Stability study of a hospital preparation of ketamine syrup (5mg/mL)

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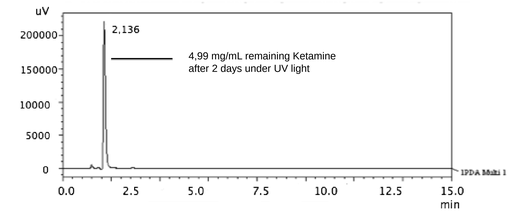
POSTER T3273

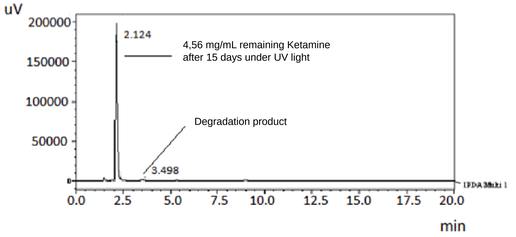
Les Hôpitaux Universitaires de STRASBOURG

PURPOSE

- Ketamine is an injectable pharmaceutical drug for analgesia therapy.
- However, oral administration could be necessary in supportive care in case of failure of conventional treatments for pain and in case of refractory neuropathy. But in France, no adapted specialty is marketed by the pharmaceutical industry.
- So Ketamine syrup (5mg/mL) was prepared at the Pharmacy of University Hospital of Strasbourg.
- The aim of this work was to carry out a physical stability study of this formulation in order to determine optimal shelf-life for storage.



Chromatogram of UV stressed sample of Ketamine syrup (5 mg/mL) diluted 1:100 in water, after 2 days of exposition.



Chromatogram of UV stressed sample of Ketamine syrup (5mg/mL) diluted 1:100 in water, after 15 days of exposition.

METHODS

- A 5mg/mL Ketamine solution in syrup was formulated with a commercial vehicle Inorpha® (Inresa).

Instrumentation

- Ketamine samples were assayed in triplicate on a C18 column (4.6 x 250 mm, 5 µm), with an isocratic mobile phase acetonitrile/ acidified water (30:70, V/V) at 30° C. The flow rate was 1 mL/min,UV detection at 220 nm and oven temperature et 30° C.

Method validation

- Validation of analytical method was performed as per ICH guideline Q2 B, over the linearity, accuracy, precision, specificity, limit of detection and limit of quantification.
- Forced degradation studies were performed to evaluate the stability indicating properties and the specificity of the method. Ketamine was subjected to stress conditions including acidic, alkaline, oxidation, photolysis and thermal degradation.

Stability study

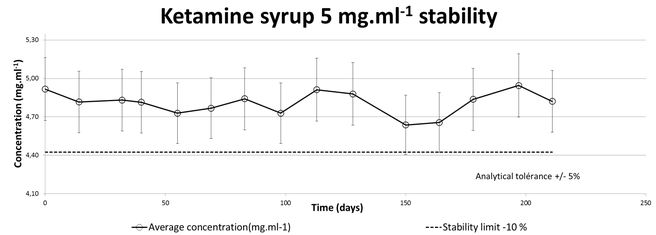
- The physical stability was assessed by visual aspect, pH determination and a ketamine concentration measurement by HPLC-UV.
- Specification for stability was a remaining concentration of at least 90% of a initial concentration (i.e. 5% of degradation and +/- 5% for analytical variation). Three batches of syrups were stored at room temperature in amber glass bottle (capacity of 250mL). Samples series were tested at different times (initially 0, 14, 32, 40, 55, 69, 83 and 98 days) until degradation revealing.

Forced degradation studies of a Ketamine solution (5 mg/mL)

Stress condition	Acid degradation	Base degradation	Oxidative degradation		Photolytic degradation		Thermal degradation
Time (Days)	15	15	2	15	2	15	15
Measured concentration (mg/mL)	4,40	3,98	4,43	0	4,99	4,56	5,24
% Degradation	11,98	20,22	11,4	100	0	8,83	0
Peak of degradation product apparition	No	No	No	No	No	**Yes**	No

RESULTS

- The analytical method for the determination of ketamine concentration was validated for linearity (r2>0.999; from 0.025 to 0.1 mg/mL), specificity, fidelity i.e. repeatability (RSD < 0.8%), reproducibility (RSD < 1.3%), and accuracy (relative error < 1.1%).
- Only UV conditions leads to a significant degradation products apparition.
- During the stability study, nor change in physical appearance, nor pH occurred for 98 days. No decrease of initial ketamine concentrations (4.92 mg/mL) superior to 5% was observed during the test period with an average concentrations of ketamine ranged from 4.73 to 4.84 mg/mL.
- Stability of Inorpha® is 90 days according to manufacturer and change of pH and visual aspect noticed after 98 days of storage of all syrup batches.



CONCLUSIONS

Currently, at room temperature, the molecule ketamine is chemically stable until 210 days in syrup. A shelf life of 3 months after the preparation date is officially recorded and printed on the label of the final product due to the Inorpha® degradation. All these results make it easier a campaign of manufacturing at hospital pharmacy before a clinical use.