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Pre-formulation and Stability Study of 20-mcg Clonidine Hydrochloride Pediatric Capsules

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OBJECTIVE Clonidine hydrochloride is an antihypertensive, centrally acting α_2 adrenergic agonist with various pediatric indications. For pediatric patients, 20-mcg clonidine hydrochloride capsules can be compounded from commercial tablets or from a pre-compounded titrated powder. These methods should be compared to ensure the best quality for the high-risk patients, and a beyond-use date should be established.

METHODS Eight experimental batches were made from commercial tablets and 8 were made from microcrystalline cellulose (MCC)-based titrated powders. Quality controls were performed to determine the best compounding protocol. Stability study was conducted on capsules compounded with the best method.

RESULTS Of 8 batches manufactured from commercial tablets, 7 were compliant for both clonidine mean content and content uniformity, whereas 7 of 8 batches manufactured from titrated powders were not. A clonidine loss during compounding was evidenced by surface sampling analyses. Clonidine hydrochloride 20-mcg capsules' mean content remained higher than 90% of initial content for 1 year when stored at 25°C with 60% relative humidity and protected from light.

CONCLUSIONS Commercial tablets should be preferred to 1% clonidine hydrochloride and MCC titrated powder made from the active pharmaceutical ingredient. Twenty-microgram clonidine hydrochloride capsules made from commercial tablets are stable for 1 year when stored under managed ambient storage condition.

ABBREVIATIONS API, active pharmaceutical ingredient; EP, European Pharmacopoeia; HPLC, high-performance liquid chromatography; MCC, microcrystalline cellulose; RH, relative humidity

KEYWORDS capsules; chromatography; high-pressure liquid; clonidine; drug compounding; quality control

Introduction

Clonidine hydrochloride is an antihypertensive α_2 agonist with analgesic and sedative effects. It has several off-label indications in pediatric practice, both in anesthesiology and intensive care,¹ and for the management of neonatal abstinence syndrome.^{2,3} It can be orally administered to neonates at various dosages.

Clonidine hydrochloride tablets are available in several dosages, but a pediatric commercial drug is lacking. In the literature, liquid formulations and their stability have already been described (Table 1).

These liquid formulations allow for the administration of various clonidine hydrochloride doses, which can be an advantage if dosage regimens need to be frequently adjusted. However, such formulations can be a source of iatrogenic events.¹⁰⁻¹² Moreover, for low-weight neonates, some prescribers sometimes prefer solid formulations (capsules) to avoid preservatives and/or hyperosmotic liquid administrations.¹³

Therefore, our pharmacy department was asked for 20-mcg clonidine capsules compounding. In the literature, the stability of 0.2 mg·g⁻¹ clonidine powder compounded from commercial tablets and lactose monohydrate was studied, but the stability of capsules was not evaluated.¹⁴ Because the French National Drug Agency requires pharmacists to prioritize the compounding with an active pharmaceutical ingredient (API) versus a commercial drug,¹⁵ we initially tried to make capsules from 1% (wt/wt) clonidine hydrochloride titrated powder. The first batches were analyzed by our quality control laboratory and were all underdosed. One batch was compounded from commercial clonidine hydrochloride tablets and was compliant. We decided to study this phenomenon in a pre-formulation study presented herein, and to evaluate the stability of 20-mcg clonidine hydrochloride capsules made from commercial tablets.

Materials and Methods

Materials. Clonidine hydrochloride European

Table 1. Formulations and Stability of Clonidine Hydrochloride Liquid Formulations

Reference	Content, mcg·mL ^{-1*}	Excipients	Stability
Ensom ⁴	10	Oral Mix or Oral Mix SF	4°C = 91 days; 25°C = 91 days
Polonini ⁵	10	Syrspend SF pH4	2°C–8°C = 90 days; 20°C–25°C = 90 days
Potier ⁶	10	Inorpha	2°C–8°C = 60 days; 20°C–25°C <30 days
Sauberan ⁷	10	Simple syrup	2°C–8°C = 35 days
Verlhac ⁸	10	WFI, potassium sorbate 3 mg·mL ⁻¹ , potassium citrate 3.46 mg·mL ⁻¹ , citric acid 2 mg·mL ⁻¹ , sodium saccharinate 0.26 mg·mL ⁻¹	2°C–8°C = 90 days; 23°C–27°C = 30 days
Merino-Bohórquez ⁹	20	Purified water 50 mL, potassium sorbate 3 mg·mL ⁻¹ , citric acid (pH 4–5), simple syrup qs 100 mL	2°C–8°C = 90 days; 23°C–27°C = 90 days

Pharmacopoeia (EP) reference standard (EDQM, ref. C2400000) was used for method validation. Clonidine hydrochloride secondary standard (LGC, Mikromol, ref. MM098300-0250) compared with the EP standard at first use was used for quality control during the stability study. Clonidine hydrochloride API (Fagron) was used for forced degradation experiments and compounding processes. Capsules were compounded with a semiautomatic capsule-filling machine (Cooper, Melun, France).

Disintegration tests were performed according to the protocol described in the US Pharmacopoeia¹⁶ and EP¹⁷ on an Agilent 100 automated disintegration apparatus. The chromatographic method was performed on an automatic high-performance liquid chromatography (HPLC) Dionex Ultimate 3000 with an ultraviolet diode array detector. The apparatus was connected to an HP 1702 computer equipped with chromatographic data processing software (Chromeleon Chromatography Management System, version 6.80 SRH Biold 3161, 1994–2011, Dionex Corporation). Quality control conformity was established with EP specifications for both uniformity of dosage units (EP, 2.9.6. not more than one individual content is outside the limits of 85% to 115% of the mean content and none is outside the limits of 75% to 125% of the mean content)¹⁸ and disintegration tests (EP, 2.9.1; all samples disintegrate before 30 minutes).¹⁷ For the assay value, as EP has monographs for the APIs but not yet for finished products; US Pharmacopoeia normal values from “clonidine hydrochloride tablets” were considered as conformity standards (90%–110% of theoretical content).

HPLC Analytic Conditions and Forced Degradation Study. Clonidine hydrochloride quantification method by HPLC was developed, validated, and found to be stability-indicating. Briefly, clonidine hydrochloride separation was performed using a Kromasyl C18 column with 5- μ m particle size (250 \times 4.6 mm). A total of 1.6

g of potassium dihydrogen phosphate (KH₂PO₄) was weighted, then solubilized in 400 mL of ultrapure water, and the pH was adjusted to 4.0 with 85% phosphoric acid. The mobile phase (pH 4 buffer: methanol, 70:30) was used at a flow of 1.0 mL·min⁻¹ in isocratic mode for 10 minutes. The injection volumes were 10 μ L and the wavelength was 210 nm.

The following parameters were evaluated in the method validation: linearity, repeatability (intraday variation), intermediate precision (interday variation), accuracy, and uncertainty. Intraday (n = 15 samples for each concentration) and interday (n = 18 samples for each concentration) measurements were performed at 3 concentrations: 1.00, 2.50, and 2.75 mcg·mL⁻¹. Linearity was investigated and demonstrated with 5 calibration curves between 0.50 and 10 mcg·mL⁻¹. The results are summarized in the Supplemental Material.

To determine clonidine hydrochloride in 20-mcg capsules, 1 capsule was opened, solubilized in 8 mL of mobile phase, vortexed for 1 minute, and centrifugated for 5 minutes (2000 rpm). One mL of the supernatant was filtered (Millipore 0.45 μ m) and the resulting solution (theoretical clonidine hydrochloride concentration 2.5 mcg·mL⁻¹) was analyzed. During pre-formulation study, 10 capsules per batch were analyzed once. During stability study, 3 capsules per batch were analyzed once.

To determine the clonidine hydrochloride content in the 1% titrated powders, 50 mg of titrated powder (500 mcg of clonidine hydrochloride) were weighed and suspended in 10 mL of methanol. The solution was vortexed for 1 minute and centrifugated for 5 minutes at 2000 rpm. One milliliter of the supernatant was filtered (Millipore 0.45 μ m) and 100 μ L of the filtered solution was added to 1900 μ L of mobile phase. The resulting solution of theoretical clonidine hydrochloride concentration 2.5 mcg·mL⁻¹ was analyzed once.

Quantification of clonidine hydrochloride on the com-

Table 2. Clonidine Hydrochloride Forced Degradation Study* Preceding Stability Study

Experimental Conditions	API Degradation, %	Degradation Products' Retention Times, min
Heat (70°C, 10 days)	8	4.0, 5.6
Light (sunlamp, 16 days)	0	—
Oxidation (H ₂ O ₂ , 30%; 1.5 hr)	6	3.2–4.4, 6.0, 7.2, 8.1, 11.8
Acid (HCl, 0.5 N; 1.25 hr)	6	—
Alkaline (NaOH, 1 N; 1.5 hr)	15	4.0, 4.9, 5.6, 7.3

API, active pharmaceutical ingredient; H₂O₂, hydrogen peroxide; HCl, hydrochloride; NaOH, sodium hydroxide

* See text for details.

pounding surfaces was done by surface sampling with the same analytic conditions than previously described. Briefly, 2 mL of dimethyl sulfoxide was poured to the test surface, and gently shaken for 1 minute. One milliliter of dimethyl sulfoxide was recovered, half diluted with mobile phase, and analyzed by HPLC-ultraviolet after filtration (Millipore 0.45 µm). Four different surfaces were analyzed for each batch: spatula and weighing cup, mortar and pestle, graduated cylinder, and capsule-filling machine.

Forced degradation studies were performed for clonidine hydrochloride under several experimental conditions: thermal, oxidation, light, alkaline, and acidic conditions. Each condition was tested in a single experiment. For thermal conditions, a 2.5 mcg·mL⁻¹ clonidine hydrochloride solution was placed in an oven at 70°C for 10 days, and for light conditions, it was placed under irradiation from a sunlamp for 16 days. For oxidation conditions, a 6.25 mcg·mL⁻¹ clonidine hydrochloride solution was made in hydrogen peroxide (final concentration 30%) and analyzed after 1.5 hours. For alkaline and acidic conditions, the same concentrations were made in, respectively, sodium hydroxide (final concentration sodium hydroxide, 1 N; analysis after 1.5 hours) and hydrochloric acid (final concentration hydrochloric acid, 0.5 N; analysis after 1.25 hours), followed by a 1:1 dilution with the mobile phase just before analysis.

Pre-formulation and Stability Study Design. First, 8 experimental batches of 1% (wt/wt) clonidine hydrochloride titrated powder were compounded by qualified personnel (pharmacy technician or interns qualified for compounding by annual skills training). A total of 100 mg of clonidine hydrochloride was weighted and placed in a mortar. A spatula tip of red carmine (tracer dye to visually inspect the homogeneity of the mixture) was added and a total weight of 9.9 g of microcrystalline cellulose (MCC) was added very gradually while the mixture was gently mixed with a pestle. Next, 8 batches of 30 capsules of 20 mcg of clonidine hydrochloride were made from the titrated powder. Sixty milligrams of clonidine titrated powder were weighted. Two milliliters of MCC were added to a 25-mL measuring cylinder, followed by the titrated powder, and finally the MCC in sufficient

quantity for 6.30 mL. The mixture was transferred to a small-size mortar with a red carmine spatula tip for gentle mixing, and batches of 30 capsules (size 4, ivory) were compounded with a semiautomatic capsule-filling machine.

Eight batches of 30 capsules of 20 mcg of clonidine hydrochloride were also made from commercial tablets (0.15 mg of clonidine hydrochloride). Four tablets were crushed with a pestle in a mortar. Two mL of MCC was added to a 25-mL measuring cylinder, followed by the crushed tablets, and finally MCC in sufficient quantity for 6.30 mL. The mixture was transferred to a small-size mortar with red carmine spatula tip for gentle mixing and batches of 30 capsules (size 4, ivory) were compounded with a semiautomatic capsule-filling machine (Cooper).

For the stability study, 3 batches of 100 capsules were compounded from tablets. Twenty micrograms of clonidine hydrochloride capsules were stored in a climatic chamber (25°C with 60% relative humidity [RH]) for 1 year after compounding. Clonidine hydrochloride content was assessed by analysis of 3 randomly collected capsules from each batch (9 measures), at time zero, and at 1, 2, 3, 4, 6, and 12 months. Disintegration tests were conducted on 6 randomly collected capsules (2 capsules from each batch) at time zero, and 1, 3, 6, and 12 months.

As reported in several publications,^{19–22} a significant change in the API content was defined as a “10 percent change in assay from its initial value.”

Results

Forced Degradation Study. The forced degradation study showed no interference with dosing method, with the appearance of several peaks corresponding to degradation products as reported in Table 2. The chromatograms are presented in the Supplemental Material.

Pre-formulation Study. All batches of clonidine hydrochloride capsules manufactured from tablets showed clonidine hydrochloride content conformity (18–22 mcg), whereas only 2 batches made from titrated powders were compliant. Six of 8 of these batches

Table 3. Comparison of Conformity for Clonidine Hydrochloride Capsules Manufactured From Tablets and From Titrated Powders*

Capsule Compound Type and Batch	Mean Clonidine HCl Content \pm SD, mcg	Homogeneity [†]		Conformity, Yes or No
		Capsules Between 75% and 85% or 115% and 125% of Mean Content	Capsules Lower Than 75% or Higher Than 125% of Mean Content	
From tablets				
1A	19.4 \pm 1.3	0	0	Y
2A	18.8 \pm 0.9	0	0	Y
3A	19.3 \pm 1.5	0	0	Y
4A	19.1 \pm 2.9	2	1	N
5A	19.6 \pm 0.9	0	0	Y
6A	21.1 \pm 0.7	0	0	Y
7A	20.1 \pm 1.5	0	0	Y
8A	18.9 \pm 1.1	0	0	Y
Mean value	19.5 \pm 1.3			
From titrated powder				
1B	14.5 \pm 0.8	0	0	N
2B	11.7 \pm 1.0	1	0	N
3B	13.4 \pm 1.2	1	0	N
4B	15.2 \pm 0.7	0	0	N
5B	18.8 \pm 1.4	1	0	Y
6B	16.8 \pm 1.6	1	0	N
7B	18.2 \pm 2.5	1	1	N
8B	16.1 \pm 0.7	0	0	N
Mean value	15.6 \pm 1.2			

HCl, hydrochloride

* The preparation fails to comply with the test if more than 1 individual content is outside the limits of 85% to 115% of the mean content or if 1 individual content is outside the limits of 75% to 125% of the mean content.¹⁸

[†] See text for details.

were underdosed (clonidine hydrochloride content lower than 90% of theoretical content). Only 1 batch of clonidine hydrochloride capsules manufactured from tablets was not compliant, because of a lack of homogeneity (1 capsule was found with an individual content lower than 75% of the batch mean content) and 1 batch of clonidine hydrochloride capsules made from titrated powders was also not compliant for the same reason (1 capsule was found with an individual content higher than 75% of the batch mean content). The results are summarized in Table 3.

From these results, we first hypothesized that the titrated powders were initially underdosed. A 1% titrated powder used for the underdosed batch 8B was analyzed for its clonidine hydrochloride content, and the result (1.02% wt/wt) corresponded to the theoretical value.

Next, we performed surface sampling on the compounding material after batches compounding. Batches 6B, 7B, and 8B made from titrated powders were analyzed, and batch 8A made from commercial tablets was analyzed. Results are summarized in Table 4.

Given that extraction yields of this method were not studied, the results are only reported on analyzed sample concentration. The limit of quantification was

not assessed in clonidine hydrochloride method validation, because this technique was originally developed only for the drug analysis of known content.

Stability Study. Quantification of clonidine hydrochloride 20 mcg capsules stored at 25°C with 60% RH showed no significant variation up to 1 year (Table 5 and Figure). In addition, the disintegration tests were compliant with EP specifications during the whole study. Finally, the degradation products did not significantly increase during this study, even after 1 year in climatic chamber.

Discussion

Before the stability study, clonidine hydrochloride HPLC dosing method was proved to be stability-indicating.²³ A forced degradation study showed that clonidine hydrochloride was not sensitive to light degradation. Several degradation products were found, but none showed coelution with clonidine hydrochloride.

In the pre-formulation study, clonidine hydrochloride batches compounded from titrated powders were mostly out of pharmacopoeia specifications, with clonidine hydrochloride underdosing ranging from 6% to 41% of the theoretical value. The clonidine hydrochloride content was less than 10% of the theoretical amount for 6 of 8

Table 4. Clonidine Hydrochloride Concentration From Compounding Element Surfaces

	Batch 6B	Batch 7B	Batch 8B	Batch 8A
Spatula and weighing cup, mcg·mL ⁻¹	0.63	<LOQ*	1.12	<LOQ*
Mortar and pestle, mcg·mL ⁻¹	2.89	0.77	4.35	<LOQ*
Graduated cylinder, mcg·mL ⁻¹	1.21	3.04	2.15	0.60
Capsule filling machine, mcg·mL ⁻¹	1.30	0.59	0.57	<LOQ*
Clonidine HCl content, mcg	16.8 ± 1.6	18.2 ± 2.5	16.1 ± 0.7	18.9 ± 1.1

LOQ, limit of quantification

* LOQ was defined as the lowest level of linearity: 0.50 mcg·mL⁻¹.

Table 5. Clonidine Hydrochloride 20-mcg Capsule Content Under Ambient Conditions*

Batch and Content	Capsule	T0	1 mo	2 mo	3 mo	4 mo	6 mo	12 mo
1, clonidine HCl (mcg)	C1	18.9	17.3	18.4	19.0	17.6	17.3	17.9
	C2	18.6	17.6	17.5	17.7	17.5	17.8	18.4
	C3	18.9	18.2	18.1	17.3	17.7	17.8	17.6
2, clonidine HCl (mcg)	C1	19.6	18.0	18.0	18.4	16.8	18.8	18.7
	C2	19.2	17.7	17.6	17.8	17.7	18.7	18.8
	C3	19.4	17.5	17.8	17.2	17.1	17.1	18.2
3, clonidine HCl (mcg)	C1	19.6	19.2	17.4	17.7	18.2	20.2	18.4
	C2	19.7	20.3	17.7	19.5	18.8	18.8	19.8
	C3	19.8	19.8	18.6	19.2	18.1	19.3	18.9
Mean ± SD	19.3 ± 0.4	18.4 ± 1.1	17.9 ± 0.4	18.2 ± 0.8	17.7 ± 0.6	18.4 ± 1.0	18.5 ± 0.6	

* Samples were stored at 25°C with 60% relative humidity and were protected from light.

batches, whereas 1 percent (wt/wt) titrated powders had a clonidine hydrochloride content in agreement with the theoretical values.

Sampling of compounding equipment (spatula, weighting cup, mortar, pestle, capsule-filling machine, graduated cylinder) proved that when clonidine hydrochloride 20-mcg capsules compounding is made from MCC titrated powder, a higher concentration of clonidine hydrochloride is found from object sampling surface than when compounding is made from commercial tablets. This API loss during compounding has been previously studied with several other APIs, and the authors found that the mortar surface was the main cause of API loss.²⁴ In addition, they found that the molecular structure of API influences the percent of API loss. Furthermore, D'Hondt and colleagues²⁴ noted for the same dosage of dexamethasone, 2 compounding methods (self-made trituration and compounding from commercial tablets) were described to have only very slight differences in percentage of API loss.²⁴ In our study, we found, for the same dosage of clonidine hydrochloride, a higher difference between self-made titrated powder and compounding from commercial tablets. The influence of clonidine molecular structure, as well as the very low theoretical dosage of capsules (20 mcg), could explain the high

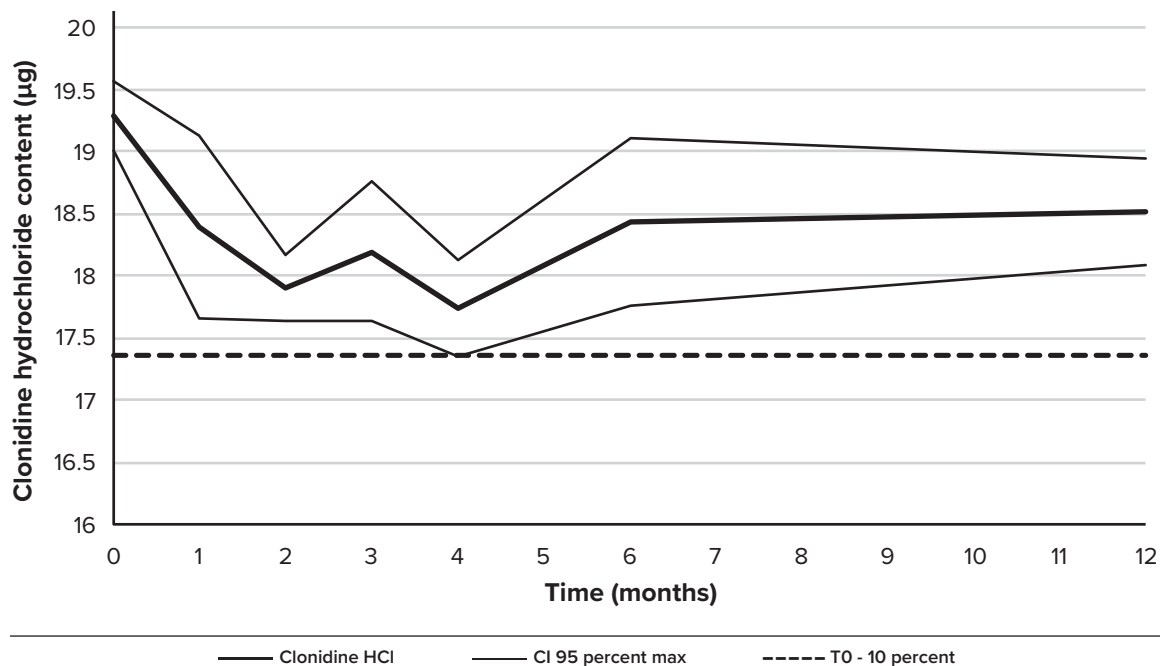
rates of API loss during compounding. The influence of the excipients in the commercial tablet's formulation, as well as the differences between the crystal structures of clonidine hydrochloride API in the tablets and in crude material may explain the difference in API loss between the 2 compounding techniques. The other excipients' influence on API loss has not been investigated.

Our study suffers from 2 limitations. First, during surface sampling analyses, because extraction yields were unknown, the exact amount of clonidine hydrochloride loss could not be determined. Second, even if a difference in API loss depending on the compounding process was evidenced, we could only speculate on the origin of this difference.

Conclusion

The results of our study demonstrate the preferability of using the commercial tablets to compound 20-mcg clonidine capsules and to most likely avoid using a pre-compounded titrated powder. Using the methods described here we found a difference between batch compliance depending on the protocol used. The best protocol (capsules made from commercial tablets) was chosen to perform a stability study. Our results show that clonidine hydrochloride 20-mcg capsules stored at 25°C

Figure. Clonidine hydrochloride 20-mcg capsules content under ambient conditions (95% CI).



with 60% RH are stable for 1 year. We recommend the use of commercial clonidine tablets and MCC as excipient to compound 20-mcg capsules with a beyond-use date of 1 year. These capsules can be prescribed routinely in pediatric practice.

Twenty-microgram clonidine hydrochloride capsules cannot be compounded with 1% (wt/wt) titrated powders and MCC. Such a protocol results in a significant loss in clonidine hydrochloride content. The influence of other excipients has not yet been studied but compounding from commercial tablets seems to be a simpler and a safer alternative. These capsules can be stored for 1 year under managed ambient conditions (15°C–25°C) and can be available in advance for clonidine hydrochloride pediatric indications.

Article Information

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