Emerging Nano and Advanced Materials (ENA)

Morphological Changes in Palbociclib by Atomic Layer Deposition

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Abstract

ALD coating of active pharmaceutical ingredient (API) is a novel coating methodology to achieve excellent conformity and uniform coating thickness at sub-nanometer level. It has the ability to amorphize APIs and improve powder processability. In addition, amorphous API has better solubility and retarded dissolution profile. Here, X-ray diffractogram, Raman Spectra and Dissolution test have been used to draw co-relations between number of ALD coating cycles and morphology of coated API. The API of interest here is an onco-drug named palbociclib.

Introduction

In pharmaceutical industry, the drug processing requires controlled and well defined surface coating. At present different drug coating techniques such as spray drying and dry particle coating are used at industrial level. Even though these techniques have proven to work, still due to the inhomogeneous nature of surfaces, irregular shape of drug powder particles and small particulate diameter, it is difficult to obtain uniform conformal coating around particles.

This study revolves around palbociclib, the first highly selective inhibitor of cdk4/6 approved by FDA to treat advanced breast cancer. Due to it's low solubility and poor bioavailability, the effectiveness of palbolciclib is reduced and it's toxic side effects are increased. Palbociclib also suffers from high electrostatic charge dissipation and poor flowability properties. These physical properties of powders can be resolved by amorphization. It is known that ALD causes amorphization. This ability has been exploited here to study the amount of loss of crystallinity and it's effect on the dissolution profile.

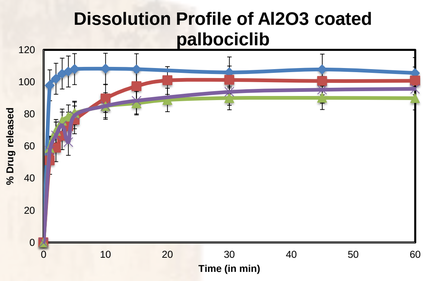
Materials and Methods

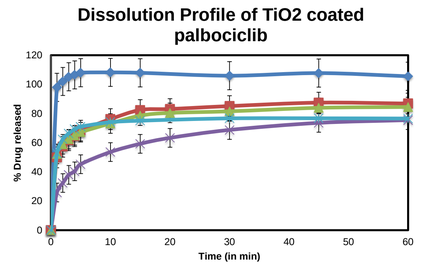
API :- Palbociclib

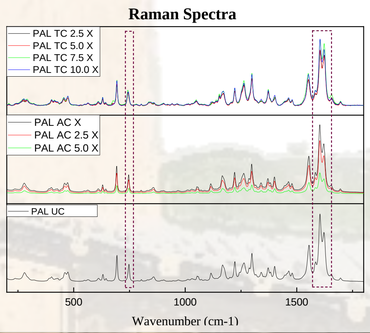
Metal Oxides used for ALD :- Aluminium dioxide (PAL AC) and Titanium oxide (PAL TC)

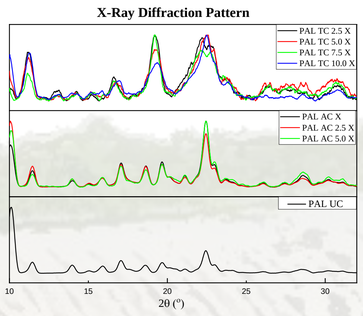
ALD Process parameters :- Number of cycles

Analytical Techniques :- XRD, Raman Mapping, Dissolution test



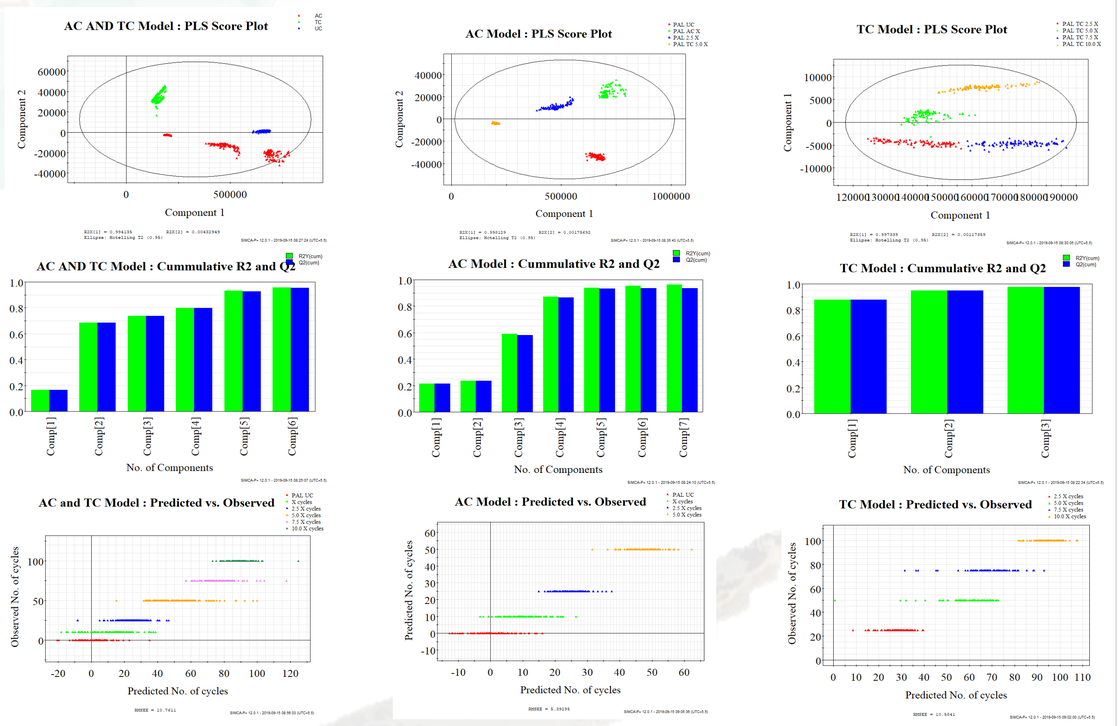






Result

		Good				Moderate		Poor	
		PAL UC	PAL AC X	PAL AC 2.5 X	PAL AC 5.0 X	PAL TC 2.5 X	PAL TC 5.0 X	PAL TC 7.5 X	PAL TC 10.0 X
Processing parameter	Number of Cycles	0	X	2.5 X	5.0 X	2.5 X	5.0 X	7.5 X	10.0 X
	Coating	N/A	Al_2O_3	Al_2O_3	Al_2O_3	TiO_2	TiO_2	TiO_2	TiO_2
Dissolution Profile	Dissolution @ 5 min	100%	77%	80%	72%	68%	68%	60%	55%
	Dissolution @ 60 min	100%	85%	87%	85%	85%	80%	63%	60%
Homogeneity by Raman	Mean Peak Ratio	2.701	3.044	3.006	2.720	8.277	6.698	8.169	5.775
	Range	2.63 - 2.74	2.96 – 3.109	2.923 – 3.07	2.64 – 2.787	7.55 – 9.19	5.91 – 7.55	7.24 – 9.22	5.37 – 6.18
	RSD	0.847	0.958	1.065	1.210	3.464	4.300	4.038	2.327
Degree of Crystallinity from X Ray Diffraction	Area of Crystal peaks	8208.82	9403.7	7376.5	5534.87	669.241	484.611	567.749	1076.56
	Area of all peaks	8456.78	9765.32	7835.7	7011.48	726.594	727.303	753.331	1444.46
	Crystallinity %	97.07	96.29	94.14	78.94	92.11	66.63	75.37	74.53



Method	Coating	Observation		Model	Variables	Model Diagnostics				
		Training	Validation			Training R2	Validation Q2	SSE	RMSE	R2adj
Raman Spectroscopy	AC & TC	800	7 fold	PLS	510	0.9582	0.954009	91831.1	11.8619	0.95789
	AC	300	7 fold	PLS	505	0.964648	0.936387	11400.9	10.6154	0.96402
	TC	400	7 fold	PLS	505	0.9763	0.975823	44360.8	6.72851	0.97616

Conclusions

- Al_2O_3 coated palbociclib are more homogenous than TiO_2 coated palbociclib as seen from the RSD of 100 raman spectra of each sample.
- Coating of palbociclib amorphized the sample as inferred from the X-ray diffraction.
- Al_2O_3 coated samples had better dissolution profile than TiO_2 coated palbociclib.
- Regression model built to correlate number of cycles of coating to Raman Spectra showed lower prediction error and cross validation error.

Industrial Significance

- The PLS model developed here gives insights about the effects of different metal oxide coating and number of ALD cycles on API. This model can potentially serve as a tool to understand the amorphization process during ALD.
- ALD not only serves as a novel coating process but it also ensures retarded dissolution and reduced crystallinity.
- Raman Spectroscopy can be used at industrial level to verify homogeneity of powder. MVDA on Raman maps can be used to monitor ALD process.

Technology Readiness Level: TRL 4 (Technology Development Stage)

References

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