deviation (SD) and relative standard deviation (RSD) are shown in Table 1. The mean content of the triplicate samples in D1 was 41.33 mg (103%), in D2 37.92 mg (94.8%), in D3 38.25 mg (95.6%), in D7 30.16 mg (75.4%), in D9 31.68 mg (79.2%) and in D14 33.37 mg (83.4%).

Figure 2. ATRA peak UV-DAD spectrum **(A)** and the ATRA standard solution chromatogram at a 20 µg/mL concentration **(B)**

(A)



(B)

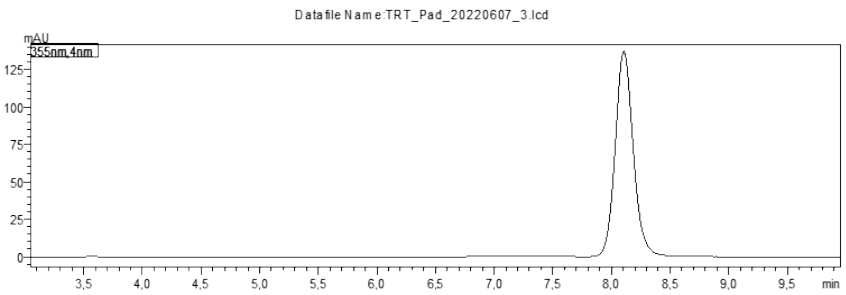


Table 1. Determination of ATRA content in the liquid oral preparation on days 1, 2, 3, 7, 9 and 14.

Test day	Conc. 1 (mg)	Conc. 2 (mg)	Conc. 3 (mg)	Mean concentration (mg)	Content (%)	SD	RSD
D1	41.64	41.68	40.68	41.33	**103.3**	0.46	**1.12**
D2	35.56	39.16	39.04	37.92	**94.8**	1.67	**4.40**
D3	36.44	39.52	38.80	38.25	**95.6**	1.31	**3.44**
D7	29.84	28.68	31.96	30.16	**75.4**	1.36	**4.50**
D9	30.92	31.96	32.16	31.68	**79.2**	0.54	**1.72**
D14	32.72	33.36	34.04	33.37	**83.4**	0.54	**1.61**

Standard deviation (SD) and relative standard deviation (RSD)

The presence of degradation compounds in the sample was analyzed, including isotretinoin, whose retention time was approximately 7 minutes. The other unidentified compounds had retention times of between 7.1 and 7.6 minutes. The retention peak areas of the compounds and their percentages compared to the ATRA peak are shown in Table 2. The area corresponding to isotretinoin increased from 1255 on D1 to 8590 on D14, equivalent to 0.16% and 1.44% of the ATRA area, respectively. Only at D7 and D14 were the other degradation compounds retained in the chromatogram. Figures 3 and 4 represent an overlay of the chromatograms obtained during the stability study.

In terms of physical stability, the liquid oral preparation showed no change in color on any of the study days. In terms of appearance, the samples remained uniform, with viscoelastic rheological behavior due to the presence of gelatin, a component of the ATRA capsule shell, with stiffening of the aqueous phase after packaging under refrigeration, from D2 onwards. This condition was solved by heating the suspension in a water bath at 40°C (± 2°C) before carrying out the tests, with redispersibility maintained. There was a change in the smell of the suspension, which, when stored at room temperature, had a bad smell from D3 onwards. For this reason, we preferred to conduct the tests considering storage under refrigeration as a way to extend the preparation's shelf life.

Table 2. Determination of liquid oral preparation degradation compounds on days 1, 2, 3, 7, 9 and 14.

Test day	Compound and retention time (min)	Peak Retention Area	% in relation to the ATRA area
D1	Isotretinoin (6.9)	1255	0.16
D2	Isotretinoin (6.9)	3605	0.5
D3	Isotretinoin (6.9)	2355	0.33
D7	Isotretinoin (6.9)	4983	0.96
	Unidentified compounds (7.1/7.6)	5951	1.15
D9	Isotretinoin (6.9)	2461	0.44
D14	Isotretinoína (6.9)	8590	1.44
	Compostos não identificados (7.1/7.6)	8360	1.40

Figure 3. Overlay of the chromatograms obtained on days 1, 3, 7 and 14, represented by the colors black, red, green, and blue, respectively.

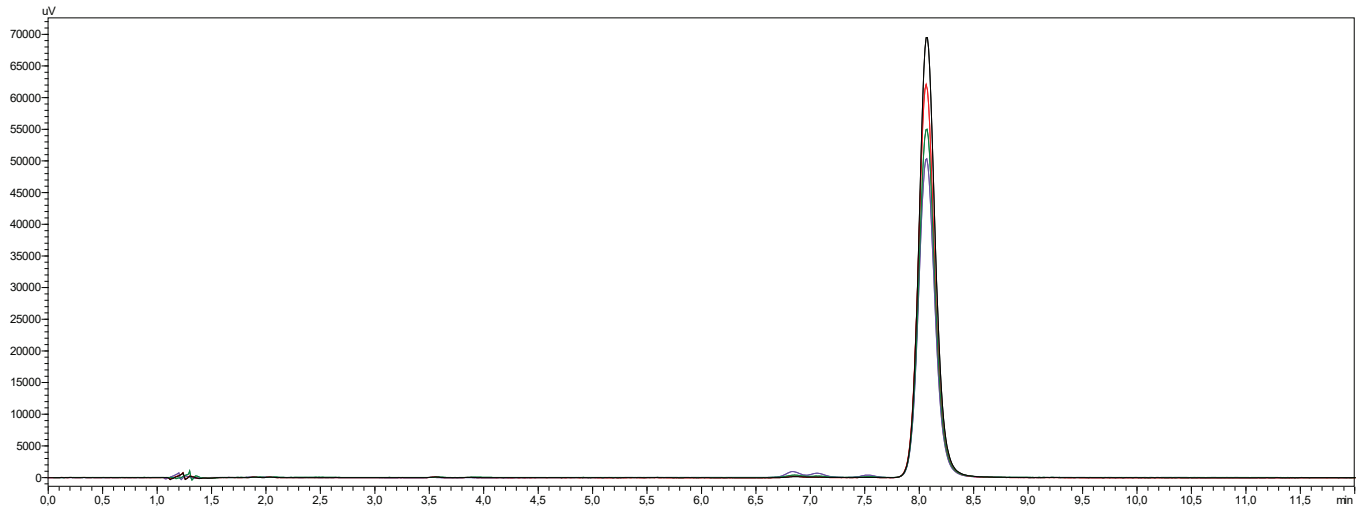
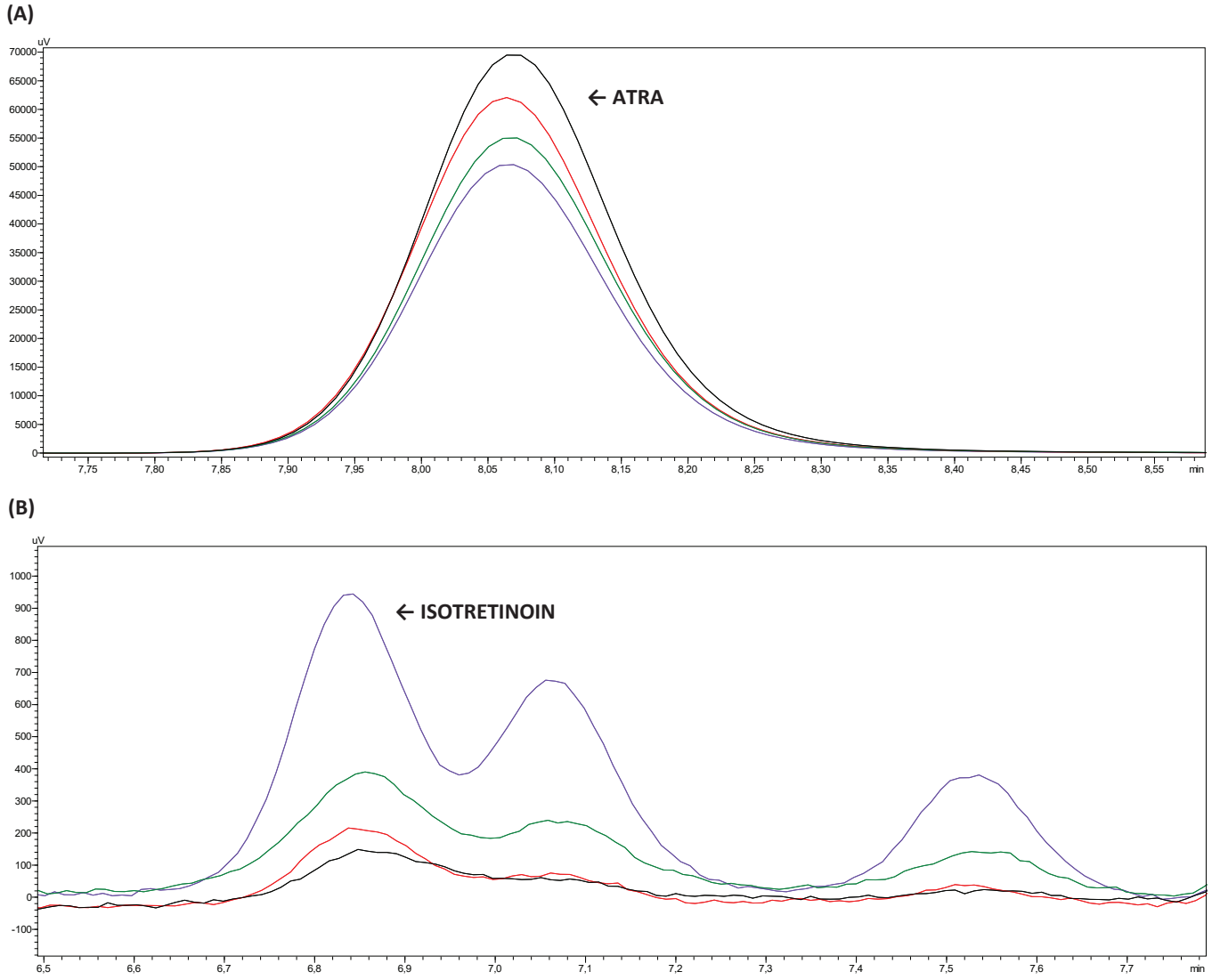


Figure 4. Image approximation of the chromatograms obtained on days 1, 3, 7 and 14, with **(A)** the ATRA peak and **(B)** the degradation compounds peaks, including isotretinoin.



Discussion

The preparation method for the liquid oral suspension used in this study is in accordance with that described by Okumura *et al*[10]. This form of preparation minimizes contact with the medication, aiming for occupational protection and optimizing the migration of the active ingredient to the oil phase, as well as being easily manipulated using low-cost and easily accessible materials. Przybylski *et al*[9] used this same form of preparation in their service, altering the proportion of oil/water vehicle and the heating temperature (37°C), and reported favorable outcomes from patients who used it, reinforcing that the preparation is satisfactory. However, no studies were found in the literature that evaluated the content and stability of liquid oral preparations based on ATRA.

Extemporaneous preparations do not have acceptable content and stability determination values stipulated by the Brazilian Pharmacopoeia (FB) 6th edition[15], since RDC 67/2007[16] defines extemporaneous preparation as "any preparation for use within 48 hours of its manipulation, under physician's prescription, with individualized formulation". However, as it is an unstable molecule and suspension with low rheological stability, the purpose of the work was to evaluate content and stability to ensure the use of the extemporaneous preparation. This analysis provides the pharmaceutical professional with greater security of administration and flexibility in terms of preparation times, given that chemotherapy manipulation services are generally not available during all hospital opening hours.

Monographs of pharmaceutical ingredients and specialties of the FB 6th edition[15] present content values only for presentations of ATRA cream, gel, and the active pharmaceutical ingredient (API) and isotretinoin capsules, and do not mention the ATRA presentation in capsules. The general content defined for commercial presentations of these substances must be at least 90% of the active ingredient amount declared on the label. Correlating these data with those obtained in this work, the liquid oral preparation met the pharmacopoeial determinations up to D3, and the mean content presented by the sample was 103.3%, 94.8% and 95.6%, on days 1, 2 and 3, respectively.

As for the physicochemical stability of the formulation, physical stability is related to the organoleptic parameters of the drug such as appearance, uniformity, unchanged dissolution and dispersibility[17]. The liquid oral preparation showed satisfactory visual physical stability with a change in appearance due to hardening of the aqueous phase from D2 onwards. Chemical stability is defined by maintaining the chemical integrity of an active ingredient in a pharmaceutical product and its declared potency within specified limits. There is a loss of stability when there is a change in the concentration of the active ingredient, leading to a reduction in the dose and the development of degradation compounds, which can be toxic[17]. During the study, we detected an increase in the degradation compound isotretinoin, which showed an increment in concentration from 0.16% on D1 to 1.44% on D14, in relation to the ATRA peak. The other possible degradation compounds were not identified due to the lack of a reference chemical. It is known that ATRA can undergo heat-induced isomerization processes giving rise to 13-cis-retinol and isotretinoin, can undergo degradation to anhydro-vitamin-A caused by the presence of water and be oxidized to 4-oxo metabolites depending on the partial pressure of oxygen[18, 19]. Roy & Chakrabarty[14] carried out a forced ATRA degradation study and found the presence of degradation compounds, including isotretinoin, which showed the highest rates in the temperature degradation tests, followed by light-induced degradation. The British Pharmacopoeia[20] determines that the isotretinoin limit in ATRA samples should not exceed 0.5% of the ATRA retention peak area and that other impurities should not exceed 0.2%. Considering the results obtained for content and the period of use stipulated by RDC 67/2007[16] and the limits stipulated for degradation compounds by the British Pharmacopoeia[20], we can consider the use of the liquid oral preparation based on ATRA for up to 48 hours after preparation when protected from light and stored under refrigeration (2°C- 8°C) to be viable.

As for microbiological stability, according to USP <795>: General Guidelines for Assigning Beyond-Use Dates[21], non-sterile oral preparations whose formulations contain water have a maximum stability of up to fourteen days, necessarily under refrigeration, and do not contain antimicrobial agents. For this reason, the ATRA stability study was conducted under refrigeration (2°C- 8°C) for 14 days, in order to assess whether the liquid oral preparation remained chemically stable during the period considered adequate from a microbiological perspective. Refrigeration was also chosen because of the change in odor of the liquid oral preparation after D3.

Another relevant aspect that can have an impact on the reduction of the active ingredient is the interaction with plastics present in hospital medical equipment. Physico-chemical properties such as lipophilicity, pKa and ionization state can have an impact on the ability of medications to adsorb onto plastics. It is known that non-ionized and lipophilic molecules are more likely to adsorb onto plastics, especially PVC[22, 23]. PVC-free oral dispensers were used to prepare and package the solutions, as a way to avoid possible interactions, since ATRA is lipophilic[24].

Studies evaluating the serum concentrations obtained by patients who used an adapted pharmaceutical form of ATRA are still needed, as there are only case reports on the use of this adaptation. Takitani *et al*[25] compared the serum concentration of patients who received ATRA orally versus by tube. The authors showed that patients who received ATRA via tube did not have satisfactory therapeutic levels. However, the way in which ATRA was prepared for administration via tube differed from that proposed in this study, since in the aforementioned study, the contents of the capsule were aspirated and administered directly into the tube.

Finally, the study's limitations include the oscillation of ATRA content values during the analysis of the samples, as well as the peak retention area of the degradation compounds. We can list a few reasons that impacted on the analyses, such as the inhomogeneity of the samples, possibly caused by the non-uniform redispersibility of ATRA in its vehicle, differences in the mineral oil/water ratio in the preparation of the suspension, since oral dosers do not have measurement precision, as well as the extraction process, in which we do not know for sure how much hexane may have interfered with the extraction of ATRA by methanol. In relation to the oscillation of the peak retention area of isotretinoin and the other degradation compounds, it can be seen from the chromatogram that the separation of the peaks was not satisfactory between the compounds, as they had an elongated tail and poor definition, which had an impact on the value of the areas defined by the chromatogram. In any case, we believe that even with the fluctuations in results and limitations of the study, we can consider it valid because it demonstrates that although the molecule is intrinsically unstable, with care in handling the suspension we can use it within the time limit stipulated by RDC 67/2007[16].

Conclusion

The ATRA liquid oral preparation in an oil/water vehicle showed satisfactory content and stability for up to 48 hours after preparation when protected from light and kept refrigerated (2-8°C), as recommended by RDC 67/2007. The liquid oral preparation suffers a change in appearance when stored in the refrigerator due to the hardening of the aqueous phase, corrected by heating in a water bath at 40°C (± 2°C). This method of preparation proved to be suitable as it guarantees the dose administered to the patient and safety for the care professional, as well as being economically viable and easy to carry out.

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Collaborators

LM, AA, LM and J took part in designing the project, analyzing and interpreting the data. LM, GM, VH and J participated in writing the article and critically reviewing the content.

Conflict of interest statement

The authors declare no conflicts of interest.

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