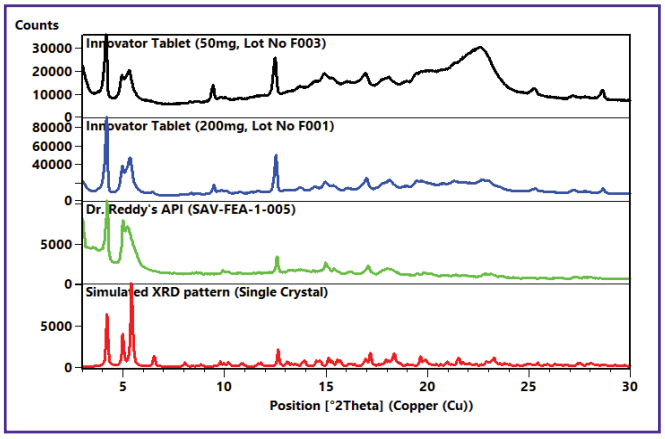
Sacubitril/Valsartan (LCZ696) – Bringing yet another advantage through innovative offerings

LCZ696 API development strategy

Our team of process and analytical experts draw on their integrated understanding in both the development and manufacturing of the API and the formulation. This is of particular importance when it comes to the characterization of a molecular complex which is critical for a successful API and formulation development. This holistic view, also helps to better understand the impact of the formulation process on the molecular integrity and stability of the product. As a result, our development of this supra molecular complex, was able to robustly match the characteristics of the reference listed drug (RLD).

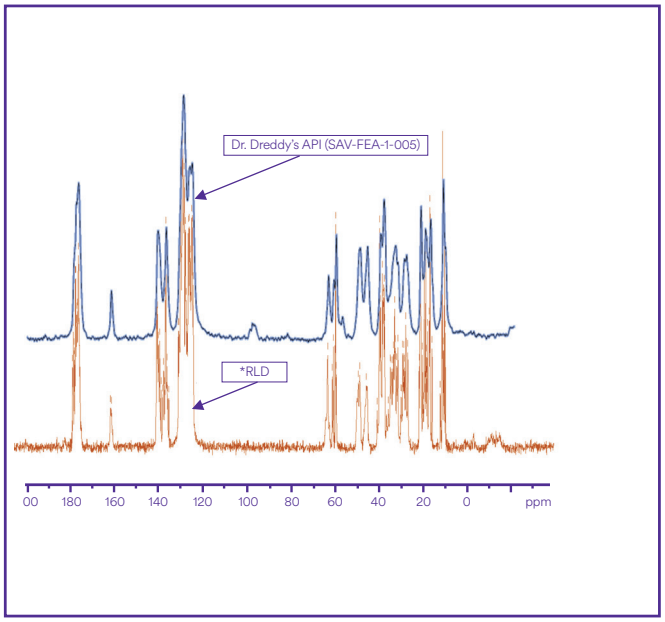
Extensive analytical tools and techniques have been adopted to demonstrate the API characterization by comparing solid state ^{13}C-NMR and ^{23}Na-NMR, IR, TGA and XRD:

PXRD comparison



- The PXRD identification peaks of Dr. Reddy's API are matching with the RLD API identification peaks.
- The polymorphic form of the Dr. Reddy's Sacubitril/Valsartan API is similar to the RLD.

Solid state NMR comparison



- Solid state data of Dr. Reddy's Sacubitril/Valsartan co-crystal studied and compared with published ^{13}C NMR of Sacubitril/ Valsartan co-crystal.
- The SS-NMR patterns were found to be similar to each other confirming the existence of the co-crystal nature of Dr.Reddy's API and RLD.
- The chemical nature of Dr. Reddy's API matches with RLD.

Sacubitril/Valsartan is a supra molecular complex comprised of the anionic forms of Sacubitril and Valsartan, together with sodium cations and water molecules in the molar ratio of 1:1:3:2.5.

This whitepaper outlines Dr. Reddy's development and characterization approach for the Active Pharmaceutical Ingredient (API) and how formulation success and early market reach can be facilitated.

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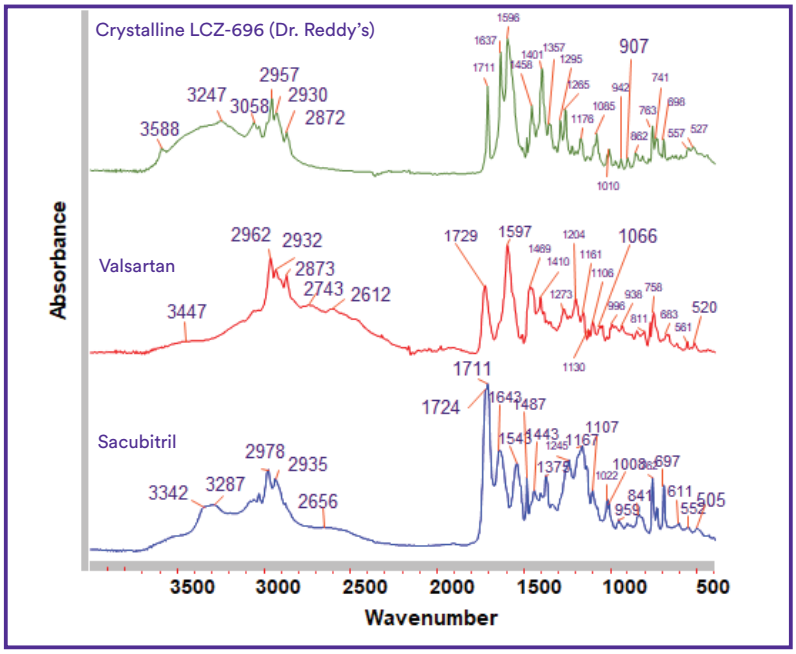
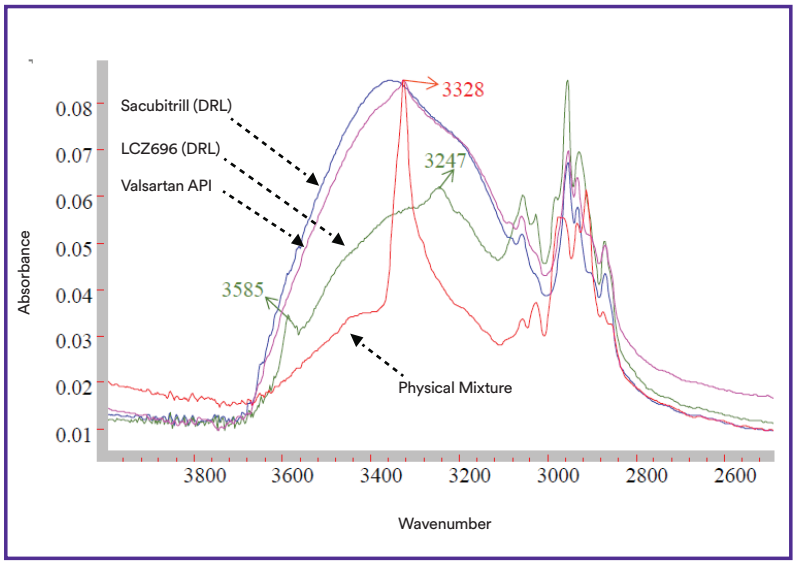
FT-IR (Fourier-transform infrared) spectroscopic studies



- FT-IR data suggest unique signatures for the innovator co-crystal form.
- N-H...N interaction is also observed by IR spectroscopy.
- N-H stretching appears at 3247 cm^{-1} in the co-crystal (LCZ696) and at 3328 cm^{-1} in the physical mixture of Sacubitril and Valsartan.
- Dr. Reddy's API is a supra-molecular complex.

IR Data: Probing H- Bonding Interaction (N-H...N)



Robust stability

The stability studies (accelerated, Zone-IVB and Zone-II stability condition) is ongoing and the more than three-year stability data shows no change either in the impurity profile or the polymorph conversion (the polymorphic signature (4.7 % of water in the crystal lattice) is retained throughout the stability period). The API is stable at ambient conditions.

Customized particle size

The crystallization process has been designed to produce preferred solid state properties amenable for formulation. However, our particle engineering experts are happy to address customised PSD requirements with size reduction operations and crystallization techniques.

Backward integrated manufacturing

With the backward integration of key starting materials (KSMs) such as Sacubitril and Valsartan and a multistep synthesis, we aim to provide a highly pure API while ensuring a reliable supply for our partners. Dr. Reddy's is a leading manufacturer of Valsartan API which is free from nitrosamine impurities by process design (**Click here** to read more on our Sartan APIs offerings) and DMFs comply with the future regulatory requirements of Europe, US, Japan, Brazil, China etc.

Beyond APIs – a flexible supply model

Dr. Reddy's is among the few API suppliers who can offer a flexible supply model, which goes beyond the supply of the API. Fully forward integrated, Dr. Reddy's is able to provide its partners with formulation technology transfers, semi-finished formulation supply or complete formulation supply.

Polymorph	DMF / Dossier filings	Oral finished dose formulation dossier availability
Valsartan; Sacubitril trisodium hemipentahydrate	• USDMF • EDMF • China DMF	—
Alternate polymorph	• Granules/tech pack	LCZ696 48% DC granules (semi-finished formulation bio equivalent to US-RLD) with tech pack available for supply/tech transfer of formulation along with technical and regulatory support for registration.
	• FDF Dossier	Finished dose formulation for Sacubitril; Valsartan is available in below presentations with BE studies against US RLD for out-licensing / drug product supply 24 mg; 26 mg Tablets 49 mg; 51 mg Tablets 97 mg; 103 mg Tablets Bulk tablets pack stability studies for all zones is available.

Dr. Reddy's is well positioned to meet the global demand for this API. Strongly driven by an integrated understanding of API attributes, manufacturing capacity and backward integrations, we are able to provide assurance of supply. Dr. Reddy's enables its partners for the successful formulation development with different polymorphic variants in the form of both semi-finished andfinished formulation for bringing their drug product to the markets faster.

To know more about various offerings and business models, log-into customer service portal **XCEED** or contact us at api@drreddys.com.