# New formulation of norepinephrine solution in prefilled cyclic olefin sterilised syringes

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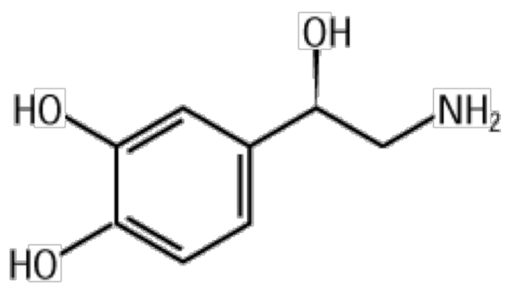
## Introduction

Norepinephrine is a potent α-sympathomimetic drug which plays an important role in acute treatment of hypotension and shock at the intensive care ward. Commercially available norepinephrine solutions contain sodium metabisulfite ($Na_2S_2O_5$) as antioxidant. However cyclic olefin polymer syringes are not compatible with sodium metabisulfite due to brown colorization of the syringe during sterilization.

The aim of this research was to develop a new formulation of 0.1mg/ml norepinephrine solution without sodium metabisulfite which is chemical stable and sterile.




## Material and methods

- Cyclic olefin polymer (COP) syringes used were the BD Sterifill AdvanceTM 50ml syringes from Becton Dickinson (BD) Medical Pharmaceutical systems, with a luer lock adaptor and screwed tip cap. Filled syringes were closed with a bromo butyl plunger stopper from Datwayler
- Formulation tests were performed with 0.1mg/ml norepinephrine solution with 0, 0.05 and 0.1% ascorbic acid added as antioxidant. Other excipients were 0.1mg/ml edetate sodium, 8mg/ml sodium chloride and water for injections.
- Production was performed under following conditions:
  - IPC pH was set to 3.8-3.9
  - Filled under nitrogen gassing
  - Stored at room temperature (20 ± 5ºC)
  - Protected from day light
- Concentration norepinephrine was determined after storage for
- 0, 1, 3, 7, 13 and 22 weeks with an UHPLC system with diode array detection.
- Based on the formulation test results the final formulation was de fined and stability testing was performed measuring concentration norepinephrine, pH, clarity, color of solution, subvisible particles and sterility at time intervals according to ICH guidelines.

## Results- Formulation study

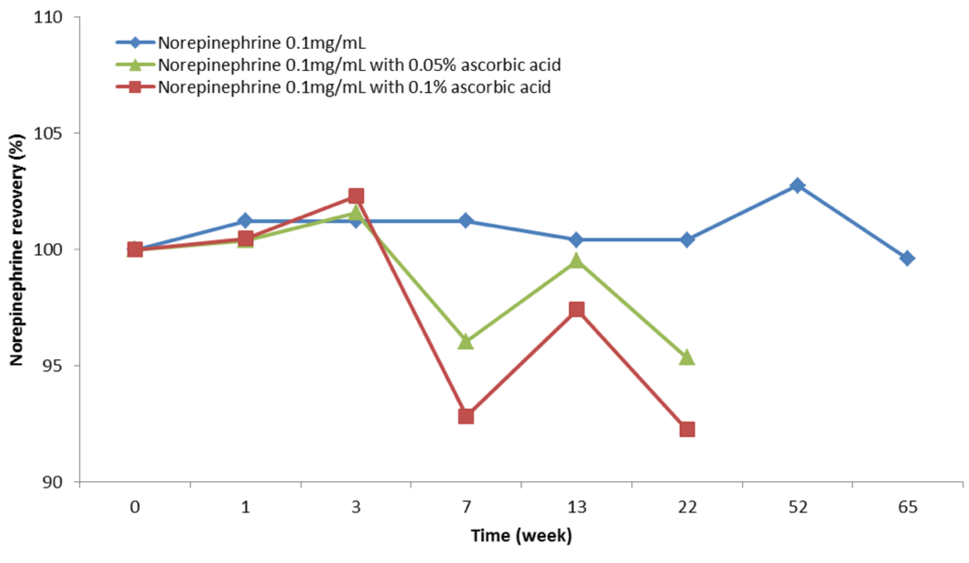



***Figure 1:*** *Norepinephrine recovery (%) formulation study, t=0 is 100%*

Based on the results of the formulation study, batches for stability testing were produced without adding any antioxidant. The following formulation was produced: norepinephrine 0.1 mg/mL, sodium edetate 0.1mg/ml, sodium chloride 8mg/L with water for injections. Based on historical data an overage of 10% norepinephrine was added to compensate for possible degradation during sterilization.
The solution was produced under GMP conditions.

## Results- Stability study

The initial pH of 3,8-3,9 did not change significantly during 9 months storage after which a pH of 3.8 to 4.0 was found. All solutions were clear at all points in time and the color of the solution was < B9, the solutions were sterile and the amount of particles was within limits (≤6000 particles/ syringe for particles ≥10µm and ≤600 particles/ syringe for particles ≥25µm). The norepinephrine recovery of the different batches is shown in figure 2. When analyzing the t=0 content of the batches 1 and 2 it was found that there was less than 2% loss during production and sterilization.

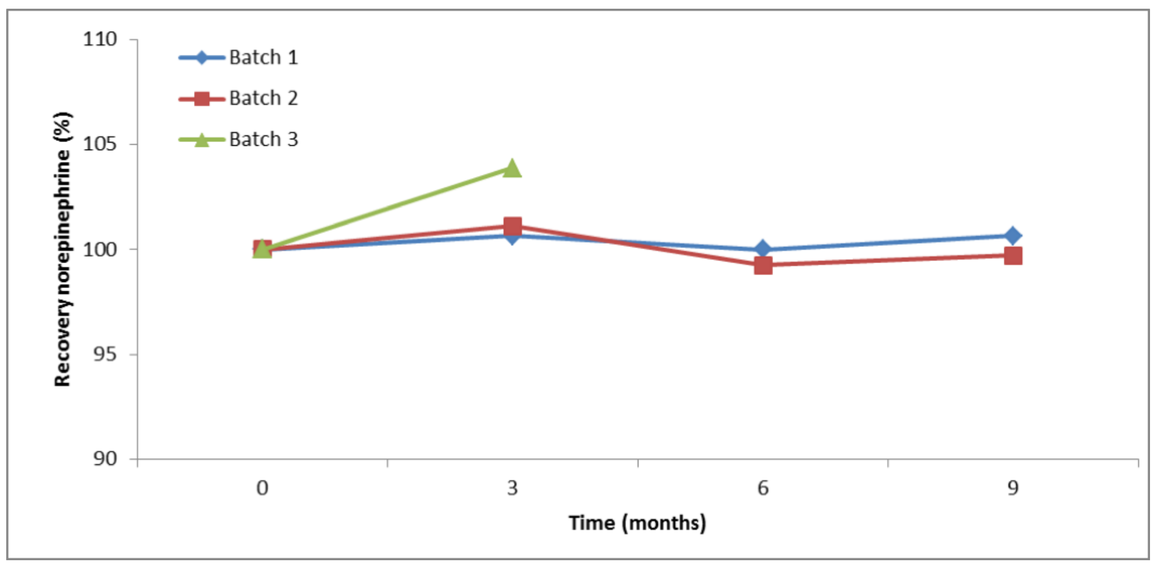



***Figure 2:*** *Norepinephrine recovery (%) stability study, t=0 is 100%*

## Conclusion

The norepinephrine (0.1mg/ml) solution containing sodium edetate and sodium chloride filled under nitrogen gassing in syringes followed by heat sterilization is stable for at least 9 months at room temperature when protected from day light. Such a formulation can be free of antioxidants, like sodium metabisulfite or ascorbic acid.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