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► **To cite this version:**

Maya Wasilewski, Christophe Curti, Cyrielle Bouguergour, Camille Panuccio, Patrick Thevin, et al.. Paediatric capsule compounding in hospital practices: by weight or by volume?. *European Journal of Hospital Pharmacy*, 2023, 30 (6), pp.363-366. <10.1136/ejhpharm-2021-003065>. <hal-04483078>

HAL Id: hal-04483078

<https://hal.science/hal-04483078v1>

Submitted on 29 Feb 2024

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Paediatric capsule compounding in hospital practices: by weight or by volume?

Maya Wasilewski,¹ Christophe Curti ,^{1,2} Cyrielle Bouguergour,¹ Camille Panuccio,¹ Patrick Thevin,¹ Nicolas Primas,^{1,2} Edouard Lamy,^{1,3} Patrice Vanelle^{1,2}

ABSTRACT

Objective Capsule compounding is common for paediatric patients. In Europe, pharmacists often use a volume-based method whereas, in the USA, the weight-based method prevails. These two methods should be compared in order to help hospital pharmacists to make their choice.

Methods We evaluated the difference between the volume-based method and the weight-based method with 10 mg spironolactone capsules. Six independent batches were made with each technique and their conformity was evaluated with a high-performance liquid chromatography assay.

Results The weight-based method showed superiority over the volume-based method for the following parameters: spironolactone content homogeneity, total weight content homogeneity, batch reproducibility and batch conformity. No differences were seen in spironolactone content between the two methods, but an overall trend towards underweighing the excipient was found with the volume-based method.

Conclusions Capsule compounding with the weight-based method increases the quality of the resulting formulation. The weight-based method requires knowledge of the galenic parameters of the active pharmaceutical ingredient and excipients, but should be preferred to the volume-based method.

the present study qualified personnel made six batches of spironolactone 10 mg capsules with the weight-based method and six batches with the volume-based method, and the analytical differences between the two batches were studied.

MATERIALS AND METHODS

Spironolactone 10 mg capsules were compounded by six qualified staff members (pharmacy technicians and pharmacy residents). Each staff member made two batches of 100 capsules, one with the volume-based method and the other with the weight-based method.

First, 1000 mg of micronised spironolactone (Inresa, Bartenheim, France) was weighed on a precision balance (Precisa XT 220 A, Precisa, Poissy, France). Then, for the volume-based method, spironolactone was gently mixed with 1000 mg microcrystalline cellulose (MCC; Cooper, Melun, France). The mixture was poured into a 25 mL measuring cylinder and MCC was added up to 21 mL.

For the weight-based method, the bulk density (Bd) and tapped density (Td) of pure spironolactone (Bd=0.17 g/mL; Td=0.28 g/mL) and MCC (Bd=0.34 g/mL; Td=0.48 g/mL) were first evaluated in our laboratory as reported in the literature.⁷ We then performed calculations without considering the possible granulometry differences between the two powders. To fill 100 size 4 capsules (V=21 mL), 1000 mg spironolactone was weighed and was supposed to fill 3.6 mL (weight/Td). To fill 17.4 mL, 8300 mg MCC was weighed (17.4 × Td). The powder was gently mixed and its bulk and tapped densities were evaluated. Bd was found to be equal to 0.34 g/mL and Td to 0.42 g/mL. To fill 21 mL, the tapped density evaluation allowed us to calculate a total weight of the spironolactone/MCC mixture equal to 8.8 g (21 × Td). Thus, 1000 mg of micronised spironolactone and 7800 mg of MCC were weighed on a precision balance.

The protocol was then similar for the two methods: spironolactone and MCC were transferred to a small size mortar, a spatula tip of red carmine was added and the mixture was gently mixed with a pestle. Finally, batches of 100 capsules (size 4, blue/white) were made with a semi-automatic capsule filling machine (Cooper).

Spironolactone quantification by high-performance liquid chromatography (HPLC) was based on a previously described stability-indicating method.¹⁰ The mobile phase (ultrapure water:methanol 34:66) was used in isocratic mode at a flow rate of 1.6 mL/min for 15 min. The wavelength

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INTRODUCTION

Paediatric patients often require non-commercial drug dosages. Drug compounding by pharmacists remains the gold standard for these patients, but practices differ widely around the world. Differences in pharmaceutical compounding reference sources between countries¹ and compounding practices in Europe² have been described. The manual preparation of capsules in Europe is often performed with a volume-based method,³⁻⁶ which involves weighing of the active pharmaceutical ingredient (API) and excipient added to the volume required to fill the capsules. In the USA a weight-based method prevails,^{7,8} and the volume required to fill the capsules must be converted to the mass of the excipient/API mixture. This calculation requires knowledge of the density of the mixture.

The weight-based method is supposed to increase batch reproducibility as the weight of each component of the preparation remains the same between batches. However, even though several published papers have assumed the superiority of the weight-based method,^{5,9} to our knowledge, the differences between the two methods have never been studied. Therefore, in

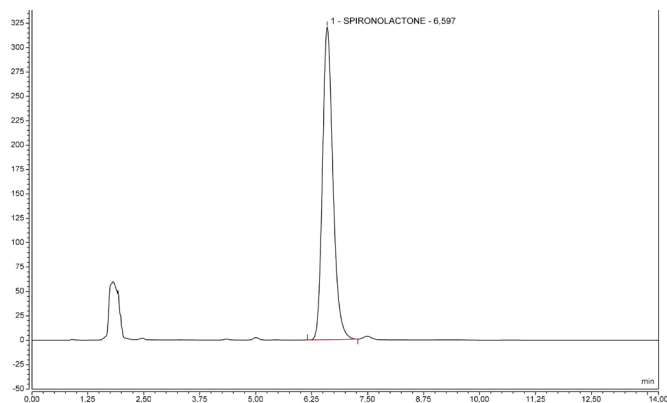


Figure 1 Representative spironolactone chromatogram.

was 254 nm and injection volumes were 20 μ L. The spironolactone retention time was 6.6 min (figure 1).

The following parameters were evaluated in the method validation: linearity, repeatability (within-day variation), intermediate precision (between-day variation) and accuracy.

Within-day and between-day measurements were performed at two concentrations (250 and 275 μ g/mL). For within-day measurements, at least 15 samples for each concentration level were analysed on the same day. Between-day measurements were performed at the same concentrations on at least 18 samples on three consecutive days. Linearity was investigated with seven calibration curves between 6.25 μ g/mL and 500 μ g/mL and was demonstrated between 25 μ g/mL and 500 μ g/mL. The results are summarised in table 1.

Capsule samples were treated as follows: 10 mg spironolactone capsules were opened and 40 mL of dimethyl sulfoxide was added. The solution was vortexed (5 min) and centrifuged (2000 rpm, 5 min). The supernatant was analysed without filtration.

For each analysis, two independent quality controls (QC1 and QC2) were performed using spironolactone European Pharmacopoeia (EP) Primary Standard (Sigma-Aldrich, St Louis, USA). QC1 was analysed once and QC2 was analysed six times. QC1 and QC2 were used to quantify the spironolactone capsule content and for System Suitability Test.

For each batch, 10 capsules were analysed by HPLC-UV to determine the uniformity of dosage units and mean amount of spironolactone, and 20 capsules were destructively weighed to determine mass uniformity. Uniformity of conformity of the dosage units was established according to EP specifications (2.9.40), with calculation of the acceptance value (AV) using the EP formula. As detailed in the EP, the maximum allowed AV is equal to 15.0. In the EP, if the AV is higher than 15.0, 20 more capsules should be analysed and the resulting AV determined. In the present work, we assume to have chosen stricter criteria (if the AV is higher than 15.0 after the first analysis, the batch is non-compliant and 20 additional capsules are not analysed)

Table 1 Repeatability, intermediate precision and accuracy

Samples	Repeatability (% RSD within-day) (n=15)	Intermediate precision (% RSD between-day) (n=18)	Accuracy (bias in %) (n=18)
Spironolactone 250 μ g/mL	0.851%	3.399%	-0.923%
Spironolactone 275 μ g/mL	2.140%	1.472%	-0.035%

RSD, relative standard deviation.

Table 2 Spironolactone content and comparison of content uniformity

	Volume-based method		Weight-based method	
	API content (mg)	Acceptance value	API content (mg)	Acceptance value
Compounder 1	9.74 \pm 0.34	9.28	9.84 \pm 0.20	4.94
Compounder 2	9.64 \pm 0.28	8.75	9.58 \pm 0.19	7.18
Compounder 3	9.20 \pm 0.47	17.73*	9.71 \pm 0.40	10.92
Compounder 4	10.09 \pm 0.54	12.95	9.64 \pm 0.30	9.41
Compounder 5	9.84 \pm 0.48	11.55	9.85 \pm 0.29	6.94
Compounder 6	9.63 \pm 0.44	12.73	9.53 \pm 0.25	9.13
Mean value	9.69 \pm 0.30	12.16 \pm 3.23	9.69 \pm 0.13	8.09 \pm 2.14
Theoretical value	10.00	<15.00	10.00	<15.00

*Non-compliant with EP 2.9.40.

to compare the results obtained on only 10 capsules per batch. The mean amount of spironolactone conformity was established between 9.5 and 10.5 mg (\pm 5% of the theoretical amount). Mass uniformity conformity was established according to EP specifications (2.9.5).

RESULTS

The analyses showed that 10 of the 12 compounded batches followed the EP specifications. One batch done with the volume-based method had an acceptance value higher than 15% (compounder 3) and another one, also done with the volume-based method, failed the mass uniformity test (more than two capsules with an individual mass which differs by more than \pm 10% from the mean mass value).

The mean content of spironolactone did not differ between the volume-based method and weight-based method, but the SD was found to be higher with the volume-based method, reflecting less uniformity. This superiority of the weight-based method was confirmed as the mean acceptance value was higher for the volume-based method (12.16 \pm 3.23 vs 8.09 \pm 2.14). Furthermore, regardless of the compounder, the acceptance values were higher for the volume-based method. Detailed results of spironolactone content and content uniformity are shown in table 2.

The mass uniformity results show that, regardless of the compounder, the mean content weight was lower for the volume-based method, resulting in a lower mean value and higher standard deviation (77.72 \pm 7.31 vs 86.85 \pm 1.04). The detailed results are shown in table 3.

DISCUSSION

Our findings support the superiority of the weight-based method over the volume-based method for compounding 10 mg spironolactone capsules. The API and excipient are weighed during the weight-based method, whereas during the volume-based method the quantity of excipient is added by volume measurement involving a tamping step. As this is the only difference between the two methods, the batch variability observed with the volume-based method can be correlated to this volume measurement step. The weight-based method involves a more reproducible protocol which yields more reproducible batches. Nevertheless, for 10 mg spironolactone capsules it also shows better results on several parameters used to evaluate batch conformity.

With the volume-based method, the amount of excipient can vary from batch to batch. In the present study the mean content of spironolactone did not differ with the volume- or weight-based method (9.69 \pm 0.30 mg and 9.69 \pm 0.13 mg). However,

Table 3 Mass uniformity comparison

	Volume-based method	Weight-based method
	Mean content weight (mg)	Mean content weight (mg)
Compounder 1	85.57±3.70	87.72±2.93
Compounder 2	78.52±1.75	86.72±1.96
Compounder 3	72.03±4.74	87.78±5.85
Compounder 4	66.64± 6.69*	85.45±5.31
Compounder 5	84.68±4.58	87.66±2.32
Compounder 6	78.90±4.83	85.78±3.17
Mean value	77.72±7.31	86.85±1.04
Theoretical value	–	88.00

*Non-compliant with EP 2.9.5.

batch uniformity was significantly lower with the volume-based method (mean AV 12.16±3.23) than with the weight-based method (mean AV 8.09±2.14). The worse results for the mean content weight and mean weight uniformity with the volume-based method are consistent with these results.

With 10 mg spironolactone capsules, the volume-based method also results in higher SD for mean API content and mean content weight, which translates into greater batch-to-batch variability.

Our study has several limitations. First, this comparison was done with 10 mg spironolactone capsules, but further work is needed on other APIs and dosages to confirm the superiority of the weight-based method for capsule compounding. We decided to perform this work with two other APIs currently compounded as capsules in our hospital: pilocarpine 5 mg and nicardipine 2 mg. The results shown in online supplemental file 1 show the same tendency of superiority of the weight-based method over the volume-based method (pilocarpine 5 mg capsules: mean AV values 10.15±4.43 for the weight-based method vs 13.52±1.62 for the volume-based method; nicardipine 2 mg capsules: AV mean values 9.91±2.10 for the weight-based method vs 14.31±1.03 for the volume-based method).

Second, the quality controls were performed only on the capsules and not on the API/MCC mixtures. Therefore, variability of the mixtures before compounding was not proved, and the differences observed between the two methods could come from random compounding errors. However, as a global tendency in better acceptance values with the weight-based method was identified in six experiments with different compounders, we can strongly assume that the weight-based method is better than the volume-based method for compounding 10 mg spironolactone capsules, whatever the reason.

Finally, the weight-based method we studied was based on the experimental determination of the tapped density of the mixture spironolactone/MCC at the selected concentration to

make 10 mg capsules. This tapped density cannot be extrapolated for other dosages as spironolactone and MCC have different granulometry (100% of the micronised spironolactone particles were ≤30 µm while 50% of MCC particles were >32 µm according to the manufacturer's certificate). The tapped density should be determined for each dosage and each API/excipient combination, with subsequent raw material lost.

In France, the majority of ambulatory¹¹ and hospital pharmacies make their capsules using the volume-based method. The French Pharmacopoeia recommends this method in its monographs.¹² Nevertheless, although the weight-based method requires pre-formulation studies to find the right weight of excipient to add, its superiority over the traditional method should encourage pharmacists to modify their protocols if possible. In addition, as 'hospital preparations' (preparations made in batches for several patients) must be as reproducible as possible, the weight-based method should be preferred for their compounding. The API/excipient ratio may influence the stability of the capsule¹³ and consequently the beyond-use date (BUD). Batch reproducibility thus improves BUD reproducibility.¹⁴ In our hospital we have already modified our protocols for these preparations. For 'extemporaneous (magistral) preparations' or 'official preparations' (preparations made for a patient, for a treatment) the weight-based method could hardly be used, but could be done for the most frequent preparations.

The general quality of compounding is promoted throughout Europe. Small changes in protocols, such as implementation of the weight-based method for capsule compounding, may lead to an improvement in quality.

Acknowledgements The authors thank Dr Christophe Jean for providing compounding material.

Contributors MW, CB, PT and CP carried out the analyses and performed/supervised the compounding. CC wrote the manuscript with support from EL, NP and PV. CC conceived the original idea and acted as guarantor. PV supervised the project.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study does not involve human participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. Not Applicable.

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What this paper adds

What is already known on this subject

- ▶ Compounding practices differs around the world, even for common formulas.
- ▶ For capsule compounding, a weight-based method is commonly used in the USA while a volume-based method remains the gold standard in several European countries.

What this study adds

- ▶ Our study compared these two methods for 10 mg spironolactone capsules and showed the superiority of the weight-based method.

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Work extension to pilocarpine 5 mg capsules and nicardipine 2 mg capsules

Pilocarpine 5 mg capsules:

Pilocarpine bulk density (Bd) = 0.57 g/mL / tapped density (Td) = 0.61 g/mL

MCC Bd = 0.34 g/mL / Td = 0.48 g/mL

Pilocarpine/MCC Bd = 0.35 g/mL / Td = 0.46 g/mL

To fill 100 size 4 capsules (21 mL), the tapped density evaluation allowed us to calculate a total weight of mixture pilocarpine/MCC equal to 9.7 g (21 X Td). Thus, 500 mg of pilocarpine hydrochloride and 9 200 mg of MCC were weighted on a precision balance. Capsules were compounded as described in the main manuscript

Table S1. Pilocarpine hydrochloride content and content uniformity comparison

	Volume-based method		Weight-based method	
	API content (mg)	Acceptance value	API content (mg)	Acceptance value
Batch 1	4.84 +/- 0.21	11.70	4.66 +/- 0.22	14.40
Batch 2	4.96 +/- 0.29	14.07	5.02 +/- 0.11	5.55
Batch 3	4.92 +/- 0.31	14.80	4.93 +/- 0.22	10.50
Mean value	4.91 +/- 0.06	13.52 +/- 1.62	4.87 +/- 0.19	10.15 +/- 4.43
Theoretical value	5.00	15.00 <	5.00	15.00 <

Nicardipine 2 mg capsules:

Nicardipine bulk density (Bd) = 0.24 g/mL / tapped density (Td) = 0.35 g/mL

MCC Bd = 0.34 g/mL / Td = 0.48 g/mL

Nicardipine/MCC Bd = 0.35 g/mL / Td = 0.47 g/mL

To fill 100 size 4 capsules (21 mL), the tapped density evaluation allowed us to calculate a total weight of mixture pilocarpine/MCC equal to 9.9 g (21 X Td). Thus, 200 mg of nicardipine and 9 700 mg of MCC were weighted on a precision balance. Capsules were compounded as described in the main manuscript

Table S1. Nicardipine hydrochloride content and content uniformity comparison

	Volume-based method		Weight-based method	
	API content (mg)	Acceptance value ¹	API content (mg)	Acceptance value ¹
Batch 1	1.85 +/- 0.08	15.47	1.94 +/- 0.08	11.43
Batch 2	1.81 +/- 0.05	13.98	1.89 +/- 0.06	10.79
Batch 3	1.86 +/- 0.07	13.49	1.90 +/- 0.03	7.51
Mean value	1.84 +/- 0.02	14.31 +/- 1.03	1.91 +/- 0.03	9.91 +/- 2.10
Theoretical value	2.00		2.00	

¹Nicardipine 2 mg capsules have a theoretical API amount below 2% (w/w), making the 2.9.5. EP test more appropriate than the 2.9.40. EP for batches uniformity. However, Acceptance Value were calculated with 2.9.40. formula to compare results with other APIs.