Pre-analytic optimization of API assays in compounded oral suspensions for pediatrics

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INTRODUCTION

The hospital pharmacy of the *Mayotte Hospital Center* produces compounded oral suspensions for pediatrics (COSPs). These suspensions are intended treat several diseases, mainly cardiovascular disease, with more than 1000 paediatric patients frequenting our hospital.

To produce these COSPs, a thick vehicle **Syrspend® SF PH4** (FAGRON) it used. This vehicule has heterogeneous and viscous characteristics that make quantitative quality controls of Active Pharmaceutical Ingredients (APIs) not easy to perform.

These assays require accurate and repeatable aliquoting, followed by an **extraction** of the **aqueous fraction** which should be clear and transparent to be analyzed by photometry.

OBJECTIVES

To **compare** several **sampling modalities** and **extraction methods** and to **standardize** these **pre-analytical steps.**

MATERIALS & METHODS:

3 COSPs were prepared using **Syrspend® SF PH4 vehicle** (FAGRON ; Netherland; density = 1,01) :

- amlodipine 1 mg/mL,
- propranolol 1 mg/mL,
- thiamine 100 mg/mL.

4 extraction methods were **compared**:

- **filtration** through a 0.45µm hydrophilic filter (Millipore),
- **acidic hydrolysis** (5% HCl 37N),
- **centrifugation** of COSPs with increasing times and speeds :
  - **pures** & **undiluted samples**,
  - **1/5th** and **1/10th water diluted samples**.

For **aliquoting standardization**, samples were taken according to **3 modalities** (n=5/modality):

- **samples weighing**,
- **direct pipetting** (without cone wetting),
- **reverse pipetting** (with cone wetting).

Figure 1 : Propranolol 1 mg/mL & amlodipine 1 mg/mL COSPs

Figure 2 : UV/Raman spectrophotometer QC Prep®

In order to analyze the sampled and extracted fractions, the contents of the aqueous phases were analyzed by **UV/Raman spectrophotometer QC Prep®**.

Recoveries (ratio of measured to theoretical content, m ± SD, n = 5) were compared between modalities by ANOVA test (p<5%).

RESULTS & DISCUSSION

MAYOTTE

Extraction:

Filtration through hydrophilic filter	✗	Very low extraction yield (10-12% of the filtered volume) Filter clogging Cloudy and opaque extract
Acidic hydrolysis	✗	Suspension destruction Milky macroscopic aspect
COSPs centrifugation :		Centrifugation : increasing speed from 1000 to 5500 rpm ; variable times : 1 to 10 min
▪ **Pure & undiluted samples**	✗	No suspension break-up
▪ **Water diluted samples**		
(i) 1/5th diluted	✗	Not analysable by photometry
(ii) 1/10th diluted	✓	**5500 rpm/10min** : usable **transparent aqueous** extract separated from a **solid** & **stable pellet**

Aliquoting:

		Aliquoting modalities		
	COSPs	**Weighing**	**Direct pipetting**	**Reverse pipetting**
Recovery (%) (m ± SD ; n = 5)	Amlodipine 1 mg/mL	104,8 ± 4,9	98.40 ± 7.83	103,0 ± 5,2
	Propranolol 1 mg/mL	103.8 ± 4.6	93,0 ± 6,4	102,2 ± 4,7
	Thiamine 100 mg/mL	104,5 ± 5,1	88,1 ± 2,7	104,0 ± 3,9
	Global average	104,4 ± 4,9	93,2 ± 5,6	103,1 ± 4,6

CONCLUSION

Our study shows that APIs concentration determinations of COSPs requires **sampling by weighing** or **reverse pipetting**.

The **aqueous phase extraction** must be performed on a **1/10th diluted samples** submitted at least to **10 min centrifugation** at **5500 rpm**. In such conditions, the obtained analytical results are satisfactory, accurate and precise.

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