

# Long-term stability of indomethacin 0.2 mg/ml ready-to-use solution for intravenous use

R. Moudry, S. Hornstein, M. Fehr-Bigger, S. Guyer  
Kantonsspital Graubünden, Institute for Hospital Pharmacy, Chur, Switzerland

## Background

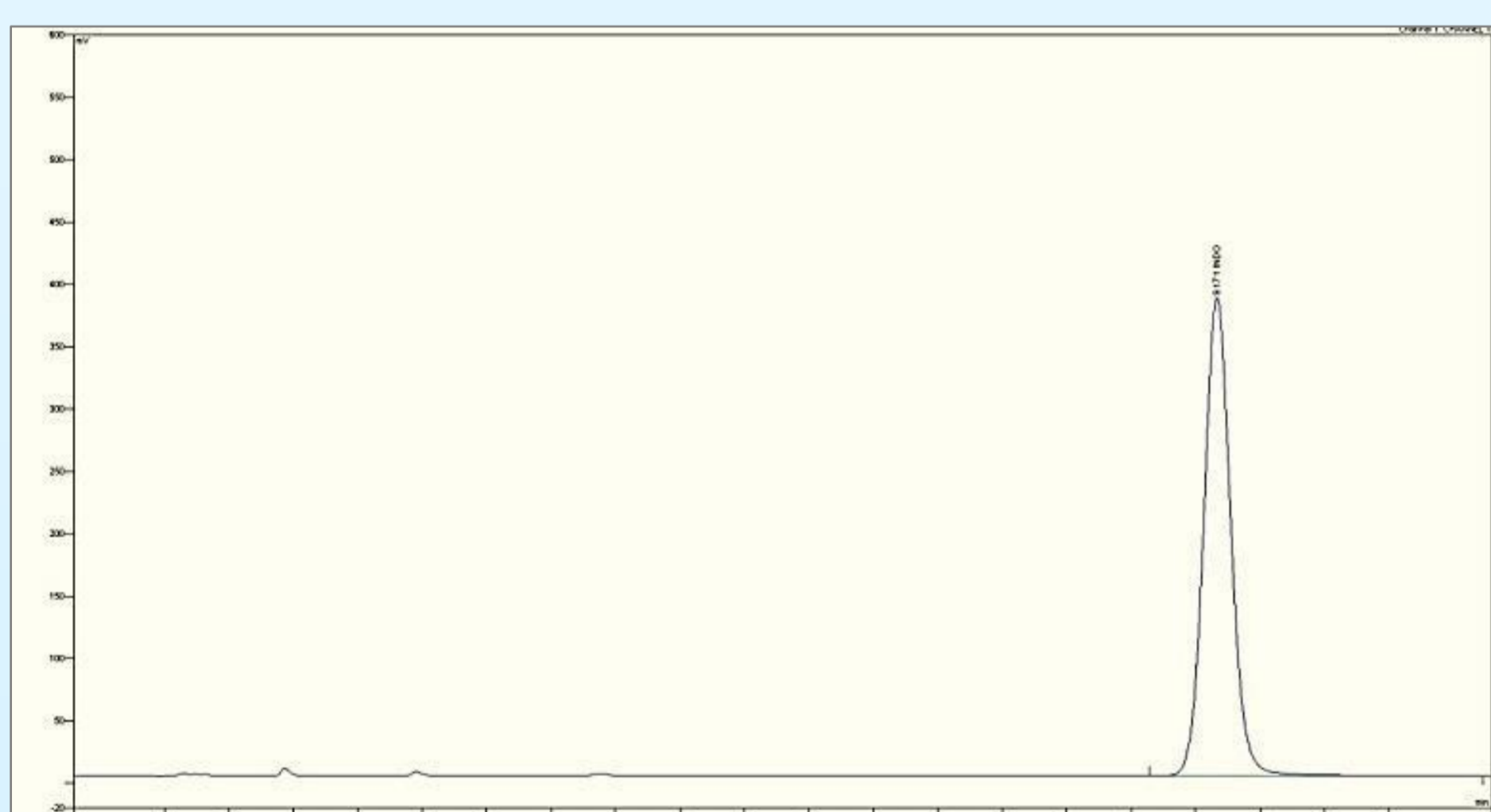
Indomethacin is used in premature infants to close the patent ductus arteriosus. The commercial product Indocid PDA® is no more available in Switzerland. Nevertheless, on our paediatric ward there is a great need for an intravenous indomethacin solution that can be used at a dose of 0.1 – 0.2 mg/kg body weight.

Our aim was to produce a parenteral ready-to-use solution containing 0.2 mg/ml indomethacin which can be stocked for at least 12 months.

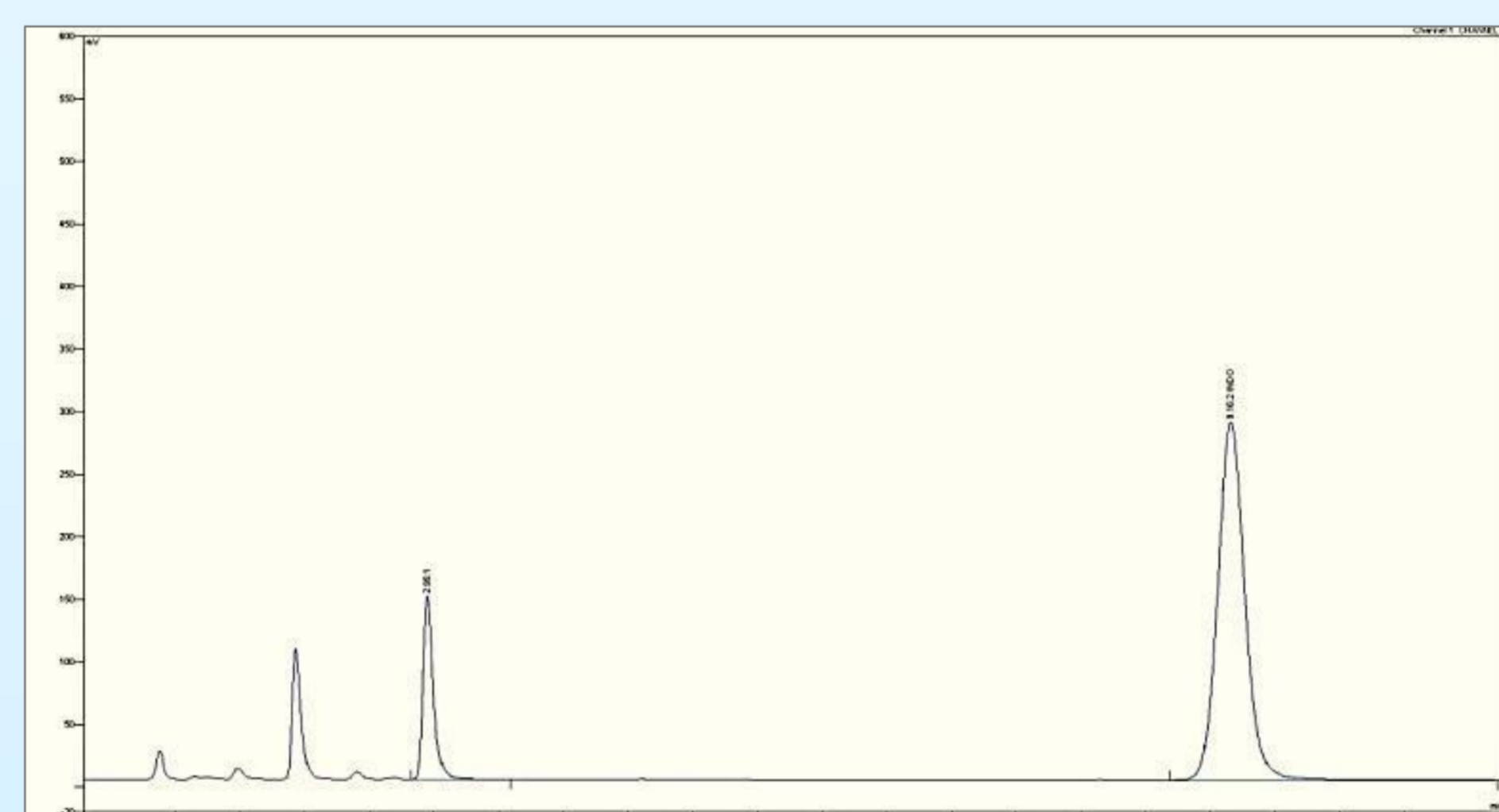


## Results

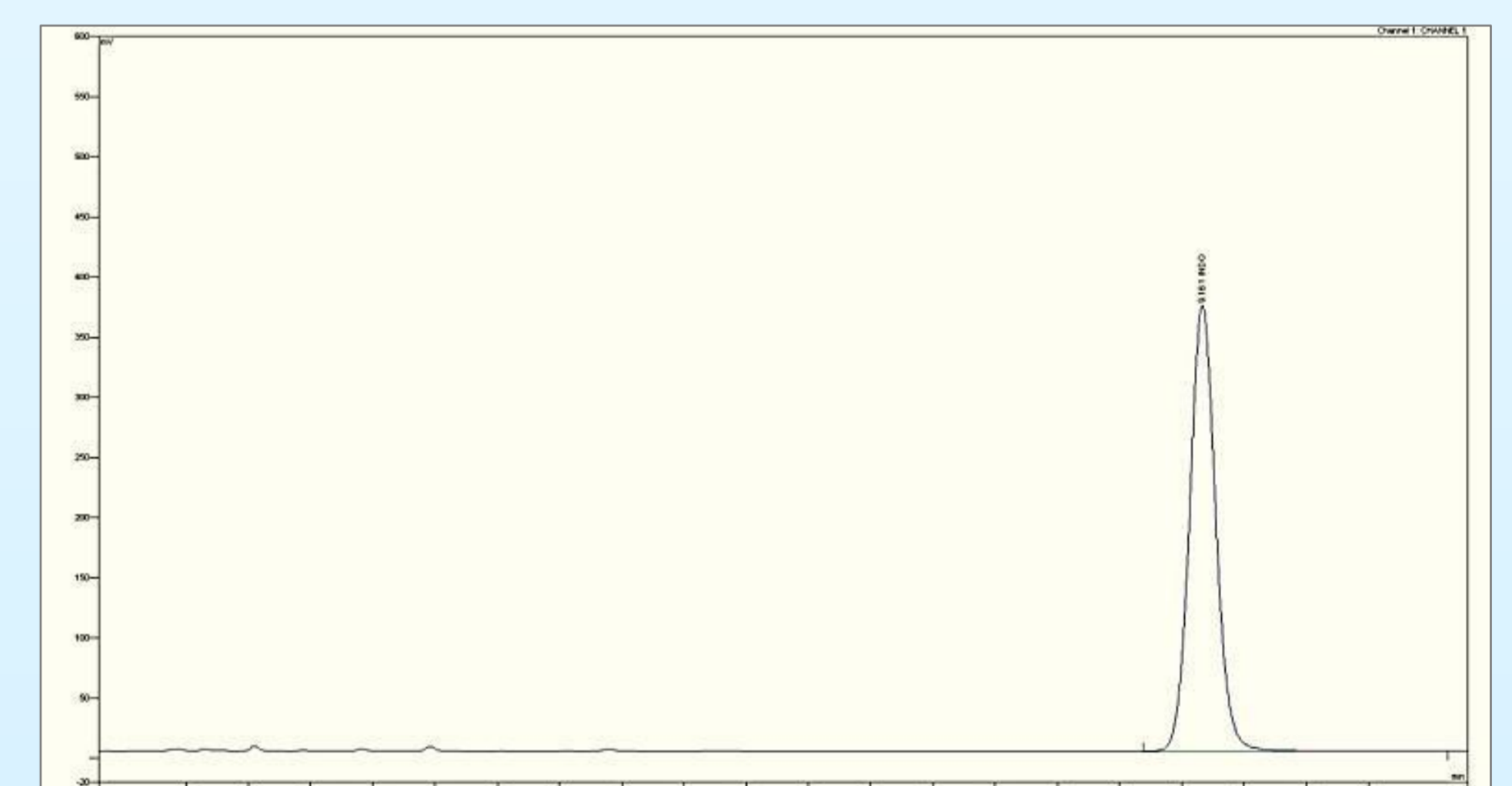
Indomethacin solutions were submitted to conditions of oxidative (H<sub>2</sub>O<sub>2</sub>) and alkaline/thermal (NaOH/120°C) degradation. After oxidative degradation, new peaks at a retention time of 2-3 min. were detected (see figure 2) and after alkaline/thermal degradation no indomethacin peak was detected. Consequently, the HPLC method was found to indicate stability.



**figure 1:** chromatogram of freshly dissolved Liometacen® (75 µg indomethacin/ml)



**figure 2:** chromatogram of Liometacen® (0.2 mg indomethacin/ml), stored for 4 months at room temperature



**figure 3:** chromatogram of Liometacen® (0.2 mg indomethacin/ml), stored for 18 months at -20 °C

Storage time	INDOMETHACIN CONTENT		
	room temperature	2-8 °C	-20 °C
PRODUCTION DAY	100 %	100 %	100 %
1 WEEK	98.3 %	101 %	100 %
3 WEEKS	95.0 %	99.0 %	102 %
3 MONTHS	85.8 %	93.2 %	98.3 %
4 MONTHS	77.0 %	85.4 %	n.d.
18 MONTHS	n.d.	n.d.	98.3 %

**table 1:** indomethacin content after different storage conditions. On production day, the indomethacin content was set to 100%.

## Methods

Liometacen®, containing 50 mg sterile indomethacin (as meglumine salt), was reconstituted with 2 ml water for injection and then diluted with 250 ml NaCl 0.9% to a final indomethacin concentration of 0.2 mg/ml.

A 5 ml indomethacin solution was filled into 10 ml sterilised brown glass vials. The entire process occurred under aseptic conditions and sterility testing was performed. The vials were stored at -20°C, at 2-8°C and at room temperature. The solutions were assessed by HPLC for indomethacin and its degradation products.

The following HPLC procedure was used:

**Column:** Purospher® STAR, RP-18e

**Eluent:** Acetonitrile/Water 50:50 (v/v), pH 2.5 with ortho phosphoric acid

**Standard:** Liometacen® (50 µg – 100 µg/ml)

**Flow rate:** 1ml/min

**Detection:** UV, 237 nm

**Retention time of indomethacin :** approximately 9 min.

**Retention time of oxidative degradation products:** 2-3 min.

The stability testing revealed that the solutions retained at least 95% of their initial indomethacin concentration when they were stored at room temperature or at 2-8 °C for 3 weeks (table 1).

In contrast, when the solutions were stored in a deep-freezer, they were stable for at least 18 months. During this time, no degradation of indomethacin occurred (figure 3).

## Conclusions

Indomethacin solutions (0.2 mg/ml) may be prepared in advance and stocked for 18 months at -20 °C. After thawing they can be kept at room temperature for 7 days or alternatively at 2-8 °C for 3 weeks. This procedure is used successfully in our hospital for the treatment of the patent ductus arteriosus.