Preparation and control of lidocaine and ketamine injectable solution for mesotherapy

Chloé Marchand[1], Camille Merienne[1], Brigitte Ducarre[1], Constantin Dupuis[1], Samira Filali[1], Damien Salmon[1,2], Christine Pivot[1], Fabrice Pirot[1,2]

[1]Pharmacy, Edouard-Herriot Hospital, Lyon, France. [2] Industrial Galenic Pharmacy Laboratory, ISPB, Lyon, France.

Context:

Our hospital pharmacy is requested to realize the preparation and the control of an **injectable solution of lidocaine and ketamine (SILK)**. It was intended to evaluate, in a double-blind clinical trial, the efficacy of ketamine administered by mesotherapy (fig.1) in the treatment of neuropathic pain.

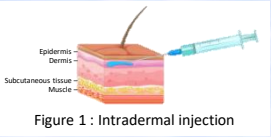

Figure 1 : Intradermal injection

Objective:

The objectives of this study were (i) the development of a SILK and (ii) to develop and to validate an analytical method stability indicating allowing the control of lidocaine and ketamine contents and the detection of their degradation products.

Materials and methods:

The SILK (lidocaine - ketamine: 20 mg – 40 mg / 6 mL) was obtained from sterile commercial specialties diluted in sodium chloride solution (0,9%), then sterile filtered. It was aseptically distributed in sterile type I glass vials, sealed with chlorobutyl stoppers, then crimped with an aluminum cap. It was autoclaved (121°C - 20 min) and stored at (i) -20 ± 5°C; (ii) 5 ± 3°C; (iii) 25 ± 2°C - 60% relative humidity (RH); (iv) 40 ± 2°C - 75% RH; (v) 60 ± 2°C - 5% RH during one month (fig. 2 and 3).

The content of lidocaine and ketamine in SILKs was determined using a high performance liquid chromatographic system and ultra-violet diode array detection (lidocaine-ketamine: 260 nm; degradation products: 200 to 400 nm), comprising a reverse stationary phase (C18, 2.6 µm 100 Å 150 x 4.6 mm; 25 °C), a mobile phase (sodium acetate buffer pH 5.0 - methanol, 75:25 v / v, flow rate: 1 mL/min). Analytical validation (i.e. linearity, fidelity, accuracy, limits of quantification, measurement inaccuracy) was carried out according to the recommendations of the ICH, GERPAC and by construction of two accuracy profiles.

Figure 2 : Components of the finished product and packaging

Figure 3 : Steps in the manufacturing process

Results:

Validation parameters of the assay method were in accordance with the specifications in the validity range (table 1). The bounds of the accuracy profile tolerance (fig. 4) were within the acceptability limits. No interference between lidocaine, ketamine and their degradation products has been observed (fig. 5).

The macroscopic appearance (color and clarity) of SILK was unchanged after one month of storage under the five predefined climatic conditions. The content of lidocaine and ketamine in the SILK was in accordance with the specifications (90% - 110%), at the end of the storage period under different environmental conditions.

Table 1 : Validation parameters of the assay method

Molecules	R^2 n = 18 ; 4 ddl (> 95%)	Precision (< ± 10%)	Recovery (90 - 110 %)	Repeatability (< 5 %)			Intermediate precision (< 8 %)		
				Low	Medium	High	Low	Medium	High
Ketamine	0.998	- 0.93 %	99.07 %	1.30 %	0.45 %	0.73 %	1.15 %	0.56 %	1.18 %
Lidocaine	0.997	- 0.11 %	99.89 %	0.80 %	0.37 %	0.66 %	0.91 %	0.57 %	0.92 %

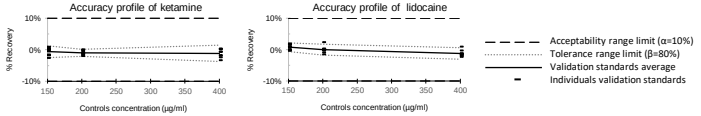

Figure 4 : Accuracy profiles of the assay method

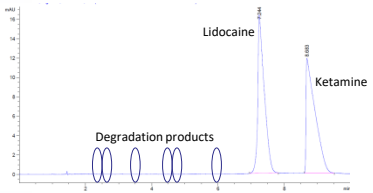

Figure 5 : Chromatogram of lidocaine and ketamine

Discussion / Conclusion:

The simplicity of the implementation of SILK and the validation of an analytical method indicative of stability allows the implementation of a stability study for 18 months according to the ICH, in the perspective of a clinical trial.