NMR studies of Sugammadex formulations complexes with steroidal neuromuscular blockers drugs Rocuronium and Vecuronium

Marcus Paulo Alves dos Santos1 · Priscila Goes Camargo2 · Felipe Oliveira1 · Carlos Rezende1

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Abstract
Sugammadex a modified γ-cyclodextrin forms strong water-soluble complexes with steroid neuromuscular blockers (NMBs) such as Rocuronium and Vecuronium, creating a concentration gradient that favors the displacement of these drugs from the neuromuscular junction to the plasma, quickly reversing the neuromuscular obstruction. This work described the comparative evaluation between two formulations of Sugammadex solution from Blau Farmacêutica S/A compared to reference formulation Bridion®, by Nuclear Magnetic Resonance (NMR) 1H and DOSY techniques. The formulations were evaluated in presence of Rocuronium and Vecuronium in the stoichiometric proportions of 1:1 and 1:0.4 for both NMBs. NMR 1H spectra of the formulations Blau and Bridion® did not show significant variations of chemical shifts showing similar physico-chemical parameters. Chemical shifts and diffusion coefficients of NMBs were influenced by the presence of Sugammadex when compared to NMBs formulations in the absence of any cyclodextrin, directly demonstrating the strong intermolecular interaction associated with the host molecule in a high proportion. No significant variation in the diffusion coefficients of the key components between formulations in the presence of NMBs in the equimolar 1:1 and 1:04 w/w ratios was observed. The constants $K_a$ and $K_D$ were determined and presented 16.7 and 0.06 mM values respectively, according to literature for this system.

Keywords Host–guest interaction · Formulation · Nuclear Magnetic Resonance (NMR) spectroscopy · Cyclodextrin

Introduction
Neuromuscular blockers (NMB) are used in clinical practice in more than 230 million surgical procedures worldwide. These compounds are considered essential because they support airway instrumentation and improve surgical conditions such as endotracheal intubation, artificial ventilation, and reduced abdominal muscle tone, complementing general anesthesia [1, 2].

Among the steroidal compounds used for this purpose, Pancuronium was first introduced in the 1968s in clinical practice. Due to its long action duration time, later in the 1990s, other NMB with intermediate action time began to be introduced such as Vecuronium, with a shorter duration of action (40 min) and a lack of hemodynamic side effects. In sequence, Rocuronium, a structural analog of Vecuronium with faster onset has also started to be used in clinical practices [3].

However, residual neuromuscular blockade may persist in the post-operative period, causing impairment of respiratory function and airway-rotective reflexes [4]. Although the introduction of intermediate-acting NMBs such as Rocuronium and Vecuronium has decreased, there is still an incidence of residual neuromuscular blockade. Thus, acetylcholinesterase inhibitors, such as neostigmine, are used as NMBs reversers, increasing the useful life of the neurotransmitter acetylcholine in neuromuscular junctions, presenting competition with NMBs molecules for postsynaptic nicotine receptors. Furthermore, in some cases, the use of acetylcholinesterase inhibitors is not indicated for inducing systemic cholinergic side effects, in addition to acting slowly and
not being indicated for the reversal of deep neuromuscular blockade [5–7].

As an alternative, a potent and rapid reversing agent for neuromuscular blockers has been developed, Sugammadex (ORG-25969), a modified γ-cyclodextrin (Fig. 1A). Sugammadex can reverse neuromuscular blockade by encapsulating steroidal agents such as Rocuronium and Vecuronium (Fig. 1B) at an average time of fewer than two minutes [8, 9].

In addition to being effective, Sugammadex (commercially available as Bridion® Merck Sharp & Dohme) is a safe drug, approved in 2008 by the European Medicines Agency (EMEA), by the American Food and Drug Administration (FDA) in 2015, and recently in 2017, approval for pediatric use by a child with ≥ 2 years old in China [9–11]. Furthermore, Sugammadex has the benefit of not affecting cholinergic receptors and eliminating the need to use the combination of acetylcholinesterase inhibitors with antimuscarinic agents with fewer adverse side effects compared to traditional reversal [12–14].

NMR spectroscopy is a powerful tool for studying the structure, interactions, and dynamics of biological macromolecules as well as has been used to study inclusion complexes between cyclodextrin and different ligands [15, 16]. This technique is the most widely used to study cyclodextrin complexes [17], including the Diffusion Ordered Spectroscopy (DOSY) method [1, 15, 18], which relies on the self-diffusion coefficients of the free guest (ligand) and host (cyclodextrin) that differ significantly in size [1, 19]. The frequencies of the signals from the hydrogen nuclei (chemical shifts) of each component of the sample are observed in the 1H NMR spectrum. The chemical shifts of hydrogen atoms present in a sample molecule are influenced by connectivity, stereochemistry, conformation, and by intermolecular interactions with other components [20].

The work aimed to apply the NMR 1H and DOSY techniques, for a comparative evaluation of Sugammadex solutions formulations from Blau Farmacêutica S/A compared to reference formulation Bridion®. In addition, an investigation of the molecular interactions measuring dissociation constant of host–guest complex, diffusion coefficient, and complexed molar fraction was provided.

**Experimental section**

**Materials and sample preparation**

Two Sugammadex formulations from Blau Farmacêutica S/A (S1 and S2) and one reference formulation Bridion® from Schering-Plough (S3) were used in the experiments both containing Sugammadex concentration of 100 mg/mL. Rocuronium Bromide was obtained from Schering-Plough containing a concentration of 10 mg/mL.

The API (Active Pharmaceutical Ingredient) of the neuromuscular blockers Vecuronium Bromide from Cristália LTDA were reconstituted in water for injections resulting in stock solutions at final concentrations of 10 mg/mL. Solutions with API of the Sugammadex from Manufacturer 1 (AP1 1) and Manufacturer 2 (API

![Fig. 1](image-url) **A** Schematic arrangement from Sugammadex sodium molecular structure; **B** Molecular structure from neuromuscular blockers Rocuronium and Vecuronium and schematic representation of aqueous inclusion complex of Sugammadex and Rocuronium. Adapt from Welliver et al. [16]
2) were reconstituted in water for injections resulting in stock solutions at final concentrations of 100 mg/mL.

A total of 11 samples (S1–S11) for binding studies were prepared by mixing appropriate quantities of each component, resulting in final concentration solutions of Sugammadex = 18 mg/mL and Rocuronium = 4.8 mg/mL or Vecuronium = 5 mg/mL at a stoichiometric equimolar ratio of 1:1, in the final volume of 500 µL. In addition, nine samples (S12–S20) were prepared similarly resulting in final concentration solutions of Sugammadex = 50 mg/mL and Rocuronium = 4.8 mg/mL or Vecuronium = 5 mg/mL at a 1:0.4 w/w ratio in the final volume of 500 µL (for more details information see supporting information).

Details and general settings for \(^1\)H and DOSY experiments

The NMR \(^1\)H and DOSY experiments were performed in a Bruker Advance III spectrometer operating at 400.13 MHz for \(^1\)H at 298 K, equipped with a 5 mm multinuclear probe. The DOSY experiments were performed using the ledbpqps2 pulse.

sequence provided by Bruker\(^{®}\), recorded with 32 scans, and two spoil gradients using 16 different gradient values varying from 5 to 95% of the maximum gradient strength, \(d_1 = 1.00\) s and \(d_20 = 0.06\) s. According to each case, the gradient pulse p30 values ranged from 1250 to 2000. A glass capillary with D\(_2\)O was inserted into the 5-mm NMR tube with aqueous solutions samples to help the magnetic field homogeneity. The water suppression was made using a pre-saturation zgpr pulse sequence provided by Bruker\(^{®}\). The diffusion dimension was processed with the processing program DOSYToolbox (Manchester NMR Methodology Research Group, Version 2.7-2016) applying a factor of 1 exponential fit of Fourier Transform Lorentzian function in the diffusion axis. The baseline was automatically corrected, and the list of diffusion coefficient (\(D\)) values was acquired in the same program.

Complexed fraction, \(K_a\) and \(K_D\) determination by DOSY

The determination of the complexed ligand fraction was performed by the acquisition of DOSY experiments and calculated by Eq. 1 [17]:

\[
f = \frac{D_G - D_{obs}}{D_G - D_{HG}}
\]  

where \(f\) is the complexed fraction, \(D_G\) is the ligand diffusion coefficient non-bonded, \(D_{obs}\) is the ligand diffusion coefficient bonded, \(D_{HG}\) is the macromolecule diffusion coefficient.

The association constant (\(K_a\)), and dissociation constant (\(K_D\)) were calculated using Eqs. 2 and 3, respectively [17, 21]:

\[
K_a = \frac{f}{(1 - f)([H] - f[L])}
\]  

\[
K_D = \frac{1}{K_a}
\]

where [H] is the total macromolecule concentration and [L] is the total ligand concentration, \(f\) is the complexed fraction.

Results and discussion

Evaluation of the formulations by \(^1\)H NMR experiments

The neuromuscular blockers Rocuronium and Vecuronium are approximately a quarter of the size of Sugammadex cyclohextrin. In this way, the comparison of the diffusion coefficient of the cyclohextrin–NMB complex with the free cyclohextrin could give information about the interactions of the formed complex [22]. Herein we report a study of the samples (S1 and S2) of the two Sugammadex solution formulations with different APIs, developed by Blau Farmacêutica compared to a reference formulation Bridion\(^{®}\) (S3) by NMR \(^1\)H and DOSY techniques.

Firstly, the \(^1\)H NMR spectrum was obtained for the three formulations and showed similar chemical shifts for the cyclohextrin proton’s signals, at 5.10 ppm, and other peaks around 2.42 to 3.97 ppm as shown in Fig. 2.

In addition, the chemical shifts of the three formulations: Blau/API1 (S1), Blau/API2 (S2), and Bridion\(^{®}\) (S3) reveal no significant variation, as shown in Table 1. This suggests that the physicochemical parameters are similar, and the differences present in the samples are not able to influence the spectral profile of these three formulations.

The same analysis was performed for the chemical shifts of the neuromuscular blockers (NMBs) Rocuronium and Vecuronium solutions in the absence of Sugammadex (S4 and S5, respectively), i.e., as free form, and we performed the comparison between their respective peaks in the solutions in the presence of cyclohextrin (bonded form) from the two Blau’s formulations and reference Bridion (S6–S11).

Herein, we showed the differences observed for the peaks of Rocuronium and Sugammadex as free solutions (S4 and S1, respectively), and in a mixed solution with
both components (S6) (Fig. 3). We can observe that in addition to the difference in chemical shifts, the signal profile of the components also had a slight distortion, especially the cyclodextrin signals in the region of 2.00 to 4.00 ppm (Fig. 3). It is reported in the literature that the complexation between the host molecule as cyclodextrin with ligands induces the structural changes and this is reflected in the changes in the chemical shift values of NMR [23, 24].

The main changes in the peak profile of the rocuronium can be observed for all signals on average of variation in chemical shifts from 0.02 to 0.14 ppm, except signals that were overlapping by cyclodextrin and could not be compared, as shown in Table 2. About the signals from Sugammadex, only one peak was observed in a clean region without superposition at 5.07 ppm and showed a variation of 0.02 ppm in the chemical shifts. A similar profile was observed for the Blau API2 and Bridion reference formulations (S7 and S8) and can be consulted in the supplementary material.

To Blau API1 (S9) formulation in the presence of Vecuronium, it was observed only two isolated signals, at 0.82 and 2.08 ppm. The other signals expected for this compound were superimposed on the signals from Sugammadex around 2.44 to 3.86 ppm (Fig. 4). Again, differences in chemical shifts and this case, a greater distortion in the signal profile were observed for both...
components, especially for the peaks at 2.50 at 4.00 ppm from Sugammadex (Fig. 4).

The main changes in the peak profile of the Vecuronium could be observed for only two signals isolated with a variation in chemical shifts from 0.04 to 0.05 ppm, the other ones were overlapping by cyclodextrin and could not be compared, as shown in Table 3. About the signals from Sugammadex, the one isolated peak was observed at 5.02 ppm and showed a variation of 0.04 ppm in the chemical shifts. A similar profile was observed for the

| Rocuronium in S4 (free) | Rocuronium in S6 (bonded) | Difference  |
|------------------------|---------------------------|-------------|
| 5.94–6.05 (m)          | 5.99–6.09 (m)             | 0.05–0.04   |
| 5.53–5.63 (m)          | 5.57–5.73 (m)             | 0.04–0.10   |
| 3.63 (br)              | sp                        | –           |
| 3.50 (q)               | sp                        | –           |
| 3.28 (s)               | sp                        | –           |
| 2.18 (s)               | 2.20 (s)                  | 0.02        |
| 2.07 (br)              | 2.09 (br)                 | 0.02        |
| 1.97 (s)               | 1.83 (s)                  | 0.14        |
| 0.81 (d)               | 0.86 (d)                  | 0.05        |

| Sugammadex (S1) (free) | Sugammadex (S6) (bonded) | Difference  |
|------------------------|---------------------------|-------------|
| 5.06 (br)              | 5.07 (br)                 | 0.01        |
| 3.93 (br)              | sp                        | –           |
| 3.83 (t)               | sp                        | –           |
| 3.52–3.55 (m)          | sp                        | –           |
| 3.02 (d)               | sp                        | –           |
| 2.86–2.90 (m)          | sp                        | –           |
| 2.74 (t)               | sp                        | –           |
| 2.38 (br)              | sp                        | –           |

sp rocuronium signals superimposed with cyclodextrin signals, br broad, d dupelet, m multiplet, s singlet, t triplet, q quartet
Blau API2 and Bridion reference formulations (S10 and S11) and can be consulted in the Supplementary Material.

These findings revealed an important variation in chemical shifts resulting from the complexation of Rocuronium and Vecuronium with the host molecule. In addition, demonstrated that the three formulations have similar physicochemical parameters in the presence of the NMBs.

**DOSY experiments and determination of diffusion coefficient host–guest complexes**

In order to investigate in more detail the interactions between Sugammadex and the NMBs Rocuronium and Vecuronium in the formulations, we applied the DOSY technique, a well-established NMR method that describes diffusion coefficients for individual resonances in NMR spectra, useful for analyzing complex mixtures of small molecules and biomolecules [17].

The diffusion coefficients ($D$) of the cyclodextrin and the neuromuscular blockers Rocuronium and Vecuronium were determined by DOSY experiments (Figs. S5–S11) of the samples S1–S11 at a stoichiometric equimolar ratio of 1:1 to compare the possible difference in complex formations (Table 4).

Diffusion coefficients observed in samples S4 of Rocuronium ($D = 4.80 \times 10^{-10}$ m$^2$ s$^{-1}$, Fig. 5A) and S5 of Vecuronium ($2.84 \times 10^{-10}$ m$^2$ s$^{-1}$, Fig. 5B) in a solution without Sugammadex are significantly higher than its diffusion observed in all three formulations solutions, Blau/API1 (Fig. 6A, B), Blau/API2 (Figs. 6–S7)
and Bridion (Figs. S8–S9) containing Sugammadex, where Rocuronium presented $D$ values between 2.00 and $2.20 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ (Table 4) and for Vecuronium $D$ values between 1.66 and $1.83 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ (Table 4).

This difference is consistent considering the expected complexation of neuromuscular blockers with cyclodextrin and demonstrates that in the solutions analyzed, Rocuronium and Vecuronium are strongly associated with the host molecule in a high proportion. In addition, the 1:04 w/w stoichiometric ratio also was evaluated, and no significant variation was observed (see more details in supporting information).

This variation in $D$ values of NMBs in the presence and absence of cyclodextrin allows the calculation of complex fractions for these neuromuscular blockers [15]. Formulations of all Sugammadex: NMBs complexes evaluated, demonstrated to associate with the host molecule, with complexed fractions ranging from 0.90 at 0.94 to samples containing Rocuronium, and approximately 1.00 to samples containing Vecuronium (Table 5).

The association constant ($K_a$) [17], and dissociation constant ($K_D$) [21] determined for samples containing rocuronium, presented $K_a$ values ranging from 16.7 at 95.5 mM and $K_D$ values between 0.01 at 0.06 mM. For samples containing vecuronium, only formulation from Blau API 2 (S10) could be determined and presented a value of $K_a = 1100$ mM, indicating a high potential of association and consequently low values of $K_D = 9.09 \times 10^{-4}$. The other samples presented complexed

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### Table 3

| Sugammadex (S5) (free) | Vecuronium (S9) (bonded) | Difference |
|-----------------------|-------------------------|------------|
| 3.50–3.73 (m)         | sp                      | –          |
| 3.04 (br)             | sp                      | –          |
| 2.73 (d$_{up}$)       | sp                      | –          |
| 2.61 (d$_{up}$)       | sp                      | –          |
| 2.06 (d)              | 2.10 (d)                | 0.04       |
| 0.76 (d)              | 0.81 (d)                | 0.05       |

$sp$ vecuronium signals superimposed with cyclodextrin signals, $br$ broad, $d$ duplet, $d_{up}$ aparent duplet, $m$ multiplet, $t$ triplet

### Table 4

| Samples | $D$ ($10^{-10} \text{ m}^2 \text{ s}^{-1}$) |
|---------|------------------------------------------|
|         | Sugammadex | Rocuronium | Vecuronium |
| S1 (Sugammadex Blau/ API1) | 1.83 ± 0.03 | – | – |
| S2 (Sugammadex Blau/ API2) | 1.84 ± 0.02 | – | – |
| S3 (Sugammadex Bridion) | 1.85 ± 0.02 | – | – |
| S4 (Rocuronium) | – | 4.80 ± 0.17 | – |
| S5 (Vecuronium) | – | – | 2.84 ± 0.04 |
| S6 (Blau/API1 + Rocuronium) | 1.91 ± 0.03 | 2.00 ± 0.00 | – |
| S7 (Blau/API2 + Rocuronium) | 2.06 ± 0.02 | 2.20 ± 0.02 | – |
| S8 (Bridion + Rocuronium) | 2.08 ± 0.08 | 2.12 ± 0.04 | – |
| S9 (Blau/API1 + Vecuronium) | 1.76 ± 0.03 | – | 1.66 ± 0.01 |
| S10 (Blau/API2 + Vecuronium) | 1.68 ± 0.01 | – | 1.83 ± 0.03 |
| S11 (Bridion + Vecuronium) | 1.78 ± 0.03 | – | 1.69 ± 0.02 |

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molar fraction close to 1.00 indicating to associate with the host molecule in a high proportion making it difficult to determine the association/dissociation constants because of strong binding. In addition, it is reported that $K_D$ values for Vecuronium can be 3.1 times higher than for Rocuronium [25]. Finally, the results of a formulation containing Rocuronium according to literature, reports that Sugammadex and NMBs are very stable complex, which presents an extremely high association constant and a very low dissociation constant because of strong binding [19].

**Conclusions**

The NMR $^1$H spectra of the formulations from Blau and Bridion did not show significant variations of chemical shifts, demonstrating that the three formulations have similar physicochemical parameters. The spectroscopic parameters, chemical shifts, and diffusion coefficients of both NMBs evaluated were influenced by the presence of Sugammadex compared to the absence of cyclodextrin, showing strong intermolecular interaction and a high association proportion of the NMBs with the host molecule. Additionally, no significant variation in the $D$ coefficients of the key components between the two Blau formulations and the Bridion reference.
in NMBs solutions, in the equimolar (1:1) and w/w (1:04) ratios evaluated were observed.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s10847-022-01162-1.

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**Author contributions** MS conceived the idea presented. MS, PC and CR developed the theory and performed the calculations. FO developed the formulation of the test drug, an injectable solution of Sugammadex Sodic. PC supervised the results of this work. FO and CR verified and

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**Table 5** Complexed fractions ($f$), association constant ($K_a$), and dissociation constant ($K_d$) from NMBs Rocuronium or Vecuronium with Sugammadex (equimolar ratio 1:1) in the analyzed samples S6–S11

| Samples                  | $f$  | $K_a$ (mM) | $K_d$ (mM) |
|--------------------------|------|------------|------------|
| S6 (Blau/API1 + Rocuronium) | 0.94 | 95.5       | 0.01       |
| S7 (Blau/API2 + Rocuronium) | 0.90 | 16.7       | 0.06       |
| S8 (Bridion + Rocuronium)  | 0.91 | 22.7       | 0.04       |
| S9 (Blau/API1 + Vecuronium) | > 1.0 | n.d.       | n.d.       |
| S10 (Blau/API2 + Vecuronium) | 0.99 | 1100       | 9.09×10^{-4} |
| S11 (Bridion + Vecuronium)  | > 1.0 | n.d.       | n.d.       |

n.d. not determined
performed the analytical methods. All authors discussed the results and contributed to the final manuscript.

**Data availability** The data that supports the findings of this study are available in the supplementary material of this article.

**Declarations**

**Conflict of interest** There are no conflicts to declare.

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