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Design of a pediatric oral formulation with a low proportion of hydrochlorothiazide

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ABSTRACT

It is a normal pediatric practice in community and hospital pharmacies to prepare a new drug formulation when no commercial forms of it are available. Any dose or stability control is usually done for these types of compounding formulations due to the effort which means to develop these types of tests in pharmacies. We have studied five different hydrochlorothiazide oral formulations prepared with traditional compounding techniques in pharmacies to treat heart failure and edemas in babies. A Standard Operating Procedure (SOP) was done for every suspension. After the strictly monitoring of the SOP, every suspension was subjected to quality control tests (pH, particle size, viscosity, dose content and stability). There is only one studied formulation that guarantees the correct dose administering and stability after 3 weeks stored at 5 °C and light protected. Both, the percentage of wetting agent and the viscosity of the suspensor vehicle in this formulation make the correct dose administering possible after the formulation is shaken.

1. Introduction

The community and hospital pharmacists are often challenged with the preparation of a dosage form not commercially available using traditional compounding techniques (Glass and Haywood, 2006). The use of these techniques is widespread in pediatric pharmacy practice (Brion et al., 2003). The proper design and formulation of a dosage form requires a consideration of the physical, chemical and biological characteristics of all drug substances and pharmaceutical ingredients to be used in formulating the product (Nahata and Allen, 2008). New dosage form must be safe and effective by using the pure drug and with the limitations of the excipients that the European Medicines Agency (EMA) recommended. In most cases the pharmacist will therefore prepare an oral liquid dosage form with the active ingredient dissolved or suspended in simple syrup (Glass and Haywood, 2006). These liquids are directly administered into the infant's or child's mouth by drop, spoon, dosing cup or oral dosing syringe. A single liquid pediatric preparation may be used for infants and children of all ages, with the dose of the drug varied by the volume administered (Allen, 2008; Sobhani et al., 2008). It is imperative that formulations can be administered accurately to ensure the correct dose and stability are provided (Walsh et al., 2011). Normally any dose or stability control is done in a pharmacy or in a hospital due to the effort which means to keep a stability indicating high performance liquid chromatography (HPLC) method for every formulation prepared (Glass and Haywood, 2006). For this reason, there are no studies either about the quality of the final product or about the dose homogeneity administering.

The hydrochlorothiazide (HCTZ) is a diuretic drug from the thiazide class widely used for years which produces dieresis due to the inhibition of the electroneutral sodium–chloride ions cotransportation system in the distal tubule level. Thus, this produces the active sodium reabsorption decreasing and the increase in its excretion. It produces a certain peripheral vascular resistance which complements the antihypertension action. It is used as a hypokalaemic, hypomagnesemiante, hyperglycaemic, hypercalcemic and hyperuricemiante. It has a paradoxical antidiuretic action in the diabetes insipidus. It is mainly used in hypertension treatment, as a single agent, or associated to other antihypertensives (as beta-blockers, vasodilators, calcium antagonist, etc.) (Acofarma Website, 2011).

HCTZ is a white or nearly white, almost odorless, crystalline powder and has a slightly bitter taste. It is highly soluble and lowly permeable and it belongs to the class III drug product in the Biopharmaceutic Classification System (BCS) (Linderberg et al., 2004; Avdeef et al., 2000). It is incompletely but fairly and rapidly absorbed from the gastro-intestinal tract. It has been estimated to have a half-life plasma of about 3 or 4 h with a subsequent longer terminal phase, its biological half-life is up to about 12 h. It appears to be preferentially bound to red blood cells. It is excreted unchanged in the urine (Martindale, 1982).

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The treatment of heart failure and edemas in babies with oral HCTZ consists of 2 mg/kg/day distributed in two doses (Flórez and Armijo, 1992). HCTZ is available in a commercial 25 or 50 mg tablet and recently in an investigation phase 1 mg novel minitablet (Stoltenberg and Breitkreutz, 2011). If no liquid commercial formulation of HCTZ (any chemical derivative of it) is available, these tablets can be cut in one-half or one-quarter, crushed and mixed with palatable drink or mixed with solid food just prior to administer (Tagliari et al., 2009). Alternatively, pharmaceutical suspensions made in a Hospital or in a Chemist's can be prepared so as to administer this drug to prematures, newborns, babies and children. The suspensions allow the development of a liquid dosage form containing an appropriate quantity of drug in an acceptable volume. Normally the suspension's resistance to hydrolysis and oxidation is generally good compared to that observed in solutions (Tabibi and Rhodes, 1996). Tagliari et al. studied the effects of hydroxypropylmethylcellulose (HPMC) and carboxymethylcellulose sodium (CMC-Na) on the physicochemical parameters of developed pharmaceutical suspensions containing HCTZ for pediatric use (Tagliari et al., 2009). They concluded that CMC-Na leads a flocculated suspension, forming a loosely linked polymer network system that is easy to be redispersed with soft agitation. Other authors use Ora-plus and Ora-sweet as excipients to elaborate HCTZ suspensions from commercial tablets (Allen and Erickson, 2011; Nationwide Children's Hospital, 2011). Other formulation use hydroxypropylmethylcellulose in simple syrup to suspend the pure drug (Atienza et al., 2011). The use of the active pharmaceutical ingredient (API) by modifying a commercially available tablet or capsule is not allowed by legislation in some countries due to the use of the drug out of its instructions. The other components of the formulation are limited for pediatric patients by the EMA (2006). And the homogeneous distribution of the pure drug is an additional problem if it is formulated in low proportion (Sundell-Bredenberg and Nyström, 2001).

The objective of this study was the design of a pediatric oral suspension with a low proportion of HCTZ and the development of a simple and feasible Standard Operating Procedure (SOP) for its use by pharmacist both in community and hospital pharmacy. This has to guarantee the correct dose administering, the efficiency of the treatment and the formulation stability during its preparation and storing.

2. Materials and methods

HCTZ and excipients were pharmacopoeia grade and were provided by Acofarma (Spain). All other reagents were those of analytical grade (Sigma–Aldrich, Spain).

2.1. Reference formulation

The most used HCTZ formulation in pharmacies at 2 mg/ml employed 1% (w/v) hydroxypropylmethylcellulose as suspending agent and simple syrup adjusted to pH 3 with 0.1 M hydrochloric acid (Atienza et al., 2011; Mollica et al., 1969), see Table 1. Any of these previous formulations take into account that a class III drug product compounded at a low dose (0.2%, w/v) in suspension needs different agents in quantities that ensure the right contact between the solid and the rest of the liquid preparation to guarantee the correct drug suspension and administering.

Due to the HCTZ dose in the formulation is over its solubility in water (0.61 mg/ml at 25 °C) and with the aim of designing the simplest suspension, we prepared four different formulations which were compounded by the minimum agents recommended by the EMA:

- A wetting agent, which decreases the interface tension between the drug as solid and the rest of the formulation as liquid. The glycerol was used at two proportions (10 and 20%, w/v) advised by the bibliography (Martindale, 1982; Handbook of Pharmaceutical Excipients, 1995).
- A suspending agent, to keep the right viscosity to maintain the suspended solid homogeneously distributed inside the formulation. The hydroxypropylmethylcellulose and methylcellulose 1000 at 1% (w/v) were used.
- A buffer, as citric acid at 4% (w/v) to keep the right pH for the HCTZ stability (3.0–3.5) (Harris and Riegelman, 1969; Mollica et al., 1969).
- And a disperser agent as water to have all the agents.

2.2. General SOP

Reference formulation and four different formulations were used to prepare the suspensions, see Table 1. At least three batch of every formulation were made.

The suspensions were elaborated according to the following Standard Operating Procedure (SOP):

- First, methylcellulose or hydroxypropylmethylcellulose vehicle is prepared.
- All the solids components are pulverized and weighed.
- The HCTZ is added to a 100 ml Erlenmeyer and then, the right amount of glycerol is added in a constant shaking until an homogeneous paste is formed.
- Then, the suspensor vehicle is added to the previous mixture and it is worked until homogeneity.
- Separately, the citric acid solution is added to the water and afterwards this solution is slowly added to the suspension.
- The formula is shaken until homogeneity, checked the pH is between 3.0 and 3.5, and bottled in an hermetic glass amber container without rest.

The elaborated suspensions were physical and chemical characterized as we describe below.

2.3. Quality control

2.3.1. pH

The pH was tested in duplicate by a pHMeter Crison GLP 21 (Barcelona, Spain).

2.3.2. Particle size

The particle size was tested in duplicate by a Mastersizer® 2000 (Malvern, UK).

2.3.3. Viscosity

The viscosity was tested in a programmable viscometer Brookfield® LVDV-II (Middleboro, MA, USA) at 25 °C. A spindle SC4-18 was used so as to determine viscosities between 1.5 and 30,000 cP with 8 ml as sample volume. The data processing was carried out with the Wingather® 32 program (Middleboro, MA, USA). All the measures were made with a torque between 10 and 90%. Every characterization was made in triplicate.

2.3.4. HPLC stability indicating method validation

The HCTZ content in the suspension was measured by Reversed Phase Chromatography (RP-HPLC) by the method described below.

The used chromatographic system (Waters, Millford, MA, USA) consists of a pump, a Model 600 E Multisolvent delivery system,

Table 1
Characterization of suspensions.

F	Wetting agent	Suspending agent (1%, w/w)	pH	Viscosity (cP)	*C* (mg/ml)	%
R	–	Hydroxypropylmethylcellulose	3.0 ± 0.4	84.5 ± 0.7	1.2 ± 0.3	60 ± 0.1
1	Glycerol 10%	Hydroxypropylmethylcellulose	3.4 ± 0.0	85.7 ± 0.0	1.1 ± 0.1	55 ± 0.3
2	Glycerol 20%	Hydroxypropylmethylcellulose	3.3 ± 0.0	46.4 ± 0.0	0.9 ± 0.1	45 ± 0.3
3	Glycerol 10%	Methylcellulose 1000	3.2 ± 0.0	17.0 ± 0.0	1.3 ± 0.4	65 ± 0.8
4	Glycerol 20%	Methylcellulose 1000	3.5 ± 0.2	18.0 ± 0.0	1.9 ± 0.0	95 ± 0.2

F, formulation; %, percentage of the theoretically calculated and labelled amount of active ingredient per unit volume; R, reference formulation; values are mean±standard deviation.

a 717 plus Autosampler, a 2487 Dual absorbance detector, and a NovaPack C18 column (3.9 mm × 150 mm) packed with 4 μm particles as stationary phase. The data acquisition software used was Millenium32 (Chromatographic Manager, Waters Corporation). The mobile phase was a mixture of methanol/water 05/95 (v/v) adjusted to pH 4.5 with acetic acid 1 M, at a flow rate of 1.5 ml/min at room temperature, and UV detection at 224 nm was used (Daniels and Vanderwielen, 1981). All chemicals and reagents were of high-performance liquid chromatography (HPLC) grade. All solvents were filtered with 0.45 μm pore-size filters (Millipore, Billerica, MA, USA). The mobile phase was filtered and degassed.

In order to validate the analytical method (ICH Q2(R1), 2005), five HCTZ standard solutions were prepared at concentrations of 2.5–20 μg/ml. Every sample was analyzed six times. The variance analysis (ANOVA) of the linear regression confirmed the linearity of the method through rejection of the null hypothesis of linearity deviation for a significance level of 0.05 ($\alpha = 0.05$); the coefficient of variation of the method was 4.0%. The equation of the regression line was: area = 91,071.7 × *C*; $r = 0.9989$ ($n = 30$), with a residual standard error of 38,470. The method precision (as repeatability) was 0.69%, it was determined by a six times analysis of the same HCTZ sample. System accuracy was expressed as percentage recovery by the assay of a known added amount of drug, being the mean value 101 ± 4.3% ($n = 9$). The detection and quantitation limits, based on the standard deviation of the response and slope, were 1.4 and 4.3 μg/ml respectively. A robustness test was performed to examine the effect of operational parameters on the analysis results. The flow-rate (1.5 ± 0.05 ml/min), injection volume (20 ± 1 μl), temperature (20.7 ± 1.5 °C), mobile phase composition (5 ± 0.1 for methanol, 95 ± 1 for water, v/v), pH (4.5 ± 0.3) and column performance over time were determined in order to confirm the method's robustness. To calibrate the RP-HPLC system and monitor its performance, we analyze an HCTZ solution sample daily as standard. The estimated area for standard concentration was 1,834,165 with a RSD of 1.6%. The upper and lower limits for the control chart were established at ±3SD of this value, taking as standard deviation the value obtained from variance of the analytical method. Fig. 1 shows the control chart for the method, where the peak's area holds between the established limits every time. The chromatographic conditions (e.g. flow-rate, relative mobile phase composition) and column performance, especially the tailing factor and column efficiency were checked. When necessary, corrective action was taken.

2.3.5. Dose content uniformity

The compounded preparations have to be prepared by ensuring that every preparation shall contain no less than 90% and no more than 110% of the theoretically calculated and labelled amount of active ingredient per unit weight or volume (The United States Pharmacopeial Convention, 2007). Every control was made in triplicate after the dilution with mobile phase of 5 ml of suspension until the concentrations interval of standards solutions studied. This dose volume was taken with an oral syringe after the suspension was shaken (Wening and Breitkreutz, 2011).

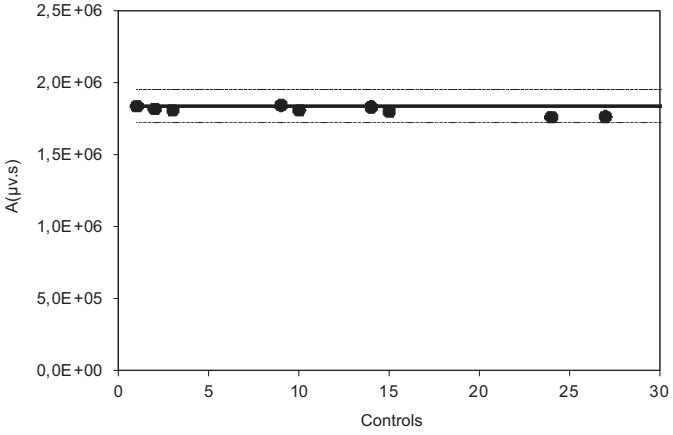

Fig. 1. Control chart for RP-HPLC method.

2.4. Stability study

An HCTZ stability study in opaque glass and light protected bottles during 30 days at 5, 25, 40 and 80 °C was made by means of HPLC. The 5 °C was considered the normal refrigeration temperature for the suspension. 40 and 80 °C were used to study the stability of the suspension in an extreme temperature of storage. Three samples of every HCTZ formulation batch were taken at predetermined intervals.

3. Results and discussion

Fig. 2 shows the chromatogram of the pure HCTZ obtained by the RP-HPLC method. Only one peak with an elution volume of 3.75 ml

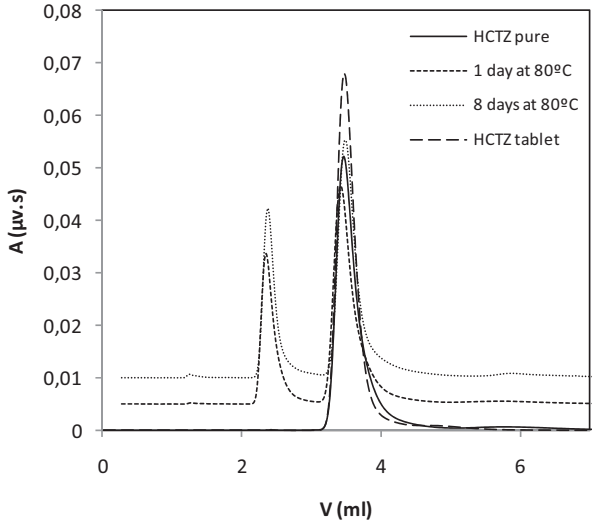

Fig. 2. HCTZ pure chromatographic peak (continuous line), after the drug was extracted from a commercial tablet, and at 1 and 8 days after the drug was stored at 80 °C. The plot of the results at 80 °C assay is up-shifted 0.005 units on the *Y*-axis.

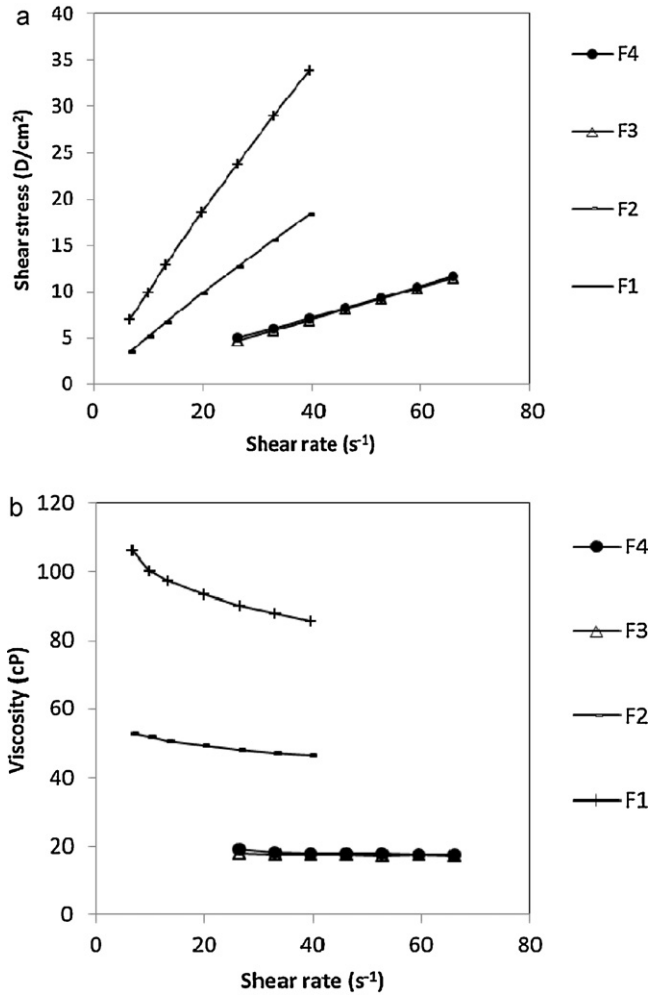

Fig. 3. Evolution of the shear stress with the shear rate (a) and the viscosity with the shear rate (b) of the different formulations.

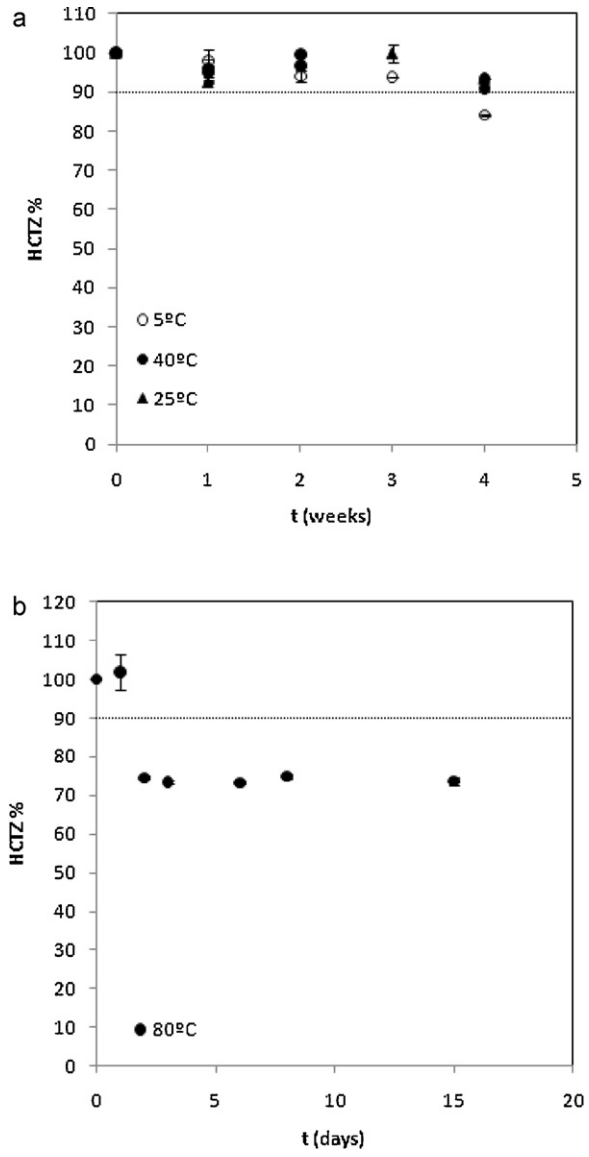

Fig. 4. Progression of the HCTZ percentage with time by HPLC after the formulation 4 was stored at 5, 25, 40 °C (a) and 80 °C (b).

was detected. In the same figure we can show the chromatogram aspect after extracting the drug from a commercial tablet and after one and eight days storing at 80 °C. Only at this extreme temperature, additional chromatographic specie appears at 2.25 ml.

Table 1 shows the physical characterization summary of the different suspensions. The measured pH was in the interval between 3.0 and 3.5 for the five suspensions, which guarantees the drug stability interval. Hydrochloric acid in the reference formulation (R) was replaced with another buffer, citric acid, a less harmful buffer to be used at pharmacies and hospitals.

The low HCTZ proportion (0.2%, w/v) used in the suspension and mainly the absence of a wetting agent in the reference formulation were the cause of the introduction of other components. Although propylene glycol is normally the most effective wetting agent, it is not recommended by the EMA (2006). Because of this, glycerol was used instead at two percentages so as to know whether it was enough to wet all the dose of the drug in the formulation. The less amount of glycerol in formulation 1 with respect to formulation 2 resulted in doubling the increase in the viscosity value of the final suspension. The reference suspension shows a high viscosity, similar to suspension 1. Suspensions 1 and 2 had a non-Newtonian and time independent fluidity wherein the viscosity of every system decreases with an increasing shear rate and with a reversible behaviour. The non-Newtonian suspensions were fitted to different mathematical models and they behaved as Bingham materials, as other oral suspensions with a yield value of about 1.96 ± 0.4 and $0.69 \pm 0.4\ D/cm^2$ for suspensions 1 and 2 respectively (Gao et al., 2004; Santoveña et al., 2010). The dose percentage recovery in these latter suspensions was less than formulations 3 and 4 (see Table 1). Then, the solid was not well dispersed in the formulation using hydroxypropylmethylcellulose which provides a high viscosity value. The suspension viscosity can stabilize the suspension but if it is high, it can make the drug dispersion more difficult. Due to the high viscosity value obtained with hydroxypropylmethylcellulose another suspensor type, methylcellulose 1000, was included in the same proportion. Formulations 3 and 4 had a Newtonian behaviour, a linear relationship between the stress and shear rate and a viscosity value independent of the shear rate (Fig. 3a and b). The poor wetting of HCTZ in formulation 3 produces the inappropriate interface tension value between the drug in solid state and the rest of the formulation in liquid state to obtain the right solid dispersion. Only formulation 4 had a percentage above 90% of the theoretically calculated and labelled amount of active ingredient per unit volume.

The particle size was not a significant factor to ensure the dose uniformity since the particle size was similar for all suspensions $106 \pm 4.4\ \mu m$.

The wetting agent percentage used and the viscosity of the final suspension establish the dose content uniformity. When the drug content of the formulation 4 was doubled with the aim of increasing the drug proportion (4 mg/ml), the recovery percentage obtained was the same (95 ± 0.1%).

By HPLC, for formulation 4 we can show how the drug keeps its initial drug concentration over 90% after 3 weeks at 5 °C, 25 °C and 40 °C (see Fig. 4a) and it is considerably stable (Glass and Haywood, 2006). The initial and rapid degradation at all studied temperatures coincides with the proportion of HCTZ that must be dissolved. This justifies that the formulation is compounded as a suspension and not as a solution because HCTZ seems to be more stable in suspension. An additional chromatographic species appears at 80 °C as a result of its degradation after it is stored at this extreme temperature (Figs. 2 and 4b).

4. Conclusions

The different suspensions studied showed a pH in the HCTZ stability interval and a similar particle size. Formulation 4 was the only suspension which had a concentration near the theoretically calculated and labelled amount of active ingredient per unit volume (2 mg/ml), with a recovery percentage between 90 and 110%. The formulations of drugs in low proportion can cause a non homogeneous drug–excipient mixture and consequently a bad drug distribution.

By HPLC we can confirm the stability of formulation 4 during 3 weeks when it is stored at 5 °C and light protected.

The Newtonian behaviour of formulation 4 ensures the constant viscosity value. This fact and the adequate percentage of wetting agent used help to take the correct dose of a class III BCS drug when it is formulated at low proportion, and after the suspension is shaken whenever the formulation is strictly made according to its SOP.

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