Sitagliptin case: Enhancing formulation development and early market access through an integrated understanding of key API attributes

Sitagliptin API Development Strategy

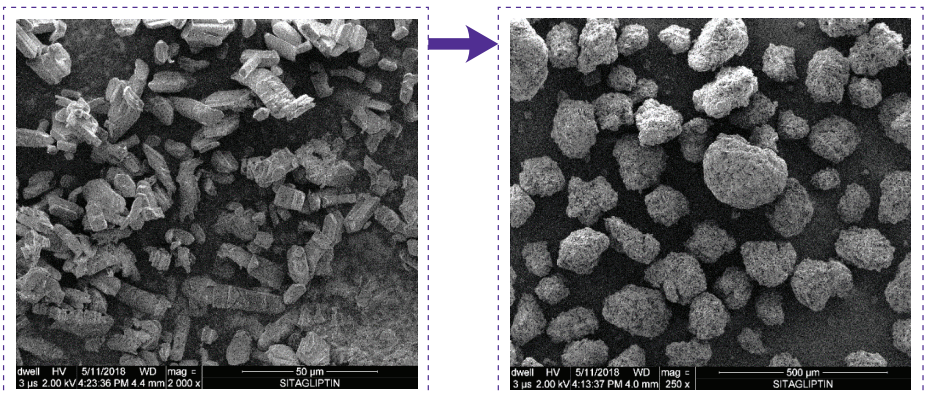
Our team of experts draw on their integrated understanding in the development and manufacturing of the API and the formulation. This is of particular importance when it comes to particle engineering and powder flow characteristics which are critical for a successful formulation development. The integrated approach, also helps to better understand the impact of the formulation process on the impurity and dissolution profile or to select the right manufacturing equipment. This in-depth of expertise has enabled Dr. Reddy's to develop a wide range of particle sizes and associated powder properties to ensure that Sitagliptin API offers critical quality attributes which are crucial for the successful formulation development (PCT application filed).

For Sitagliptin, Dr. Reddy's has chosen a synthetic route, which is cost competitive and sustainable, and optimization techniques such as design of experiments (DoE), telescoping and process intensification are applied. This approach resulted in a consistently high purity of the API (>99.99 %).

Particle Engineering Innovation

The above mentioned approach is further complemented by a robust crystallization technique which is able to transform needle shaped particles into spherical agglomerate shaped particles. The most amenable particle size for formulation has been shown in the phosphate anhydrous form of Sitagliptin. The key advantage of the particle size optimization has resulted in superior flow properties, which aid formulation processability and reduce the probability of product wastage, assay variability and delays during formulation.

Needle Shape converted into Spherical Shape



Needle Shape
with poor flowability

Spherical Particles
with improved flowability

The comparison of needle shape particles and spherical particles of Sitagliptin Phosphate Anhydrous is as below:

Particle Shape	Spherical Shape	Needle Shape
Typical PSD (Un milled)	D90: 100-200 µm	<50 µm
BD (g/ml)	0.54	0.33
TD (g/ml)	0.68	0.65
CI (%) Compressibility index (< 25 gives good flow)	21	50
Hausner Ratio (<1.25 is indicative of good flow)	1.2	2
Uniformity of dosage unit (acceptance value <15)	<5	>10
API behaviour during formulation process	Suitable for dry granulation process. No granules build-up on surfaces.	Granules build-up is high on surfaces leading to API loss and assay variability.

A thorough understanding of the API's solid form and its alternate salts, powder properties and impurity profile can significantly minimize the risk of unexpected issues during formulation development. Understanding of its impurity profile and its variation during formulation, strongly influences the outcome, cost and timing in the development of the final drug product. Together with the right selection of the solid state form considering IP rights, and a flexible supply model which goes beyond the API, the time to market can be significantly accelerated.

This whitepaper outlines the multipronged strategy for the development and supply of Sitagliptin.

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Sitagliptin HCl API is available in a range of particle sizes from D90 < 20 microns by crystallization to D90 > 300 microns by compaction to meet different formulation needs (wet or dry granulation) or technology preferences.

Sitagliptin phosphate monohydrate is available with PSD around 100 to 150 microns by crystallization, and around 20 microns by micronization.

Robust Stability

The stability of Sitagliptin API has been tested under thermal, open stress conditions. The stability studies (accelerated, Zone-IVB and Zone-II stability condition) is ongoing and 1+ year stability data shows no change either in the impurity profile or the polymorph conversion (the PXRD pattern is retained throughout the stability period). The total impurity is controlled below 0.1 % (USP limit 0.5 %)

Backward Integrated Manufacturing

With the backward integration of Key Starting Material (KSM) and a multistep synthesis, we aim to provide high purity API with cost in control which provide our partners reliable supply assurance. The complete backward integration of critical KSM is planned by mid-2021.

In view of generic launches starting from July 2022 in various geographies, Dr. Reddy's is currently expanding its production capacity by setting-up a dedicated state-of-the-art API facility in India to manufacture Sitagliptin in multi ton quantities and large batch sizes. This will enable us to supply within short lead times, reduced testing time while meeting the increased market demands.

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, DMFs and complete formulation supply.

Sitagliptin is available in the following salts and formulations in different geographies

Polymorph	DMF filing	Oral finished dose formulation dossier availability
Sitagliptin HCl Monohydrate	• USDMF • EMDF • KDMF	• Sitagliptin HCl Monohydrate 25, 50 and 100 mg tablets • Sitagliptin HCl Monohydrate + Metformin HCl 50 mg / 500 mg, 50 mg / 1000mg tablets
Sitagliptin Phosphate Anhydrous	• USDMF	• Sitagliptin Phosphate 25, 50, 100 mg tablets • Sitagliptin Phosphate + Metformin HCl IR - 50 mg / 500 mg , 50 mg / 1000mg tablets • Sitagliptin Phosphate + Metformin HCl XR - 50 mg / 500 mg; 50 mg / 1000mg ; 100 mg / 1000mg tablets
Sitagliptin Phosphate Monohydrate form	• Brazil DMF, China DMF, US DMF & CEP filing planned in 2020	• Development planned in 2021

Dr. Reddy's is well positioned to meet the global demand for Sitagliptin API strongly driven by an integrated understanding of API attributes and capacity to manufacture. Dr. Reddy's enables its partners for successful formulation development with different polymorphic variants and a backward integrated manufacturing strategy.

To know more about various offerings and business models, log-into customer service portal XCEED (https://api.drreddys.com/customer_portal/login) or contact us at api@drreddys.com.