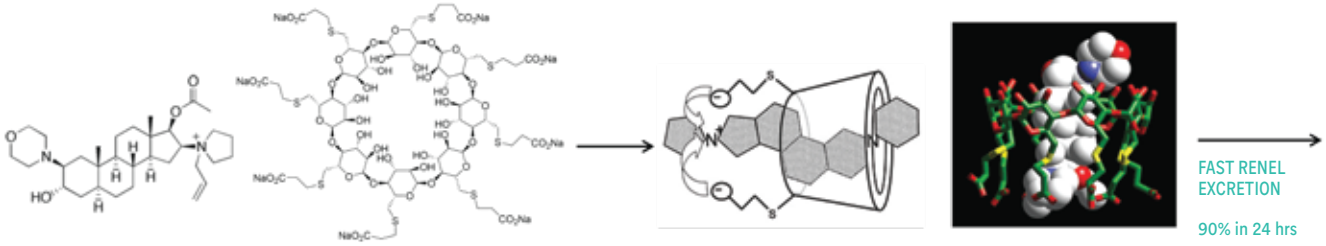
SUGAMMADEX SODIUM – the impact of an integrated understanding from API to formulation on injectable formulation success.

Sugammadex sodium is one of the key molecules in Dr. Reddy's API portfolio and an ideal use case on how a thorough understanding of the interaction between API and formulation can significantly improve the robustness of the formulation process considering the drug substance's proneness to degradation in the formulation process, specifically during the terminal sterilisation (TS) process for intravenous injection.

Structural features and Characteristics of Sugammadex

Sugammadex is an agent for the reversal of neuromuscular blockade induced by rocuronium and vecuronium in general anaesthesia.



Sugammadex sodium is a modified γ-cyclodextrin, which contains eight recurring glucose units each with five asymmetric carbon atoms, in a total of 40 asymmetric carbon atoms in the whole molecule. The active substance is a octa-sodium salt, which is highly but reversibly hygroscopic and quite sensitive to oxidative stress. The synthesis of sugammadex sodium is challenging as it requires the complete conversion of eight identical functional groups per molecule, giving rise to multiple permutations of high levels of impurities. Most of these impurities are structurally close to sugammadex and have similar physico-chemical characteristics, which require advanced analytical methods to be reliably separated, identified and quantified.

Our development approach

We adopted QbD (Quality by Design) and an integrated drug developmental approach, looking not only at the API but also studying the formulation. The QTPP (Quality Target Product Profile) of the API was determined considering the drug substance's proneness to degradation in the formulation process, specifically during the terminal sterilisation (TS) process for intravenous injection.

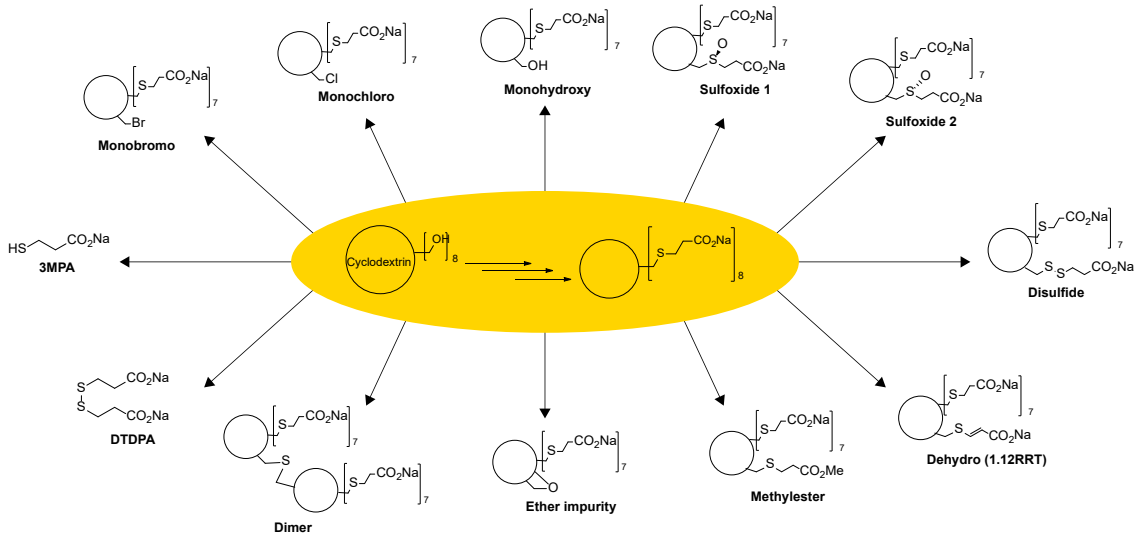


Figure 1. Potential impurities formed during the synthesis

The product by process relationship was understood and monitored using PAT (Process Analytical Testing) tools to determine the kinetics of the reactions and reaction pathways, and iterative DoEs (Design of Experiments) establishing the individual and interactive variables' impact on selected CQAs (critical quality attributes of drug substance) to determine a robust design space which enables a robust scale-up of operations. The CMAs (Critical Material Attributes) were defined by studying the impurity carryovers and their impact on the drug substance and the product quality resulting in an established control strategy for starting raw materials. The same approach has been established for the CPPs (Critical Process parameters) during all API synthetic steps.

Since, Sugammadex sodium is the TS (Terminal Sterilisation) product, it can undergo oxidation and degradation during the terminal sterilisation process. The resulting drug product should be either superior or in-line with RLD. The key to successful drug development is to start with high purity (>99%) API and with adequate control on specified potential degradation impurities so as to ensure that impurities at all stages of formulation manufacturing and also in the stability period are well within the target specifications of the finished formulation. In summary, we have established an interrelationship between the quality of the drug substance and the drug product to define the CQAs (Critical Quality Attributes) of the API. Figure 2 below shows the behaviour and the impurity profile of the Dr. Reddy's API during the formulation process and an exemplary comparison with the innovator product.

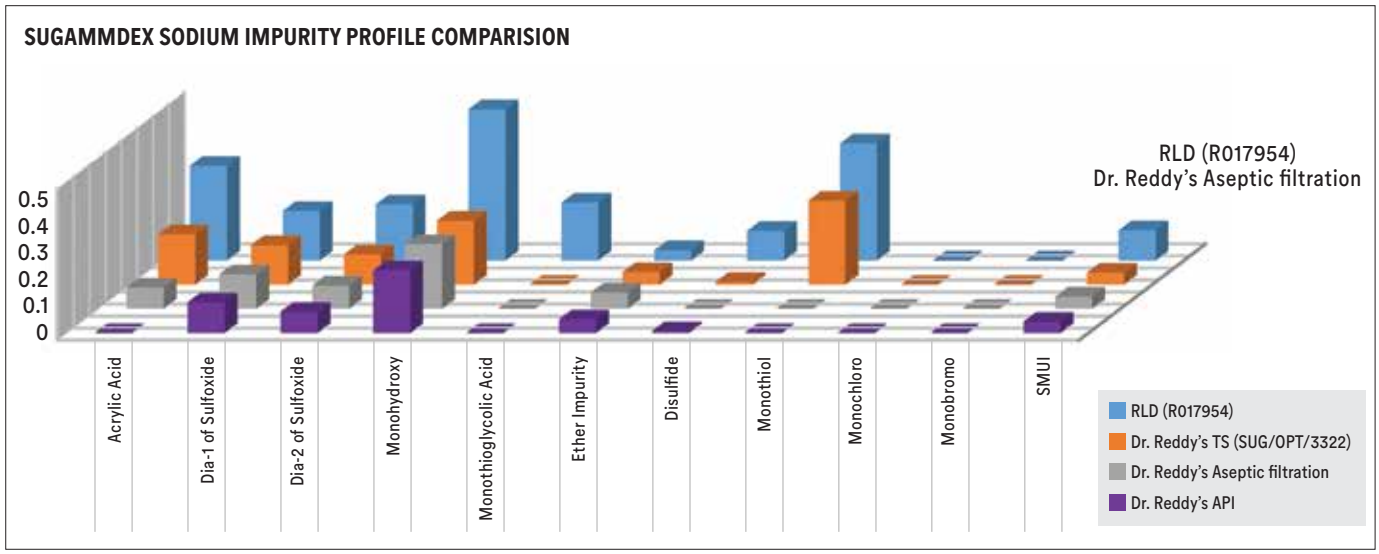


Figure 2. Impurity profile of the API during formulation steps, showing the drug substance's proneness to degradation, specifically during the terminal sterilisation (TS) process for intravenous injection.

Development outcome

- Consistent API quality (Purity > 99%) and compliance with ICH1 quality
- Identified, characterised and synthesised nearly 18 complex impurities
- Advanced analytical tools (React IR, Raman spectroscopy, FBRM for real time particle size analysis etc.) and techniques used for process development
- Reaction calorimetry (RC1), powder safety studies , dynamic vapour sorption (DVS), TGA, and DSC performed to understand molecule behaviour under different environmental conditions
- Innovative chromatographic purification technique adopted to achieve highest quality (Purity >99%)
- State of the art manufacturing facility designed to handle sensitive APIs and capable of producing multi tons of sugammadex sodium annually
- Strict facility controls in place to control the microbial load essential for sterile injectables

Dr. Reddy's has the capabilities and expertise to reliably supply sugammadex sodium. Our team of experts are happy to discuss the specific and unique features of sugammadex sodium supporting the rapid development of your drug product.

Log in to our digital service portal XCEED or get in touch with us to know more about our API portfolio.

References

1. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-guideline-q11-development-manufacture-drug-substances-chemical-entities-biotechnological/biological-entities_en.pdf