OPTIMIZATION OF THE LIQUID ORAL FORMS PROCESS: EXAMPLE OF A SEMI-AUTOMATED DEVICE AND ITS QUALIFICATION

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INTRODUCTION & AIM

•**Context** : Manual production of oral suspensions causes operator musculoskeletal issues and limits batch sizes. Increasing batch sizes is essential due to rising hospital demand. The pharmacy has a mixer (Topitec® Touch, Wepa Pharma, Germany) that could potentially mix liquid forms.

Objectives : The study aimed to **evaluate** the **Topitec® Touch** ability to **produce oral suspensions** of **Melatonin 2 mg/mL** by optimizing and qualifying the semi-automated process.

MATERIALS & METHODS

→ The study focused on an oral suspension of melatonin 2 mg/mL with content uniformity issues.
→ Using melatonin powder (Inresa, France), Syrspend® SF PH4 liquid (Fagron, Netherlands) and the mixer Topitec® Touch

1-Optimum parameters

a-Powder trituration
- 3 speeds tested : 300, 500, 1000 rpm
- 3 times tested : 1, 4, 10 minutes
= 9 suspensions from top, middle, bottom

b-Mixing powder
- 2 speeds tested : 300 rpm and 500 rpm
- 3 times tested: 1, 4, 10 minutes
= 6 suspensions from top, middle, bottom

2-Larger batches

Optimal parameters used

3 batches :
- 500 mL ➔ 1 000 mL
- Increase optimum parameters until reach compliance
- Validated by 2 different technicians

Content assessment

Homogeneity by High Performance Liquid Chromatography (HPLC):
- Column: Waters CORTECS® C18 (150 x 3.0 mm; 1.6 µm)
- Column temperature: 25°C
- Mobile phase: Water pH 3/Acetonitrile (50:50) (v/v)
- UV detection (λ=278 nm)

Statistical analysis

Test : two-factors **ANOVA** test without repeating the experiment
Alpha risk defined as 5%

RESULTS

Powder Trituration

9 suspensions :
- **Content assessment conform**
  - ✓ Mean content ± 10%
  - ✓ RSD <5%
- Between samples $F_{calculated}$ =1.69 < $F_{theorical}$ = 3.53
- Between experiments $F_{calculated}$ =1.67 < $F_{theorical}$ = 2.69

No significant differences between samples (p-value = 0.22) and experiment (p-value = 0.18)

Mixing Powder

6 suspensions :
- One out : not mixing enough macroscopically
- **Content assessment conform**
- Between samples $F_{calculated}$ =0.14 < $F_{theorical}$ = 4.46
- Between experiments $F_{calculated}$ =1.25 < $F_{theorical}$ = 3.84

No significant differences between samples (p-value = 0.87) and experiment (p-value = 0.36)

Larger Batches

3 batches :
- **Content assessment conform**

Batch 1 : mean content= 1.91 mg/mL ; RSD = 2.5 %
Batch 2 : mean content= 1.93 mg/mL ; RSD = 2.6 %
Batch 3 : mean content= 1.85 mg/mL ; RSD = 3.1 %

To limit wear, the **trituration speed** was **300 rpm for 1 minute**, the **mixing speed** was **300 rpm for 4 minutes**.
For 1 000 mL batches, **trituration speed** was **300 rpm for 1 minute**, and **mixing speed** was **500 rpm for 4 minutes.**
The method was validated by two different technicians

Difficulties encountered included static electricity, which interfered with the proper mixing of the powder due to friction.

CONCLUSION

The semi-automated process using the Topitec® Touch for Melatonin oral suspensions was optimized, qualified, and validated. It is possible to produce larger batches and save operators time.

Investigation of the applicability to other molecules and other vehicles (Inorpha® for example).