Design and stability study of oral capsules and suspension of riboflavin

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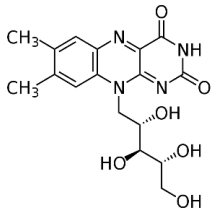

Introduction

Riboflavin, or vitamin B2, is recommended for the management of rare metabolic diseases. The treatment is initiated in childhood and then continued into adulthood, requiring dose adjustments. The specialty Beflavine® was recommended in cases of vitamin B2 deficiency but is no longer marketed.

Objective

Development of an oral suspension
Dedicated to pediatric patients

Development of capsules
Children able to swallow- adults

Material/Methods

Galenical formulation

- Study of the composition of the excipients : notorious effects?
- Physicochemical characteristics of the vehicles available
- Preformulation and palatability studies

Physico-chemical stability study

- **Development and validation of an HPLC assay method** by ion pairing (ICH Q2)
- **Physico-chemical stability study**:

3 batches x 100 gélules → Ambient

→ *Concentration at D0, D3, D7, D14, D28, D56, D84 et M6*

3 batches: Ambient → 1 multidose (60 ml) + 20 single-dose (3 ml)
4 – 8 °C → 1 multidose (60 ml) + 20 single-dose (3 ml)

→ *pH, osmolarity and concentration at D0, D3, D7, D14, D28, D56, D84*

Microbiologic stability study

Development and validation (European pharmacopoeia 2.6.12 et 2.6.13) : total viable aerobic microbial count, total combined yeasts/moulds count and test for specified micro-organism (*Escherichia coli)*

3 batches: Ambiant → 1 multidose bottle (60 ml)
4 – 8 °C → 1 multidose bottle (60 ml)

→ *Microbiologic stability study at D0, D14, D28, D56 and D84*

Results

1. Choice of the concentration and the excipients :

→ Suspension at 10 mg/ml of riboflavin in **Inorpha®**

→ Capsules of 50mg of riboflavin + **mannitol**

2. Validation of the assay method by HPLC : validation of a stability indicating method

3. Stability study : *see tables 1 and 2*

4. Microbiologic stability study of the suspension : results in colony forming unit (CFU)/ml at D84 :

- $<10^2$ total viable aerobic microbial count
- $<10^1$ total combined yeasts/moulds count
- No *Escherichia coli*

→ **Microbiologic stability demonstrated at D84**

	pH	Osmolarity	Riboflavine (mg/ml)
Acceptance criteria	*Variation < 1 unit*	*161 ± 10%*	*10 ± 10%*
D0	4,48 ± 0,11	157,00 ± 4,58	10,10 ± 0,15
D84 - 2-8°C - unidose	4,59 ± 0,07	156,67 ± 4,51	9,84 ± 0,20
D84 - 2-8°C - multidose	4,66 ± 0,06	157,67 ± 4,51	9,89 ± 0,16
D84 - 20-25°C – unidose	4,61 ± 0,06	158,00 ± 5,00	10,09 ± 0,22
D84 - 20-25°C - multidose	4,55 ± 0,05	158,00 ± 5,00	9,73 ± 0,07

Table 1 : Results of the stability study of the suspension depending on storage conditions

	Riboflavine (mg)
	50 ± 10%
D0	48,94 ± 1,22
D3	49,11 ± 1,43
D7	49,44 ± 1,56
D14	49,08 ± 1,27
D28	49,52 ± 1,53
D56	48,40 ± 1,23
D84	48,25 ± 0,98
M6	48,56 ± 0,72

Table 2 : Results of the stability study of the capsules

Conclusion

→ **Development of two new formulations intented for children and adults**

→ **Physico-chemical and microbiologic stability of the suspension at D84 and chemical stability of the capsules at M6 at ambient temperature and protected from light**