SIROLIMUS NANOPARTICLES TABLETS

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OBJECTIVES

Nanonization is now considered as a mature formulation strategy to increase the bioavailability of poorly soluble drugs. For the 6 marketed drug products containing drug nanoparticles, nanosuspensions are produced by "top-down" techniques and further transformed into solid dosage forms.

Rapamune® is an oral tablet formulation incorporating nanoparticles of the immunosuppressant drug Sirolimus produced by wet ball milling.

The StaniTab® formulation strategy has been assessed for the formulation of Sirolimus nanoparticles tablets.

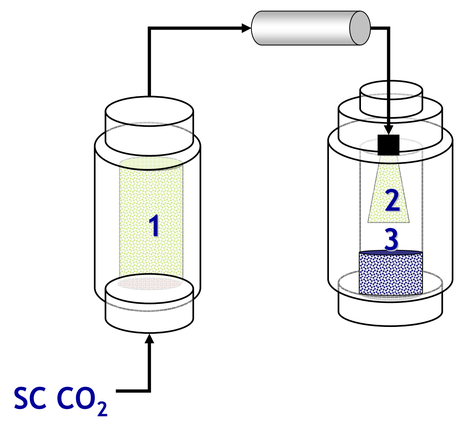
In a first step, the production of semi-finished solid formulations made of Sirolimus nanoparticles dispersed onto excipient particles has been studied using a proprietary solvent-free crystallization process.

Sirolimus tablets have then been produced by direct compression.

The StaniTab® Technology

The StaniTab® Technology is a solvent-free technology consisting in :

1- Dissolving the drug in a supercritical fluid
2- Expanding the drug supercritical solution according to a finely controlled thermodynamic pathway in a low pressure vessel
3- Contacting the expanded solution with an excipient powder so as to produce a dry semi-finished solid formulation

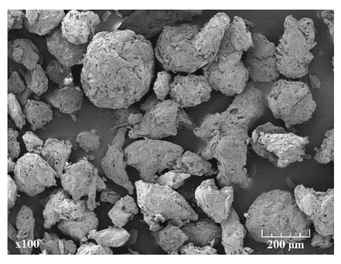


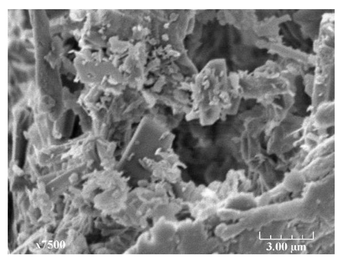
SEMI-FINISHED FORMULATIONS

Crystallization process operating conditions

Supercritical fluid	CO_2
Temperature	60 °C
Pressure	33 MPa
Trapping excipient	Microcrystalline cellulose (Avicel PH 200)
Batch size	50 g

SEM



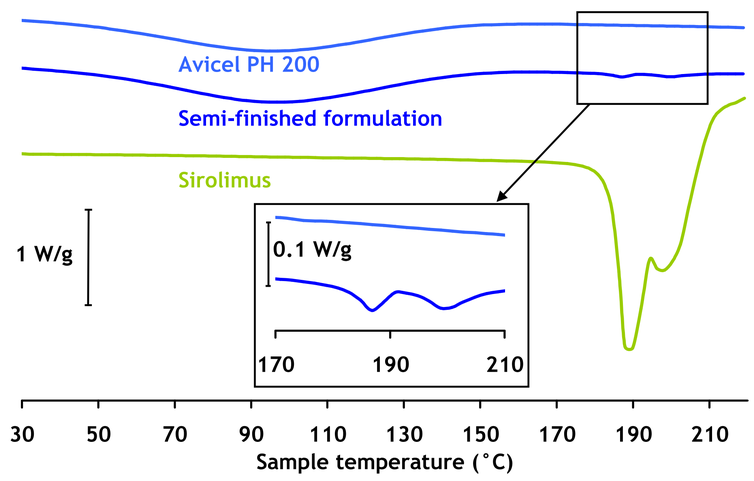


Sirolimus content & chemical stability

Sirolimus content	18.3 mg / g (RSD 0.7 %)

RRT	Raw API (%)	Semi-finished formulation (%)
0.09	0.74	0.69
0.13	0.09	0.09
0.20	0.06	0.09
0.30	0.10	0.12
0.45	0.29	0.23
0.59	0.70	0.68
0.71 (*Isomer*)	2.38	2.44
1.00 (*Sirolimus*)	89.53	88.91
1.33 (*Isomer*)	5.96	6.55
1.52	0.14	0.21

Solid state morphology (DSC)



Crystallinity of Sirolimus nanoparticles confirmed by XRPD

TABLETS

Manufacturing of Sirolimus tablets

Tablet Components	mg / unit	%	g / batch
Mixing: *Cubical mixer, 15 min - 10 rpm + 2 min lubrication* Direct compression: *Tablet press PR12 (SVIAC), 13x6 mm punches, 20 rpm, forced feed 3 rpm, 4.5 kN*			
Semi-finished formulation : *Sirolimus + Avicel PH 200*	109.29	30.57	275.7
Diluent : *Microcrystalline cellulose (Avicel PH 200)*	224.34	62.75	565.8
Lubricant	3.37	0.94	8.5
Coating: *Perforated pan (Trislot)*			
Sub-coating formulation	10.11	2.83	25.5
Coating formulation	10.41	2.91	26.3
TOTAL	357.52	100.00	901.8

Tablets properties

Tests	Results
Weight	362.3 mg (RSD 1.9%)
Hardness	229 N (RSD 7%)
Dosage	1.94 mg / unit (RSD 3.2%)

In vitro dissolution

SDS 0.4%, 500 ml, 40 rpm, basket, n = 6

CONCLUSION

The StaniTab® formulation strategy makes it possible to produce a semi-finished formulation composed of Sirolimus nanoparticles dispersed onto microcrystalline cellulose.

In-process stability and production of crystalline Sirolimus particles are achievable using this « bottom-up » solvent-free technique.

The one-step crystallisation process produces a dry formulation which can be readily processed to manufacture tablets using conventional mixers and tablet press.

2 mg Sirolimus tablets exhibit a highly uniform drug content and an *in vitro* dissolution profile similar to those of the marketed drug product Rapamune®.