Surface Measurement Systems
World Leader in Sorption Science

DVS Application Note 119

Moisture Induced Solvate to Hydrate Conversion of Elacestrant Dihydrochloride Insights from DVS and XRPD

Mahesha G R[2], Majid Naderi[1], Manaswini Acharya[1] & Dan Burnett[1],
Gunaseelan S[2], Kondagudur Ravindrachary[2], Manikanteswar Y[2], Ramkumar Ganesh[2]
[1] Surface Measurement Systems Ltd., [2]Particle Characterisation Laboratories. 4th Floor, Plot No. C-1, Block III IDA, Uppal, Hyderabad, Telangana-500039, India.

The moisture sorption behaviour of Elacestrant Dihydrochloride API was evaluated using Dynamic Vapor Sorption and iso-humidity exposure followed by XRPD analysis. The DVS sorption desorption profile showed solvate to hydrate conversion events at high humidity levels (90% RH), indicated by unusual mass loss during sorption. In the subsequent sorption cycle, moisture uptake was consistent with the formation of a hemi pentahydrate phase. Iso-humidity studies demonstrated physical stability of the compound at 0% and 60% RH , while exposure to 92% RH resulted in a clear polymorphic transformation, as verified by XRPD. These findings demonstrate moisture-induced crystallization[5] and hydrate formation at high humidity, with important implications for formulation and storage.

Introduction

DVS Resolution system[1,2] is designed to accurately measure a sample's change in mass as it adsorbs precisely controlled concentrations of water or organic vapours or gas molecules. A schematic of the system is shown in Figure 1.

In this study, a Benzyl Alcohol solvate of Elacestrant dihydrochloride[4] was selected to investigate its moisture-dependent phase behaviour.

Material details

Elacestrant dihydrochloride (Benzyl Alcohol-solvate) was provided by Dr. B S Natarajan (Alembic Pharmaceuticals, Alembic Road, Vadodara, Gujarat, India)

Molecular Formula: $C_{30}H_{38}N_2O_2 \cdot 2HCl$

Molecular Weight: 531.56 g/mol

Benzyl Alcohol Molecular weight: 108.14 g/mol

Elacestrant dihydrochloride benzyl alcohol solvate (1:1).

Therapeutic use: Elacestrant is used to treat advanced or metastatic ER-positive, HER2-negative breast cancer, especially after endocrine therapy[4].

Molecular structure

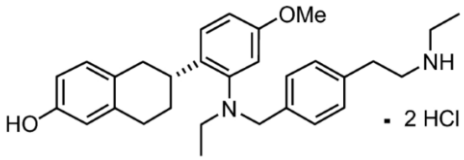

Figure 1. Molecular structure of Elacestrant dihydrochloride

Dynamic Vapor Sorption (DVS) was employed to evaluate the sorption–desorption profile and to monitor humidity-induced structural transitions. The DVS results revealed that the solvate exhibits clear moisture-triggered crystallization events at higher relative humidity, leading to a progressive solvate to hydrate conversion. To confirm the phase transformation, the sample was exposed to controlled humidity conditions and further characterized using X-ray Powder Diffraction (XRPD)[3], which verified the formation of a distinct and stable hydrate phase.

XRPD is one of the primary characterization techniques used in pharmaceutical research for

analyzing crystalline materials[10]. It provides unique diffraction patterns based on the crystal lattice, enabling differentiation between polymorphs[6], including solvates, hydrates, and amorphous forms, as well as identification of phase transitions.

In this study, XRPD analysis following iso-humidity exposure (0%, 60%, and 92% RH) using DVS confirmed that the crystalline structure remained stable at low humidity, while a transformation to a stable hydrate phase occurred at 92% RH. These findings demonstrate moisture induced solvate to hydrate conversion[8], highlighting the sensitivity of the material to high humidity. The combined DVS–XRPD approach provides a comprehensive understanding of humidity-driven solid-state transformations.

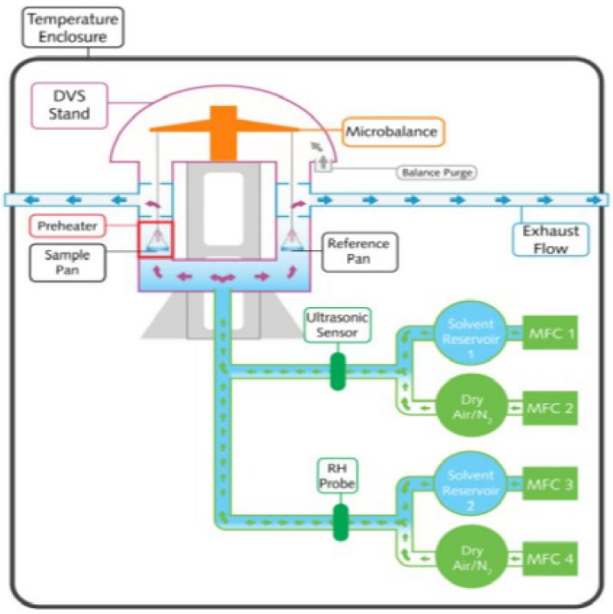

Figure 2: *Schematic of the DVS Resolution*

Methods

Dynamic Vapour Sorption:

Method 1: DVS analysis was conducted at 25°C using a DVS Resolution system equipped with a high-sensitivity low-mass balance. The gravimetric profile consisted of an initial sorption cycle started at 25°C and 50% RH conditions which is from 50–90% RH and followed by desorption cycle 90–0% RH and a subsequent second sorption cycle 0–90% RH in 10% RH increments. To ensure the completion of moisture-induced crystallization and desolvation events, a stringent equilibrium criterion (dm/dt) of 0.002%/min was applied, with a maximum stage timeout of 360 minutes.

Method 2: Iso-humidity experiments were conducted on the sample using separate experimental setups at fixed relative humidity conditions of 0%, 60%, and 92% at 25 °C. Each RH level was maintained for 2 hours under a time-controlled method.

X-ray Powder Diffraction (XRPD)

Analysis was carried out using a Bruker D8 ADVANCE diffractometer equipped with a Cu-Kα radiation source (λ = 1.5406 Å). Samples were mounted on zero-background holders and scanned over a 2θ range of 2–50° with a step size of 0.02° and a step time of 0.3 Seconds. Samples previously exposed to individual RH conditions using DVS were used for the analysis.

Result

DVS: Analysis of the first sorption cycle (50–90% RH) revealed a distinct mass loss between 80% and 90% RH (Figures 3 and 4), interrupting the expected moisture uptake trend. This anomalous weight reduction is characteristic of moisture-induced crystallization. The data suggests that the initial solvated state is metastable at elevated humidities; as water molecules penetrate the lattice, they facilitate a structural rearrangement, leading to the expulsion of excess solvent and the formation of a more thermodynamically stable hydrate phase.

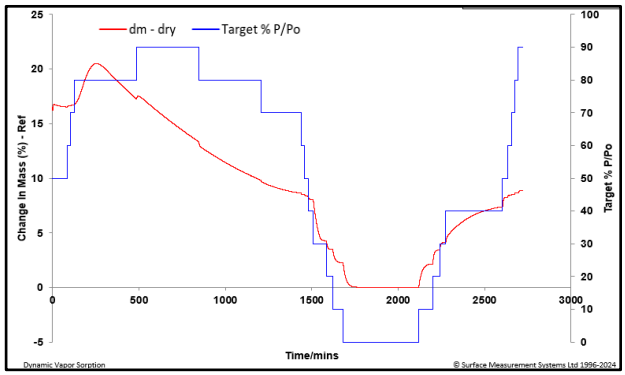

Figure 3: dm/dt Plot of sample Elacestrant dihydrochloride

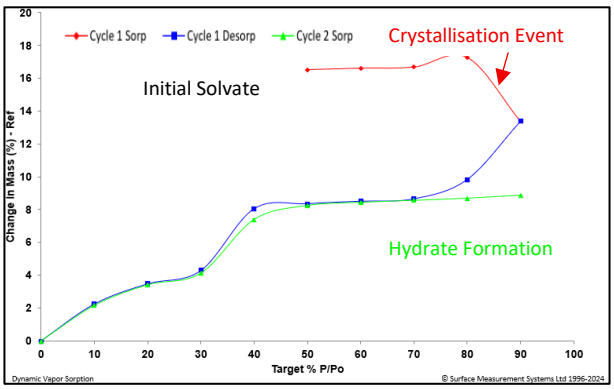

Figure 4: DVS Isotherm Plot of Elacestrant dihydrochloride

The total mass loss observed during the end of sorption-desorption phase at 0% RH ~16% to 17% indicated the presence of benzyl alcohol solvate molecules, within the crystal lattice refer DVS Isotherm Report (Figure 5).

The benzyl alcohol solvate content present in the API was calculated using the following relationship:

Hydrate/solvate stoichiometry = (Weight gain / 100) × (M.W. sample / M.W. solvent)

Based on the DVS isotherm data, the solvate content present in the API at 50% RH conditions was approximately 16.52%. As the sample exhibited complete desorption of the solvent during the desorption cycle, it was assumed that this value corresponds to the initial solvent content present in the material.

(17/100)/* (531.56/108.14) = 0.84

Since the stoichiometry is not an exact integer, likely due to the loss of Benzyl Alcohol during the sorption cycle, the calculated stoichiometric value of 0.84 can be considered as equal to 1. This suggests that the API exists as a 1:1 benzyl alcohol solvate, with one molecule of benzyl alcohol per molecule of API.

During subsequent sorption cycles, the samples displayed mass gain of approximately 8–9%, consistent with the theoretical hemi Pentahydrate formation.

For the calculation of hydrate content using Equation 1, the moisture uptake at 60% RH was considered.

Molecular weight of Water: 18 g/mol

(8.4/100)/* (531.56/18) = 2.5

The calculated stoichiometric value of 2.5 indicating that the API converts to a hemi Pentahydrate, i.e., Elacestrant dihydrochloride hydrate (1:2.5), corresponding to two and half molecules of water per molecule of API.

	Target % P/Po	Change In Mass (%) - ref Sorption	Desorption	Hysteresis
Cycle 1	0.0		0.00	
	10.0		2.24	
	20.0		3.48	
	30.0		4.28	
	40.0		8.04	
	50.0	16.52	8.35	-8.17
	60.0	16.61	8.51	-8.10
	70.0	16.68	8.65	-8.03
	80.0	17.26	9.82	-7.44
	90.0	13.36	13.36	
Cycle 2	0.0	0.00		
	10.0	2.16		
	20.0	3.42		
	30.0	4.12		
	40.0	7.39		
	50.0	8.24		
	60.0	8.43		
	70.0	8.55		
	80.0	8.68		
	90.0	8.87		

Decrease in mass indicates Crystallisation event

Figure 5: DVS Isotherm Report of Elacestrant dihydrochloride

The iso-humidity studies further confirmed these findings. Upon exposure to 0% RH for 2 hours, the sample exhibited a weight loss of approximately 2%, likely due to the removal of surface moisture or residual solvent. At 60% RH, a negligible weight gain of about 0.3% was

observed (Refer Figures 6 and 7), indicating that the compound remains physically stable under low to moderate humidity conditions, as supported by the PXRD data (Figure 9).

In contrast, exposure to 92% RH resulted in a significant mass increase of approximately 5.5%, confirming active moisture uptake and a solvate-to-hydrate transformation (Figure 8).

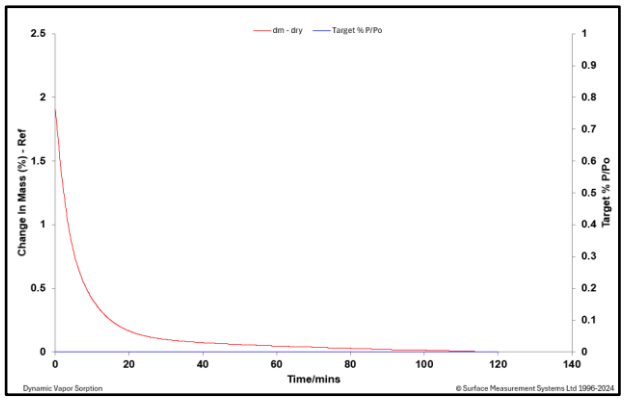

Figure 6: dm/dt Plot of Elacestrant dihydrochloride at 0% RH.

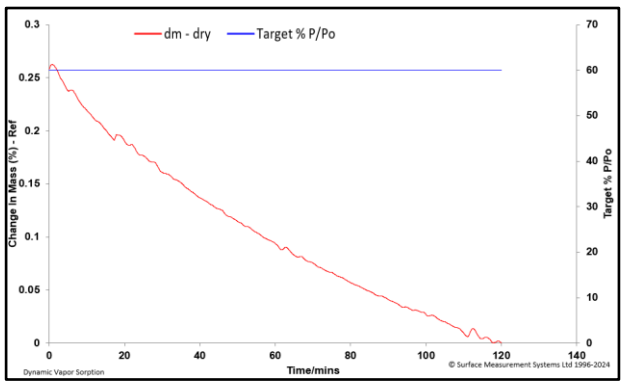

Figure 7: dm/dt Plot of Elacestrant dihydrochloride at 60% RH.

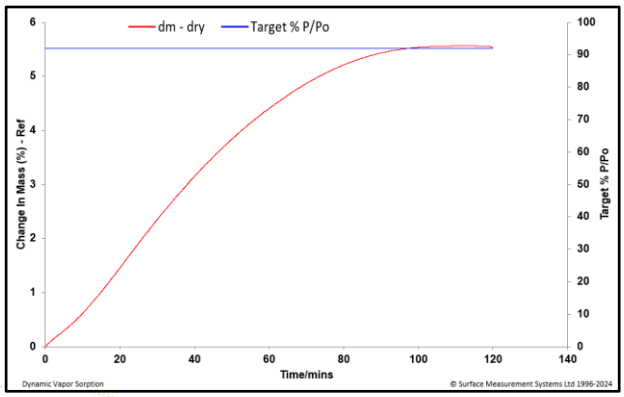

Figure 8: dm/dt Plot of Elacestrant dihydrochloride at 92% RH.

Iso-humidity analysis at 92% RH was conducted for 120 minutes, during which the sample absorbed approximately 5.5% moisture, which was sufficient to induce recrystallization of the API. Water acts as a plasticizer, increasing molecular mobility and enabling structural rearrangement. As a result, benzyl alcohol was released from the lattice due to reduced free volume and lower affinity of the crystalline structure for loosely bound solvent.

The conversion from benzyl alcohol solvate to hydrate occurs because water, being smaller and having stronger hydrogen-bonding ability, preferentially interacts with the API. This leads to displacement of benzyl alcohol and its replacement by water molecules, resulting in the formation of a more stable hydrate form.

XRPD Characterization

XRPD analysis was performed immediately after exposing and analyzing the sample at 0%, 60%, and 92% RH using the DVS instrument. The diffraction pattern for the sample remained unchanged at 0% and 60% RH, supporting the conclusion that the solvate remains polymorphically stable under low and moderate humidity. However, after exposure to 92% RH, distinct changes in the XRPD patterns were observed, including the appearance of new peaks corresponding to the hemi pentahydrate form. These alterations clearly indicate a polymorphic conversion[6, 7] from solvate to hydrate, consistent with the DVS observations (see Figures 8 and 9).

The combined analysis of DVS and XRPD demonstrates that the solvate structure of Elacestrant dihydrochloride is hygroscopically[2] sensitive and prone to crystallization[8] at high humidity. While the material is stable under 70% RH and moderate conditions, the formation of a stable hemi pentahydrate occurs rapidly when exposed to RH above 90%. This

behavior highlights the importance of controlled environmental conditions during sample storage, handling, and formulation development.

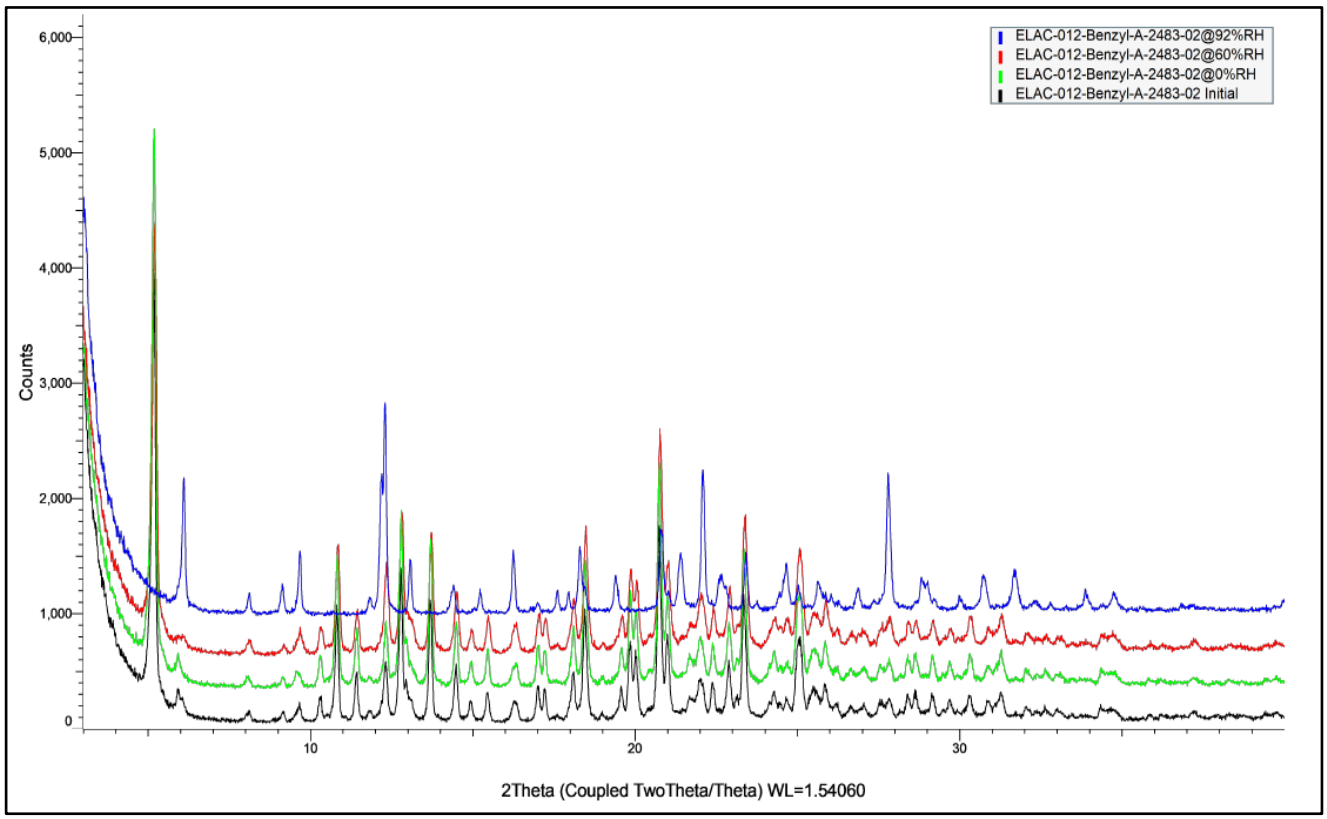

Figure 9: PXRD Compilation data of Elacestrant dihydrochloride initial, 0% RH, 60%RH and 92%RH exposed samples.

Conclusion

This study demonstrates that the benzyl alcohol solvate form[7,9] of Elacestrant dihydrochloride exhibit pronounced moisture sensitivity, undergoing a clear solvate to hydrate transformation upon exposure to high relative humidity[5]. DVS analysis effectively captured real time mass changes associated with desolvation, crystallization[8], and subsequent hydrate formation, while iso-humidity experiments confirmed that the solvates remain stable at low to moderate humidity (0–60% RH) but convert rapidly to a stable hemi pentahydrate above 90% RH. Complementary XRPD characterization validated these humidity driven phase transitions, revealing distinct crystallographic differences following high humidity exposure.

Together, the combined DVS–XRPD approach provides a comprehensive understanding of the humidity induced structural behavior of Elacestrant dihydrochloride solvates. The findings highlight the critical importance of controlling environmental moisture during manufacturing, handling, and formulation development. Moreover, the rapid and reproducible formation of the hydrate form highlights its thermodynamic preference at elevated humidity, which must be considered during solid-form selection and stability assessment in pharmaceutical product development.

Acknowledgement

The authors gratefully acknowledge Dr. B S Natarajan (Alembic Pharmaceuticals, Alembic

Road, Vadodara, Gujarat, India) for his contributions to this work.

References

1. DVS Resolution User Manual

2. USP General Chapter <1241> Water–Solid Interactions in Pharmaceutical Systems

3. USP General Chapter <941> Characterization of Crystalline and Partially Crystalline Solids by X-Ray Powder Diffraction (XRPD).

4. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. http://ascopubs.org/doi/full/10.1200/JCO.22.00338

5. Burnett DJ, Thielmann F, Booth J. Determining the critical relative humidity for moisture-induced phase transitions. Int J Pharm. 2004;287:123–133.

6. Brittain, H.G. "Polymorphism in pharmaceutical solids." J. Pharm. Sci. 2009

7. Griesser, U.J. "The importance of solvates & hydrates in pharmaceuticals." Adv. Drug Deliv. Rev., 2006

8. D.J. Burnett Investigating the moisture-induced crystallization kinetics of spray-dried lactose https://doi.org/10.1016/j.ijpharm.2006.01.012

9. Masum, Z. U.; Spoors, P. G.; Burke, M. D.; Gupta, V. Novel Polymorphic Patterns for Elacestrant Dihydrochloride. Pharmaceutics, https://doi.org/10.3390/pharmaceutics17060745

10. Pindelska E, Sokal A, Kołodziejski W. Pharmaceutical cocrystals, salts and polymorphs: Advanced characterization techniques. Adv Drug Deliv Rev. 2017;117:111–146. https://doi.org/10.1016/j.addr.2017.09.014