

Formulation and Control of a Pediatric Oral Hospital Preparation of 0.1% Ferrous Fumarate

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Context:

Ferrous ascorbate:
suspected to be involved in rectal
bleeding in neonatology



Ferrous fumarate:
unavailable on the national territory



Requiring our hospital pharmacy to provide a
pediatric oral formulation of ferrous fumarate
(FF)

Objectives:

1/ To develop a hospital preparation (HP)
of FF (0.1%) adapted for pediatric oral use

2/ To validate an analytical method allowing the
control of FF content by microwave atomic emission
spectrometry (MP-AES)

Materials and methods:

The dispersion of the FF was performed using a high performance dispersing device, in a ready-to-use commercial oral route vehicle, suitable for pediatric enteral administration and facilitated acceptability.

The FF quantification was performed using microwave atomic emission spectrometry (MP-AES). The quantification wavelength of iron was 371.9 nm. The analytical validation was conducted by building the accuracy profile according to the SFSTP¹ recommendations. It allows estimating the linearity, the fidelity, the accuracy and the limits of quantification as well as the estimate of the measurement inaccuracy as a function of the concentrations.

The development included a research for a potential matrix effect in the ready-to-use commercial oral route vehicle according to the recommendations of the Annals of Analytical Toxicology². The oral suspension was diluted 1000 times in a 1% nitric acid solution.

Table 1 : HP's characteristics

Parameters	HP	
Osmolality	170 mOsm/L	
Ready-to-use commercial oral route vehicle composition	Purified water Glycerol Hydroxyethylcellulose Citric acid monohydrate Sodium citrate dihydrate	Bitterness masking Caramel aroma Sucralose Potassium sorbate
FF concentration	1 mg/mL	

Table 2 : FF chemical and physical properties

Parameters	Fumarate ferrous
Molecular Formula	C ₄ H ₂ FeO ₄
Molecular Mass	169,9 g/mol
Solubility in water	13 mg/L
Log P	0,83

Results:

No evidence of instability (e.g., color change, flocculation, sedimentation) of this HP was observed during the storage time at room temperature.

The matrix effect observed in the vehicle doubled the signal intensity. Therefore validation protocol "V5" was then used, involving calibration in the presence of the matrix. The parameters of accuracy, repeatability and reproducibility were in accordance with the specifications in the validity range (<10%, 5% and 8% respectively).

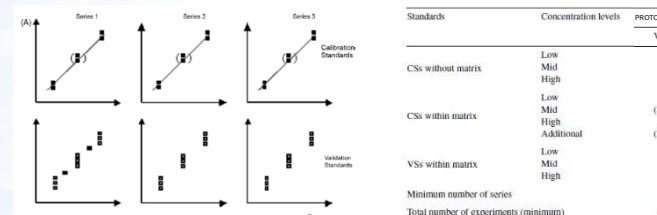


Figure 1 : Description of protocole V5: evidence of matrix effect ;
CSs: calibration standards; VSs: validation standards.

Table 3 : Validation criteria for the determination method

R ² n = 6 4 ddt (> 95%)	PRECISION (< ± 10%)	RECOVERY (90 - 110 %)	REPEATABILITY (<5%)			INTERMEDIATE PRECISION (<8%)		
			LOW	MEDIUM	HIGH	LOW	MEDIUM	HIGH
0.98	0.52%	100.52%	3.21%	2.79%	2.40%	3.10%	2.55%	2.41%

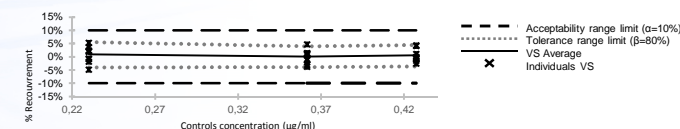


Figure 2 : Accuracy profile

Discussion / Conclusion :

The simplicity of implementation of this HP and the validation of a content control on the whole mixture before distribution in individual containers guarantee a safe use of the FF for pediatric use.

¹Ph. Hubert et al. Harmonization of strategies for the validation of quantitative analytical procedures, Journal of Pharmaceutical and Biomedical Analysis 45 (2007) 70–81

²Annales de Toxicologie Analytique, vol. XVI, n° 2, 2004