

# Precipitation of Sugammadex With Nicardipine And Labetalol

Jiwon Han

Seoul National University Bundang Hospital

Ah-Young Oh (✉ [ohahyoung@hanmail.net](mailto:ohahyoung@hanmail.net))

Seoul National University Bundang Hospital

Bo Young Kim

Independent researcher

---

## Research Article

**Keywords:** Sugammadex, Nicardipine, Labetalol, Precipitation

**Posted Date:** January 3rd, 2022

**DOI:** <https://doi.org/10.21203/rs.3.rs-1209442/v1>

**License:**  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

# **Abstract**

## **Background**

There is a paucity of clinical data about whether sugammadex forms precipitates with other medications. This laboratory experimental study was performed to determine the drugs that produce precipitate with sugammadex.

## **Methods**

Samples of 1 mL of sugammadex were prepared in transparent cylinders, to which 1 mL of test drugs (rocuronium, neostigmine, glycopyrrolate, atropine, nitroglycerin, dobutamine, dopamine, epinephrine, vasopressin, norepinephrine, phenylephrine, ephedrine, esmolol, nicardipine, labetalol) was then added. The precipitation reaction was observed by eyes and light microscope. The pH of each drugs before and after mixing with sugammadex was measured.

## **Results**

White crystals were formed when sugammadex mixed with nicardipine or labetalol.

## **Conclusions**

Sugammadex formed precipitate when mixed with nicardipine or labetalol. Sufficient fluid flushing is required between injections of each drug to prevent these reactions.

# **Introduction**

Precipitation reactions in which two ions in aqueous solution bond together to form an insoluble solid occur frequently between drugs. Alkalised local anaesthetics (e.g. ropivacaine, bupivacaine) and corticosteroid, thiopental sodium and aminosteroidal neuromuscular blocking agents (e.g. rocuronium, vecuronium) are known to form precipitates via acid-base reactions, which can lead to unexpected medical events, such as occlusion of intravenous (IV) tubing or embolism [1–3]. A great deal of care is required when applying anaesthesia, because various drugs are often injected together within a short time.

Sugammadex antagonises aminosteroidal muscle relaxants by encapsulation. It allows rapid and complete reversal and can even be used for deep and profound neuromuscular blockade. Compared with neostigmine, sugammadex minimises residual neuromuscular blockade and does not have cholinergic side effects, such as bradycardia, nausea and vomiting [4]. Therefore, sugammadex is increasingly being used in anaesthesia.

However, there is a paucity of clinical data about whether sugammadex forms precipitates with other medications widely used in clinical practice. Only a few short reports of crystal formation of sugammadex with amiodarone, dobutamine, protamine and labetalol have been published to date [5–7].

This *in vitro* study was performed to determine the drugs commonly administered with sugammadex that produce such precipitation reactions.

## Methods

Sugammadex and a number of drugs commonly used in anesthesia, i.e. rocuronium, neostigmine, glycopyrrolate, atropine, nitroglycerine, dobutamine, dopamine, epinephrine, vasopressin, norepinephrine, phenylephrine, ephedrine, esmolol, labetalol and nicardipine, were prepared. All drugs were tested at the concentrations used in the clinical setting. Table 1 provides information on the manufacturer and undiluted and diluted concentrations of the drugs. Nitroglycerin, vasopressin and norepinephrine were diluted with 5% dextrose water, while epinephrine, phenylephrine and ephedrine were diluted with 0.9% normal saline. The pH of each drug was measured using a pH meter (inoLab® pH 7110, xylem Analytics Germany GmbH, Weilheim, Germany). Samples of 1 mL of sugammadex were prepared in transparent cylinders, to which 1 mL of test drug was then added. Each mixture was observed by eye and light microscopy (BX-43; Olympus, Tokyo, Japan), and images were acquired. The existence and appearance of the particles of each mixture were evaluated by light microscopy. After observation, the pH of mixtures was determined using the pH meter.

Table 1  
Information of tested drugs

Agent	Original concentration	Experienced concentration	Trade name	Manufacturer
Sugammadex	100 mg ml <sup>-1</sup>		Bridion	MSD, New Jersey, USA
Rocuronium	1 mg ml <sup>-1</sup>		Esmeron	MSD, New Jersey, USA
Neostigmine	5 mg ml <sup>-1</sup>		Neostigmine	DAI HAN Pharm. Co., Seoul, Korea
Glycopyrrolate	0.2 mg ml <sup>-1</sup>		Mobinul	Myungmoon Pharm. Co., Seoul, Korea
Atropine	0.5 mg ml <sup>-1</sup>		Atropine Sulfate	DAI HAN Pharm. Co., Seoul, Korea
Nitroglycerin <sup>a</sup>	1 mg ml <sup>-1</sup>	0.25 mg ml <sup>-1</sup>	Nitrolingual	Pohl-Boskamp Co., Hohenlockstedt, Germany
Dobutamine	2 mg ml <sup>-1</sup>		DobutaminePremix	CJ HealthCare, Seoul, Korea
Dopamine	2 mg ml <sup>-1</sup>		Dopamix	CJ HealthCare, Seoul, Korea
Epinephrine <sup>b</sup>	1 mg ml <sup>-1</sup>	10 mcg ml <sup>-1</sup>	Epinephrine	DAI HAN Pharm. Co., Seoul, Korea
Vasopressin <sup>a</sup>	20 IU ml <sup>-1</sup>	1 IU ml <sup>-1</sup>	Vasopressin	HANLIM Pharm. Co., Seoul, Korea
Norepinephrine <sup>a</sup>	1 mg ml <sup>-1</sup>	10 mcg ml <sup>-1</sup>	Norpip	Dalim Biotech. Co., Gangwon-do, Korea
Phenylephrine <sup>b</sup>	10 mg ml <sup>-1</sup>	100 mcg ml <sup>-1</sup>	Phenylephrine HCl	HANA Pharm. Co., Seoul, Korea
Ephedrine <sup>b</sup>	40 mg ml <sup>-1</sup>	5 mg ml <sup>-1</sup>	Ephedrine HCl	Je il Pharmaceutical, Daegu, Korea
Esmolol	10 mg ml <sup>-1</sup>		Brevibloc	JEIL Pharmaceutical, Seoul, Korea
Nicardipine	1 mg ml <sup>-1</sup>		Perdipine	Dong-A ST., Seoul, Korea
Labetalol	5 mg ml <sup>-1</sup>		Labesin	Myungmoon Pharm. Co., Seoul, Korea

<sup>a</sup>Dilution with 5% dextrose water (JW Pharmaceutical, Seoul, Korea)

<sup>b</sup>Dilution with 0.9% saline (CJ HealthCare, Seoul, Korea)

## Results

Table 2 lists the pH of the drugs before and after mixing. The most marked reaction was observed with nicardipine, where white crystals formed on the top of the mixture and remained undissolved. The second strongest reaction was seen with labetalol, where the mixture appeared turbid to the naked eye but the precipitate dissolved after several minutes. There was no visible precipitate in the other mixtures. Figure 1 shows the control and sugammadex/nicardipine and sugammadex/labetalol mixtures. Figure 2 shows the results of microscopic analysis of the mixtures. Circular aggregates measuring 5–10 µm in diameter were observed in the mixture of nicardipine and sugammadex contained floating circular aggregates 2–6 µm in diameter. No visible precipitate was observed in the other mixtures.

Table 2  
pH of each drug before and after mixing with sugammadex.

Drugs	Before mixing	After mixing
Sugammadex	7.3	
Rocuronium	3.67	5.55
Neostigmine	4.77	7.35
Glycopyrrolate	2.03	7.16
Atropine	4.5	7.45
Nitroglycerin <sup>1</sup>	3.67	7.41
Dobutamine	2.83	7.18
Dopamine	3.21	7.15
Epinephrine <sup>2</sup>	4.39	7.38
Vasopressin <sup>1</sup>	4.04	7.45
Norepinephrine <sup>1</sup>	3.99	7.46
Phenylephrine <sup>2</sup>	4.4	7.3
Ephedrine <sup>1</sup>	4.75	7.29
Esmolol	4.65	6.84
Labetalol	3.78	7.28
Nicardipine	3.88	7.33

<sup>1</sup>Dilution with 5% dextrose water (JW Pharmaceutical, Seoul, Korea)

<sup>2</sup>Dilution with 0.9% normal saline (CJ HealthCare, Seoul, Korea)

## Discussion

The results showed that sugammadex reacts with nicardipine and labetalol under *in vitro*, producing precipitates that could be observed by both the naked eye and light microscopy.

A previous study also reported the formation of white precipitates when sugammadex was mixed with labetalol and, to a lesser degree with epinephrine, vasopressin and hydralazine [7]. Another experiment, in which 57 drugs used in anaesthesia were mixed with sugammadex, indicated that precipitation occurred with amiodarone (50 mg/ml), dobutamine (12.5 mg/ml), and protamine (1000 IU/ml); however, nicardipine and labetalol were not included in this previous study [5]. In contrast, we observed no precipitation in the mixtures of sugammadex with epinephrine, vasopressin or dobutamine. These discrepancy between the studies were probably due to differences in the drug concentrations and manufacturers.

Sugammadex, which is modified gamma-cyclodextrin, has a hydrophobic internal cavity and eight hydrophilic side chains. These structural properties make the complexes of lipophilic molecules and sugammadex water-soluble [8, 9]. Sugammadex and rocuronium form a rigid complex by two mechanisms. Firstly, hydrophobic interactions trap steroidal neuromuscular blocking agents in the cavity. Secondly, electrostatic binding occurs between the negatively charged carboxyl side chain of sugammadex and the positively charged quaternary nitrogen of rocuronium [10, 11]. In addition to aminosteroidal neuromuscular blocking agents, caution is required when using some other medications because they react with sugammadex. For example, the hormonal steroidal contraceptive, etonogestrel, is captured at a rate of 34% by 4 mg/kg sugammadex due to hydrophobic interactions [12]. Interactions due to the side chains of sugammadex have also been reported. For example, negatively charged sugammadex has been reported to react with positively charged protamine to form precipitate [6]. This mechanism may explain our experimental results, i.e. the positively charged amino groups of nicardipine and labetalol were assumed to react with the negatively charged sugammadex. These findings have clinical implications for anaesthesiologists. Firstly, nicardipine, labetalol and sugammadex can be administered within a short time in emergence situations. Insufficient fluid flushing between administrations of these drugs could lead to precipitate formation, resulting in occlusion within the IV tubing. Secondly, changes in the efficacy of sugammadex are also possible, suggesting that residual neuromuscular blockade can occur despite administration of the appropriate dose. Thirdly, the precipitate may form emboli that obstruct blood vessels, resulting in organ damage. Red blood cells have a diameter of 7 µm, so particles larger than this size can clog capillaries. In animal experiments, it has been reported that particles larger than 30 µm caused pulmonary embolism and cerebral infarction [13, 14].

This study had several limitations. Firstly, not all drug classes were included in the investigation. Additional experiments on the interactions of sugammadex with sedatives, narcotic drugs, analgesics, anti-emetics and fluids are required. Secondly, the drugs in this study were selected based on the author's clinical setting. Drugs made by other manufacturers may show different reactions due to differences in additives or concentrations. Thirdly, it is not yet clear how various substances and enzymes in the plasma

affect precipitation. The temperature and pH of plasma are also different from the experimental environment in the present study. Further studies regarding the effects of these reactions on the efficacy of sugammadex are required.

## Conclusions

In conclusion, sugammadex formed precipitate when mixed with nicardipine or labetalol *in vitro*. Sufficient fluid flushing is required between injections of each drug to prevent these reactions.

## Abbreviations

IV: intravenous

## Declarations

### Ethics approval and consent to participate

Ethic approval and patient consent was waived due to the retrospective design.

### Consent for publication

Not applicable

### Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests

### Funding

No funding received

### Authors' contributions

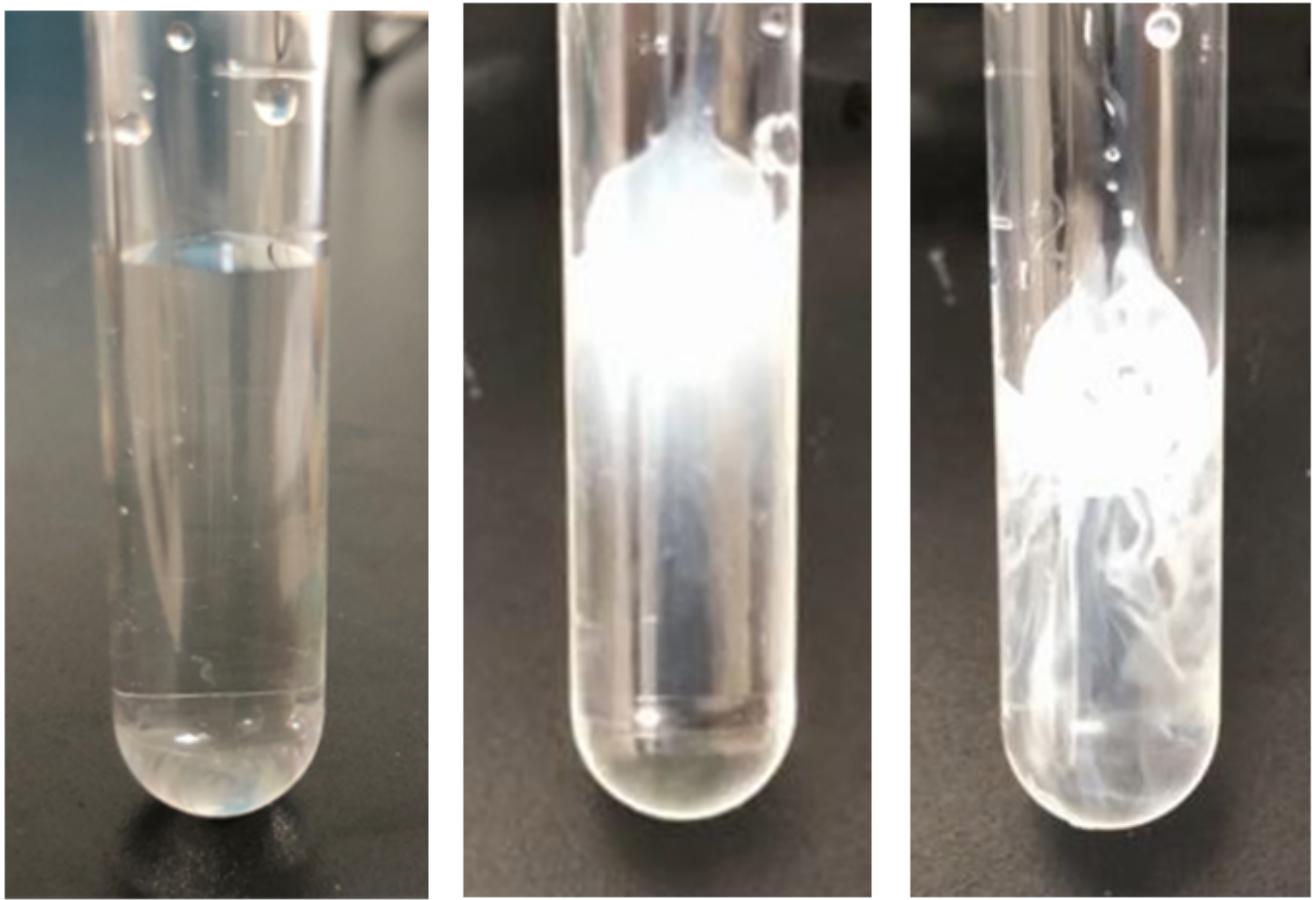
Conceptualization: J.H., B.Y.K; Study validation: B.Y.K.; Data Acquisition: J.H.; Data analysis and interpretation: J.H., A.-Y.O.; Writing original draft: J.H.; Revising and Editing draft: A.-Y.O.; Supervision: A.-Y.O. All authors have read and approved the submitted manuscript. All authors have agreed both to be personally accountable for the author's own contributions and all aspects of the work.

**Acknowledgements:** The authors thank division of Healthcare Innovation Park at Seoul National University Bundang Hospital for laboratory use.

## References

1. Hwang H, Park J, Lee WK, et al. Crystallization of Local Anesthetics When Mixed With Corticosteroid Solutions. *Ann Rehabil Med.* 2016;40(1):21–7.
2. Taniguchi T, Yamamoto K, Kobayashi T. The precipitate formed by thiopentone and vecuronium. *Can J Anaesth.* 1996;43(5 Pt 1):511–3.
3. Khan S, Stannard N, Greijn J. Precipitation of thiopental with muscle relaxants: a potential hazard. *JRSM Short Rep.* 2011;2(7):58.
4. Hristovska AM, Duch P, Allingstrup M, Afshari A. Efficacy and safety of Sugammadex versus Neostigmine in reversing neuromuscular blockade in adults: a Cochrane systematic review with trial sequential analysis. *Acta Anaesth Scand.* 2017;61(8):967–8.
5. Hanci V, Kiraz HA, Omur D, Ekin S, Uyan B, Yurtlu BS. Precipitation in Gallipoli: sugammadex / amiodarone & sugammadex / dobutamine & sugammadex / protamine. *Braz J Anesthesiol.* 2013;63(1):163–4.
6. Alston TA. Precipitation of sugammadex by protamine. *J Clin Anesth.* 2011;23(7):593.
7. Olsen KR, Lupi R, Dillon F, White JD. Sugammadex and labetalol precipitation. *J Clin Anesth.* 2020;61:109680.
8. Zhang MQ. Drug-specific cyclodextrins: the future of rapid neuromuscular block reversal? *Drug Future.* 2003;28(4):347–54.
9. Nag K, Singh DR, Shetti AN, Kumar H, Sivashanmugam T, Parthasarathy S. Sugammadex: A revolutionary drug in neuromuscular pharmacology. *Anesth Essays Res.* 2013;7(3):302–6.
10. Adam JM, Bennett DJ, Bom A, et al. Cyclodextrin-derived host molecules as reversal agents for the neuromuscular blocker rocuronium bromide: synthesis and structure-activity relationships. *J Med Chem.* 2002;45(9):1806–16.
11. Bom A, Bradley M, Cameron K, et al. A novel concept of reversing neuromuscular block: chemical encapsulation of rocuronium bromide by a cyclodextrin-based synthetic host. *Angew Chem Int Ed Engl.* 2002;41(2):266–70.
12. Zwiers A, van den Heuvel M, Smeets J, Rutherford S. Assessment of the potential for displacement interactions with sugammadex: a pharmacokinetic-pharmacodynamic modelling approach. *Clin Drug Investig.* 2011;31(2):101–11.
13. Taniguchi T, Yamamoto K, Kobayashi T. Precipitate formed by thiopentone and vecuronium causes pulmonary embolism. *Can J Anaesth.* 1998;45(4):347–51.
14. Macdonald RL, Kowalcuk A, Johns L. Emboli enter penetrating arteries of monkey brain in relation to their size. *Stroke.* 1995;26(7):1247–50; discussion 50-1.

## Figures



(a)

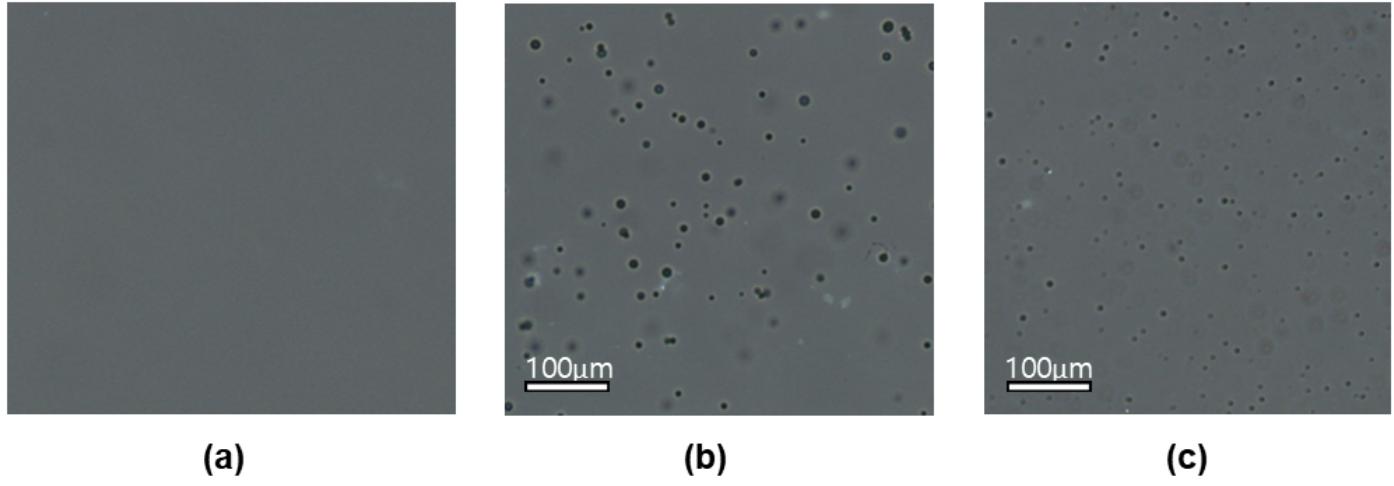
(b)

(c)

**Figure 1**

**Mixtures of sugammadex and nicardipine, labetalol**

(a) Control (b) Nicardipine with sugammadex (c) Labetalol with sugammadex



**Figure 2**

**Optical micrographs (100x) of precipitations**

(a) Control (b) Nicardipine with sugammadex (c) Labetalol with sugammadex