Improving the Stability of a Spray-Dried Peroxide-Susceptible Drug in Tablets

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PURPOSE

Compound X (Cmp-X) belongs to the class of PDE-5 inhibitors and is a BCS Class II candidate with equilibrium solubility <3 µg/mL, thus exhibiting a dissolution rate limited bioavailability. The purpose of this work is to develop an amorphous solid dispersion (ASD) by spray drying and monitor and **improve the physical and chemical stability** upon storage for developing a successful solid dosage formulation.

OBJECTIVE(S)

The following approaches were investigated to improve chemical stability of ASD:

1. **Addition of BHT**, an antioxidant, in spray dried dispersion
2. Use of **low peroxide copovidone** and **crospovidone**
3. Use of **low moisture microcrystalline cellulose**

METHOD(S)

ASD of Cmp-X were prepared using spray drying (SD) and formulated as immediate release tablets. Cmp-X, copovidone, and sodium lauryl sulfate with or without BHT were dissolved in a solvent mixture of tetrahydrofuran-water and the solution was processed in a ProCepT (Procept , Belgium) spray dryer. Spray dried powder was dried using a lab scale convection oven. Roller compaction and compression were carried out using Gerties Mini-Pactor and Natoli single station tablet press (NP-RD10A) , respectively. To evaluate chemical stability, spray dried powder and tablets were stored at 25˚C/60% RH and 40˚C/75%RH. The samples were evaluated for API content and related substances (RS) by HPLC. Design Expert® was used to generate a two-level fractional factorial experimental design (2^4-1) and determine the effect of above-mentioned variables on the chemical stability. The composition of spray dried dispersions and tablet prototypes are presented in the **Table 1**.

RESULT(S)

- Com-x converted to amorphous form during spray drying (data not shown)
- RS grew for the ASD without stabilizer (control) and exceeded the limit (<0.30% per USP) at 6 months for tablets stored at 40˚C/75%RH **(Fig 1)**
- Impurity levels also increased for tables stored at 25˚C/60% RH, approaching the specification limit **(Fig 1)**
- The RS growth in new prototypes was significantly reduced during storage
- At the 6-month time point: tablets containing low peroxide crospovidone (Prototype 1, 3, 6 & 7) showed 50% lower degradants compared to the prototypes containing the regular crospovidone **(Fig 2)**
- Moisture content in microcrystalline cellulose and peroxide level in copovidone had no impact on stability.

Table 1. Composition of spray dried dispersions and tablet prototypes

Material	% w/w	Control	Prototype 1	Prototype 2	Prototype 3	Prototype 4	Prototype 5	Prototype 6	Prototype 7	Prototype
Spray Dried Dispersion[1]										
Compound X	7.5	N	N	N	N	N	N	N	N	N
Copovidone	15	N	LP	LP	LP	LP	N	N	N	N
Sodium Lauryl Sulfate	7.5	N	N	N	N	N	N	N	N	N
BHT	150 ppm	None	N	N	N	N	N	N	N	N
Intragranular[2]										
Microcrystalline Cellulose	12.7	N	LM	LM	N	N	LM	LM	N	N
Magnesium Stearate	1.0	N	N	N	N	N	N	N	N	N
Extragranular										
Microcrystalline Cellulose	30.3	N	LM	N	N	LM	LM	N	LM	N
Crospovidone	25.0	N	LP	N	LP	N	N	LP	LP	N
Magnesium Stearate	1.0	N	N	N	N	N	N	N	N	N

N, Nominal refers to the regular grade; LP, Low peroxide grade; LM, Low Moisture grade

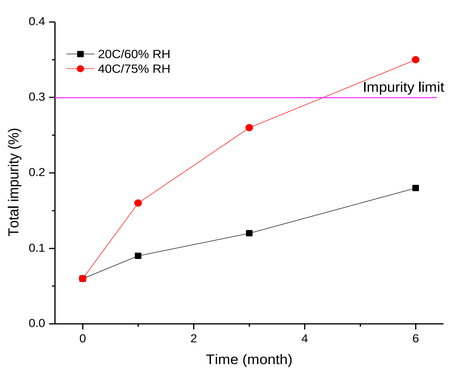

Fig. 1: Total impurity vs time profile of 5 mg Compound X tablets of control formulation exposed to 25˚C/60% RH and 40˚C/75%RH.

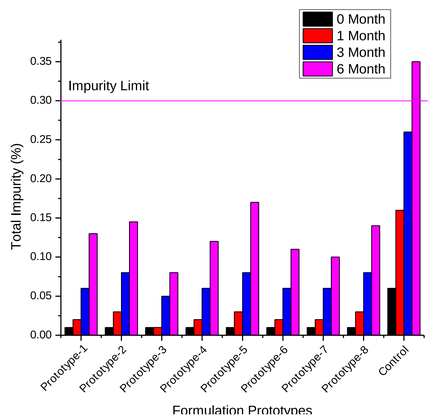

Fig 2: Total impurity vs time profile for 5 mg Compound X tablets in closed vial exposed to 40˚C/75%RH. (n=2).

- The determine the effect of variables on total RS, design of experiment was used
- Total RS found to be significantly impacted by peroxide in crospovidone **(Table 2)**
- Other variables, moisture content in intragranular and extranuclear MCC and peroxide in copovidone, did not show significant impact on total RS **(Fig 3)**

Table 2. ANOVA Table for Total RS at 6 Months

Source	Sum of Squares	df	Mean Square	F-value	p-value
Model	0.0044	3	0.0015	7.42	0.0412
A-Copovidone	0.0004	1	0.0004	1.92	0.2380
B-Intra-Granular MCC	0.0014	1	0.0014	7.00	0.0572
D-Crospovidone	0.0026	1	0.0026	13.35	0.0217

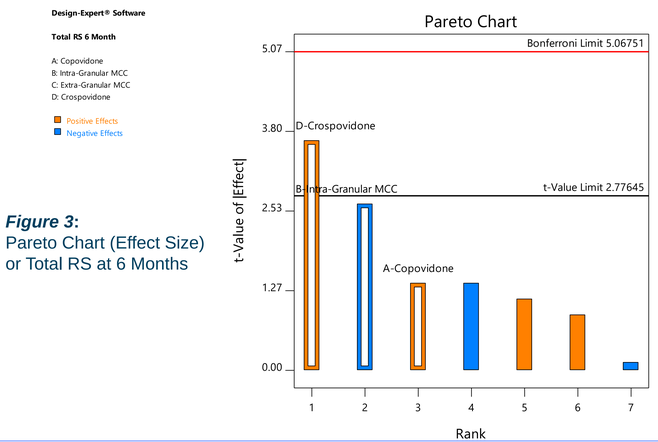

Figure 3: Pareto Chart (Effect Size) or Total RS at 6 Months

CONCLUSION(S)

- This BCS class II Cmp-X was successfully converted to an amorphous form during spray drying.
- Tablets prepared with **antioxidant (BHT) and low peroxide crospovidone significantly reduced drug degradation** and improved chemical stability.

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