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INCREASING SOLUBILITY AND THERMAL STABILITY OF AMORPHOUS SOLID DISPERSION VENETOCLAX PREPARED BY SPRAY DRYING METHOD

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ABSTRACT

Venetoclax is a selective BCL-2 inhibitor used in the treatment of hematological malignancies such as chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML). Despite its clinical importance, it is classified as a Biopharmaceutical Classification System (BCS) Class IV compound due to its low water solubility and permeability, making oral formulation development challenging. The overall objective of this study was to improve the solubility of venetoclax by preparing an amorphous solid dispersion (ASD) and to provide an alternative venetoclax dispersion with a more stable structure than the reference product produced using a hot melt extruder manufacturing method under high stress conditions.

KEYWORDS: Venetoclax Amorphous Formulation, Amorphous Quality by Design (QbD) for Scale-Up, Spray Drying and Hot Melt Extrusion, Solubility Enhancement BCS Class IV API's.

INTRODUCTION

At the beginning of the studies, a solid dispersion of Venetoclax was obtained using equipment from the Chinese brand using a hot melt extruder, a production method equivalent to the reference product. However, the high processing temperatures required for the hot melt extruder (>300°C) and the thermal sensitivity of Venetoclax led to concerns about degradation of samples obtained by the HME method under stress conditions. Alternatively, spray drying was used to obtain amorphous solid dispersions at lower temperatures, preserving the integrity of the active pharmaceutical ingredient.

Following several production trials, the designed unit formula was formulated using spray-dried dispersions, polymers such as polyvinylpyrrolidone (PVP), and surfactants such as polysorbate, poloxamer, and SLS. The feasibility of the study was assessed according to physical and chemical analysis specifications in accordance with European Pharmacopoeia standards.

Data from the studies confirm that spray drying is a feasible and scalable approach to improve the solubility of thermally labile drugs such as venetoclax and offers a practical alternative to traditional HME techniques.

Hot Melt Extruder General Information

In the pharmaceutical industry, the Hot Melt Extruder (HME) is one of the most modern and advanced formulation technologies. It plays a critical role in many areas, including increasing the solubility and bioavailability of poorly water-soluble active ingredients (APIs), developing controlled release systems, and enabling solvent-free production.[3]

Picture 1: Twin-Screw Extruder Device (Commercial Size).

Applications of HME in the Pharmaceutical Industry are as follows;[4]

- **Amorphous Solid Dispersions (ASD):** Enhance solubility of poorly water soluble APIs.
- **Controlled Release Formulations:** Use of polymers to regulate drug release.
- **Orodispersible Films (ODF):** Rapidly dissolving oral strips.
- **Multi-layer Systems (Co-Extrusion):** Different release profiles or APIs in one dosage.
- **Pediatric Formulations:** Taste masking, chewable structures.

The advantages and disadvantages of using HME technology in the pharmaceutical industry are as follows.[5]

Table 1: Advantages and Disadvantages of Using Hot Melt Extruders in the Pharmaceutical Industry.

ADVANTAGES	DISADVANTAGES
Solvent-free and environmentally friendly	Not suitable for heat-sensitive APIs
Continuous manufacturing compatible	High initial equipment cost
Improved bioavailability for poorly soluble APIs	Requires polymer-API compatibility studies
Taste masking for pediatric formulations	Complex process validation needed
Scalable from lab to commercial production	

Spray Drying General Information

Spray drying is a drying technology widely used in the pharmaceutical industry. This method rapidly produces a dry powder from a liquid solution, suspension, or emulsion. [6]

Picture 2: Spray Dryer Lab. Scale Device.

Applications of Spray Dryer in the Pharmaceutical Industry are as follows;[7]

- **Drying of Thermolabile Substances:** Allows drying of heat-sensitive active pharmaceutical ingredients (APIs) without degradation by exposing them to hot air for milliseconds.
- **Development of Powder Formulations:** Produces powders suitable for inhalation, oral, nasal, or parenteral delivery routes.
- **Control of Particle Size & Morphology:** Enables control over particle size, shape, surface area, and porosity, affecting solubility and bioavailability.
- **Production of Amorphous Forms:** Converts crystalline APIs into amorphous forms to enhance solubility and dissolution rate.
- **Encapsulation with Excipients/Polymers:** APIs are spray-dried with polymers to achieve controlled release, taste masking, and improved stability.
- **Improved Solubility for Poorly Soluble APIs:** Ideal for BCS Class II & IV drugs to enhance solubility via solid dispersion or particle size reduction.

The advantages and disadvantages of using Spray Drying technology in the pharmaceutical industry are as follows:[5]

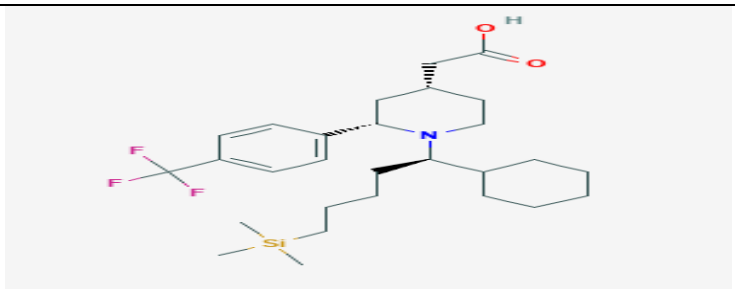
Table 2: Advantages and Disadvantages of Using Spray Dryer in the Pharmaceutical Industry.

ADVANTAGES	DISADVANTAGES
Fast and continuous process	Suitable for industrial-scale manufacturing
Minimal thermal degradation	Protects heat-sensitive drugs
Tailored particle properties	Adjustable size, density, surface area
Suitable for amorphous solid dispersions	Improves dissolution and bioavailability
Compatible with GMP production	Widely used in pharmaceutical manufacturing under regulatory standards

Chemical Characteristics of Venetoclax

The characteristic features of Venetoclax raw material, which is supplied from ALEMBIC source in all product development processes, are as follows:

Table 3: Physical, Chemical and Characteristic Properties of Venetoclax.

Physical, Chemical And Characteristics Of Venetoclax	
Structure [8]	
Drug Name (INN) [9]	Venetoclax
CAS Number [8]	1257044-40-8
Molecular Formula [8]	$C_{45}H_{50}ClN_7O_7S$
Molecular Weight [8]	868.4 g/mol
Chemical Class [10]	BCL-2 inhibitor, Aromatic sulfonamide derivative
Mechanism of Action [10]	Selective inhibition of B-cell lymphoma-2 (BCL-2) protein to promote apoptosis
Physical Appearance [10]	Light yellow to dark yellow solid
Melting Point [8]	~138 °C
Boiling Point [8]	Not available (decomposes)
Solubility in Water[8], [10]	< 0.0042 µg/mL at pH 7.4 (practically insoluble)
pKa [8]	~11.6 (basic piperazine nitrogen)
BCS Classification [8]	Class IV
Hygroscopicity [9]	Non-hygroscopic
Crystallinity [9], [10]	Polymorphic, converted to amorphous via ASD
Thermal Stability [9]	Sensitive >160 °C
Photostability [9]	Light sensitive.
Oxidative Sensitivity [9]	Prone to oxidative degradation
Storage Conditions [10]	Store below 25°C, protected from light and moisture
Regulatory Status [8], [10]	FDA/EMA approved for CLL and AML

MATERIAL AND METHOD

MATERIAL

Venetoclax active substance was procured by (ALEMBIC) The excipient which are used as respectively; Polyvinylpyrrolidone (BASF), Calcium Hydrogen Phosphate (LIANYUNGANG), Polysorbate (CRODA), Sodium Lauryl Sulfate (HUNTSMAN), Poloxamer (BASF), Colloidal Silicon Dioxide (EVONIK), Sodium Stearyl Fumarate (PRUV-JRS), Opadry II Yellow (COLORCON) and Acetone (MERCK) supplied. All raw materials used suitable for European Pharmacopoeia.

METHOD

Formulation Trial and Scale Up Studies

Experimental studies were conducted to develop the formulation of Venetoclax Film Coated Tablets. The formulation table for the experimental studies is detailed below.

Table 4: Composition of Venetoclax Film Coated Tablet Formulations (Spray-Dried Method).

Ingredients	Function	Trial 1 (% w/w)	Trial 2 (% w/w)	Trial 3 (% w/w)	Trial 4 (% w/w)	Trial 5 (% w/w)	Trial 6 (% w/w)	Trial 7 (% w/w)
Venetoclax	Active Substance	1–15	1–15	1–15	1–15	1–15	1–15	1–15
Polyvinyl Pyrrolidone (PVP)	Binder	10–40	10–50	20–60	25–65	30–70	-	-
Calcium Hydrogen Phosphate	Filler	10–70	10–60	10–50	10–40	10–30	10–40	10–30
Polysorbate	Surfactant	0–10	0–10	0–10	0–10	0–10	0–10	0–10
Poloxamer	Surfactant	-	-	-	-	-	0–10	-
Sodium Lauryl Sulfate	Surfactant	-	-	-	-	-	-	0–10
Colloidal Silicon Dioxide	Glidant	0.5–5	0.5–5	0.5–5	0.5–5	0.5–5	0.5–5	0.5–5
Sodium Stearyl Fumarate	Lubricant	0.25–2.50	0.25–2.50	0.25–2.50	0.25–2.50	0.25–2.50	0.25–2.50	0.25–2.50
Opadry Yellow	Film Coating Agent	2–5	2–5	2–5	2–5	2–5%	2–5	2–5%
TOTAL		**100.00**	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**

Manufacturing Method

Batch Size: 1,056 kg / 1000 Tablets

- All formulation trials were carried out with the spray drying method using the following production information and parameters.
    - Polysorbate, Polyvinylpyrrolidone and Venetoclax are mixed in Acetone until they dissolve.
- The solution was filtered using a 0.45 µm membrane filter. In case of clogging, a pre-filter system was used.
- The solution was processed using a standard spray dryer under the conditions shown in Table 5.

Table 5: All Trials Spray Drying Parameters.

	Value Ranges
Inlet Air Temperature	60–80 °C
Outlet Temperature	40–60 °C
Aspirator	100%
Pump Speed	5–10% (Approximately 3–6 mL/min)
Nozzle	0.7 mm (Standard Twin Fluid)
Atomization Gas (N_2 or Air)	600–800 L/h

Note: *Spray drying was preferred over HME to avoid thermal degradation. HME trials using brand extruder showed limitations due to excessive thermal exposure, which supports the selection of a low-temperature spray drying approach.*

The dried amorphous powder was sieved and blended with excipients including Calcium Hydrogen Phosphate and Colloidal Silicon Dioxide. Lubrication was completed with Sodium Stearyl Fumarate.

The flow properties of the final mixtures obtained during the studies were evaluated comparatively with the Carr Index and Hausner Ratio in Table 7 below.

Table 6: Carr Index and Hausner Ratio Results Evaluation Table.

Flow Properties	Carr's Index (%)	Hausner Rate
Excellent	5-15	1,05-1,18
Good	12-16	1,14-1,19
Appropriate	18-21	1,22-1,27
Weak	23-35	1,30-1,54
Very Weak	33-38	1,49-1,61
Extremely Weak	>40	>1,67

$$Carr's\ \text{Index} = \frac{Ptab - Pbulk}{\text{Ptab}}\ x\ 100 \qquad Hausner\ \text{Rate} = \frac{\text{Ptab}}{\text{Pbulk}}$$

Table 7: Carr Index and Hausner Ratio Results of Trials.

Trials Number	Carr Index	Hausner Ratio	Flow Properties
Trial 1	19.32	1.23	**Appropriate**
Trial 2	20.85	1.25	**Appropriate**
Trial 3	13.85	1.14	**Good**
Trial 4	15.10	1.17	**Good**
Trial 5	15.72	1.19	**Good**
Trial 6	18.05	1.22	**Appropriate**
Trial 7	19.27	1.22	**Appropriate**

- Final granules were compressed into tablets using a Rotab Bilayer tablet press machine, which ensured precise layer uniformity and consistent compaction force during tablet manufacturing.
- Core tablets were coated with Opadry Yellow solution using a standard film coating technique.

The comparative dissolution analysis results of trial productions and the reference product are as follows.

Table 8: Comparative Dissolution Profile of Reference Product and Entire Trial Production.

Comparative Dissolution Rates (%) Media: pH: 6,8 Phosphate %0,4 Sodium Lauryl Sulfate Method: 900 mL, 50 rpm, pedal				**Specifications** Maximum 50% after 5 hours Maximum 80% after 10 hours			
Samples	**30 min. (Half an Hour)**	**60 min. (1st Hours)**	**120 min. (2nd Hours)**	**240 min. (4th Hours)**	**300 min. (5th Hours)**	**480 min. (8th Hours)**	**600 min. (10th Hours)**
Original Product VENCLYXTO (Hot Melt Ex.)	**5,17**	**11,49**	**21,30**	**42,10**	**47,13**	**71,64**	**74,92**
Trial-1 (Spray Drying)	2,03	5.69	12,75	20.06	33,71	51,02	60,99
Trial-2 (Spray Drying)	2.15	7.50	15.36	26.90	39.00	57,11	67,79
Trial-3 (Spray Drying)	4.92	9.41	19.50	33.66	43.06	57,90	73,01
Trial-4 (Spray Drying)	**6.81**	**13,19**	**22,20**	**39,85**	**48,01**	**67,00**	**77,50**
Trial-5 (Spray Drying)	**8,18**	**19,05**	**28,27**	**45,71**	**55,14**	**75,45**	**92,61**
Trial-6 (Spray Drying)	0,88	2.55	8.62	15.99	31.02	39.75	45.33
Trial-7 (Spray Drying)	0,88	2.55	8.62	15.99	31.02	39.75	45.33

When we evaluated the results of the trial productions produced in order to prevent thermal degradation in Venetoclax and to reach higher solubility data with the alternative production method, the results of Trial-4, which exhibited a similar profile to the reference product dissolution values with the spray drying production method, and Trial-5, which had higher dissolution data than the reference product, were obtained.

It was decided to subject Trial-4, whose dissolution rate data were closer to the reference product, to stress conditions of 40°C ± 2°C – 75% RH ± 5, along with the reference product. The stability analysis results for Trial-4 and the reference product are as follows.

Table 9: Original Product Accelerated Term Stability Results.

Original Product (VENCLYXTO) Accelerated Stability 40°C ± 2°C – 75 % RH ± 5				
Tests	**Specifications**	**The Beginning Of Stability**	**3rd Month**	**6th Month**
Appearance	Yellow-yellowish oblong tablet.	Complies	Complies	Complies
Identification *Venetoclax*	Retention times of main peaks which are obtained from sample and standard solutions chromatograms should be similar.	Complies	Complies	Complies
Water Content	NMT 5.00 %	1,04 %	2,75 %	4,18 %
Assay *Venetoclax*	100 mg/fct ± 10.0% (90.00– 110.00 mg/fct)	100.81	95.03	92.75
Dissolution *Venetoclax*	Maximum 50% after 5 hours Maximum 80% after 10 hours	5th h: 47.13% 10th h: 4.92%	5th h:33.62% 10th h:65.05%	5th h:28.69% 10th h:61.25%
Related Substances				
Impurity-S1	Not more than 0.15% w/w	<D.L.	0.05 %	0.27 %
iImpurity-S1A	Not more than 0.15% w/w	<D.L.	0.10 %	0.24 %
Impurity-K3	Not more than 0.15% w/w	<D.L.	0.04 %	0.11 %
Impurity-S2B	Not more than 0.15% w/w	<D.L.	0.08 %	0.13 %
Impurity-S2C	Not more than 0.15% w/w	<D.L.	0.15 %	0.32 %
Impurity-S2G	Not more than 0.15% w/w	<D.L.	0.05 %	0.11 %
Any Individual Unspecified Impurity	Not more than 0.10% w/w	<D.L.	0.47 %	1.18 %
Total impurities	Not more than 0.50% w/w			

Table 10: Trial-4 Accelerated Term Stability Results.

Trial-4 Accelerated Stability 40°C ± 2°C – 75 % RH ± 5				
Tests	**Specifications**	**The Beginning Of Stability**	**3rd Month**	**6th Month**
Appearance	Yellow-yellowish oblong tablet.	Complies	Complies	Complies
Identification *Venetoclax*	Retention times of main peaks which are obtained from sample and standard solutions chromatograms should be similar.	Complies	Complies	Complies
Water Content	NMT 5.00 %	1,18 %	1.36 %	1.85 %
Assay *Venetoclax*	100 mg/fct ± 10.0% (90.00– 110.00 mg/fct)	102.72	99.50	97.08
Dissolution *Venetoclax*	Maximum 50% after 5 hours Maximum 80% after 10 hours	48.01% 77.50%	45.82% 73.29%	43.72% 70.75%
Related Substances				
Impurity-S1	Not more than 0.15% w/w	<D.L.	<D.L.	<D.L.
iImpurity-S1A	Not more than 0.15% w/w	<D.L.	0.05 %	0.08 %
Impurity-K3	Not more than 0.15% w/w	<D.L.	<D.L.	0.04 %
Impurity-S2B	Not more than 0.15% w/w	<D.L.	<D.L.	0.10 %
Impurity-S2C	Not more than 0.15% w/w	<D.L.	0.04 %	0.12 %
Impurity-S2G	Not more than 0.15% w/w	<D.L.	0.02 %	<D.L.
Any Individual Unspecified Impurity	Not more than 0.10% w/w	<D.L.	0.11 %	0.34 %
Total impurities	Not more than 0.50% w/w			

Scale Up Study Manufacturing Method

Batch Size: 10.560 kg / 10.000 Tablets

The Scale-Up study is planned to be 10 times larger than laboratory-scale manufacturing. The obtained samples were placed in accelerated stability (40°C ± 2°C/75 ± 5% RH) and monitored.

- Polysorbate, Polyvinylpyrrolidone and Venetoclax are mixed in acetone until they dissolve.
- The solution was filtered using a 0.45 µm membrane filter. In case of clogging, a pre-filter system was used.
- The solution was processed using a standard spray dryer under the conditions shown in Table 11.

Table 11: Scale Up Study Spray Drying Parameters.

Parameters	Value Ranges
Inlet Air Temperature	60–80 °C
Outlet Temperature	40–60 °C
Aspirator	100 %
Pump Speed	5–10% (Approximately 3–6 mL/min)
Nozzle	0.7 mm (Standard Twin Fluid)
Atomization Gas (N_2 or Air)	600–800 L/h

- The dried amorphous powder was sieved and blended with excipients including Calcium Hydrogen Phosphate and Colloidal Silicon Dioxide. Lubrication was completed with Sodium Stearyl Fumarate.

Table 12: Carr Index and Hausner Ratio Results Evaluation Table.

Flow Properties	Carr's Index (%)	Hausner Rate
Excellent	5-15	1,05-1,18
Good	12-16	1,14-1,19
Appropriate	18-21	1,22-1,27
Weak	23-35	1,30-1,54
Very Weak	33-38	1,49-1,61
Extremely Weak	>40	>1,67

$$Carr's\ \text{Index} = \frac{Ptab - Pbulk}{\text{Ptab}}\ x\ 100 \qquad Hausner\ \text{Rate} = \frac{\text{Ptab}}{\text{Pbulk}}$$

Bulk Density ($\mathbf{p}_{bulk}$): 0.51 (g/ml) Tapped Density ($\mathbf{p}_{tap.}$): 0.60 (g/ml)

Carr's Index: $\frac{0.60 - 0.51}{0.60} * 100 = 15.00$ Hausner Ratio (HR): $\frac{0.60}{0.51} = 1.18$

As indicated in the above formula and tables, both the Carr's index value is between 12-16 (15.00) and the Hausner Ratio (HR) is between 1.14 -1.19 (1.18) indicating that the dust flow is good.

- Final granules were compressed into tablets using a Rotab Bilayer tablet press machine, which ensured precise layer uniformity and consistent compaction force during tablet manufacturing.
- Core tablets were coated with Opadry Yellow solution using a standard film coating technique.

Scale Up Study Results

The analysis results of the finished product obtained from the scaling-up study were also found to be consistent when compared with the reference product. Since the analysis results of the samples obtained from the scaling-up study were consistent, a stability study was conducted on the product. The samples were subjected to accelerated stability testing (40°C ± 2°C/75 ± 5% RH) and monitored. Impurity specifications for the batch whose stability was monitored were

determined based on the impurity specifications in the "ICH Q3b R2 Impurities in New Drug Products" document. The stability results are presented in the tables 13 below.

Table 13: Scale up Study Finished Product Analysis Results.

Scale Up Study Accelerated Stability **40°C ± 2°C – 75 % RH ± 5**				
Tests	**Specifications**	**The Beginning Of Stability**	**3rd Month**	**6th Month**
Appearance	Yellow-yellowish oblong tablet.	Complies	Complies	Complies
Identification *Venetoclax*	Retention times of main peaks which are obtained from sample and standard solutions chromatograms should be similar.	Complies	Complies	Complies
Water Content	NMT 5.00 %	1.25 %	1.62 %	2.08 %
Assay *Venetoclax*	100 mg/fct ± 10.0% (90.00– 110.00 mg/fct)	101.75	97.49	95.25
Dissolution *Venetoclax*	Maximum 50% after 5 hours Maximum 80% after 10 hours	46.05% 78.33%	44.02% 75.10%	43.15% 72.00%
Related Substances *Impurity-S1* *Impurity-S1A* *Impurity-K3* *Impurity-S2B* *Impurity-S2C* *Impurity-S2G* *Any Individual* *Unspecified Impurity* *Total impurities*	 Not more than 0.15% w/w Not more than 0.15% w/w Not more than 0.15% w/w Not more than 0.15% w/w Not more than 0.15% w/w Not more than 0.15% w/w Not more than 0.10% w/w Not more than 0.50% w/w	 <D.L. <D.L. <D.L. <D.L. <D.L. <D.L. <D.L.	 0.02 % 0.07 % 0.01 % 0.03 % 0.06 % 0.05 % 0.24 %	 0.06 % 0.10 % 0.03 % 0.05 % 0.12 % 0.08 % 0.44 %

RESULTS AND DISCUSSION

1. PHYSICAL CHARACTERIZATION AND POWDER FLOW

The amorphous solid dispersions (ASDs) of Venetoclax produced via spray drying exhibited satisfactory powder flow properties across all formulation trials. Carr's Index values ranged from 13.85% to 20.85%, corresponding to "Good" to "Appropriate" flow, while Hausner ratios varied between 1.14 and 1.27 (Table 6). Trials 3 and 4 demonstrated the best combination of low Carr's Index (13.85% and 15.10%, respectively) and Hausner ratios within the ideal 1.14–1.19 range, indicating minimal interparticle cohesion and favorable processability during downstream unit operations such as tablet compression .

2. DISSOLUTION PERFORMANCE

Comparative dissolution testing against the reference product (VENCLYXTO ®, HME) was conducted in pH 6.8 phosphate buffer containing 0.4% SLS (900 mL, 50 rpm). The reference exhibited 47.1 % release at 5 h and 74.9 % at 10 h. Among the seven spray-dried trials, Trial 4 closely matched the reference profile (39.9% at 4 h, 48.0% at 5 h and 77.5% at 10 h), while Trial 5 surpassed it (45.7% at 4 h, 55.1% at 5 h and 92.6% at 10 h) (Table 8). These results confirm that appropriate selection of polymer-to-API ratio and surfactant levels in the spray-drying feed solution can yield dissolution performance equivalent or superior to HME-based ASDs, underscoring the efficacy of the low-temperature spray drying approach for thermolabile APIs .

3. ACCELERATED STABILITY

Accelerated stability studies (40 °C ± 2 °C/75% RH ± 5%) were carried out for both the reference product and Trial 4. After 6 months, Trial 4 maintained assay values within 97.1–102.7% of label claim and achieved 43.7% and 70.8% dissolution at 5 h and 10 h, respectively comparable to the reference (28.7% and 61.3%) (Tables 10). Total impurities remained below ICH-specified limits (<0.50% w/w), indicating that spray-dried ASDs preserved chemical stability and did not promote impurity formation under stress conditions.

4. SCALE-UP AND PROCESS DURABILITY

A ten-fold scale-up batch (10 kg) of the optimized formulation (Trial 4) was produced under identical spray-drying parameters. Bulk and tapped densities yielded a Carr's Index of 15.0% and Hausner ratio of 1.18, confirming reproducible powder flow at larger scale. Finished tablets retained assay (95.3–101.8%) and dissolution (43.2% at 5 h; 72.0% at 10 h) profiles comparable to laboratory scale batches and the reference product (Table 13). Accelerated stability of the scale-up batch further substantiated product robustness, with all quality attributes remaining within specification after 6 months .

5. IMPLICATIONS FOR MANUFACTURING

Collectively, these findings demonstrate that spray drying is a viable and scalable alternative to hot-melt extrusion for improving the solubility of Venetoclax. Operating at significantly lower temperatures minimizes thermal degradation and provides robust dissolution performance and stability for ASDs. This study, supported by experimental procedures, clearly demonstrated the cross-scale process reproducibility of Venetoclax Film Coated Tablets and their compliance with European Pharmacopoeia requirements.

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