Accelerated stability assessment for an oral N-type calcium channel blocker

Stephanie Buchanan and Sanjay Konagurthu PhD

stephanie.buchanan@thermofisher.com | sanjay.konagurthu@thermofisher.com

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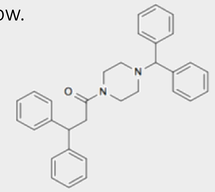
PURPOSE

Bioavailability Enhancement

Z-160 is an oral N-type calcium channel blocker for chronic neuropathic and nociceptive pain. The crystalline form exhibits low solubility and is poorly bioavailable (BCS class II). Physico-chemical properties for Z160 are reported below.



Property	Result
T_m	128°C
T_g	43.5°C

The amorphous form of Z160 along with the dispersion polymer enables fast dissolution and sustained supersaturation in bio-relevant media, which increases bioavailability. The lead formulation was selected based on manufacturability and is a 40:60 Z160:PVP-VA64 spray-dried intermediate (SDI).

The chemical stability of the amorphous form of Z160 is reduced in comparison to the crystalline form. During the formulation development process, it is important to understand the degree of reduction in stability as a result of the amorphous form. Accelerated Stability Assessment Program (ASAP) studies were conducted to determine any changes to product shelf-life predictions in the enabled form.

OBJECTIVE

Quick Stability Assessment

Long-term stability data for Z160 formulation often displayed complex degradation kinetics and historical accelerated stability predictions were typically very conservative. This is hypothesized to be due to the different microenvironments present in the SDI sample.

The moisture-modified Arrhenius model built into ASAPprime® only models the initial rate to the specification limit and provides more accurate predictions.

METHODS

Accelerated Stability Assessment Program (ASAP)

- Tg and water sorption data were used to define limits in the stressing conditions due to phase transitions.
- Total degradation was modeled instead of individual degradant peaks due different species growing in for the crystalline sample than in the SDI sample. ASAPprime® was used to model time to the specification limit, i.e., isoconversion time.

Representative ASAP sample with saturated salt solution in vial with Gore-Tex lid, and sample with perforated foil covering.

Chemical Analysis

- Samples were analyzed for related substances by HPLC.
- Degradants above 0.04% were reported and summed for the total% degradant in the sample.

Condition Selection

Sample No.	Sample Condition time (day)	°C/%RH	Saturated Salt[1]
1	21	40/82	potassium chloride
2	21	70/0	calcium sulfate
3	21	55/21	potassium fluoride
4	21	55/64	potassium iodide
5	15	40/82	potassium chloride
6	13	40/82	potassium chloride
7	11	55/21	potassium fluoride
8	7	75/27	magnesium chloride
9	4	55/64	potassium iodide
10	4	90/0	calcium sulfate
11	4	70/0	calcium sulfate
12	1	75/76	sodium chloride
13	1	90/0	calcium sulfate
14	1	85/76	sodium chloride
15	1	75/27	magnesium chloride

[1] saturated salt solution to maintain equilibrium target humidity

(a)

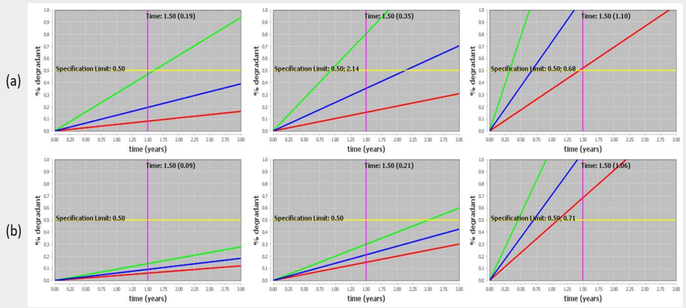
Sample No.	Sample Condition time (day)	°C/%RH	Saturated Salt[1]
1	21	55/21	potassium fluoride
2	21	55/28	sodium iodide
3	21	55/30	magnesium chloride
4	21	70/0	calcium sulfate
5	20	70/11	lithium chloride
6	15	55/21	potassium fluoride
7	13	55/28	sodium iodide
8	13	55/30	magnesium chloride
9	10	55/21	potassium fluoride
10	9	55/28	sodium iodide
11	8	55/30	magnesium chloride
12	8	70/0	calcium sulfate
13	6	70/11	lithium chloride
14	3	70/0	calcium sulfate
15	2	70/11	lithium chloride

[1] saturated salt solution to maintain equilibrium target humidity

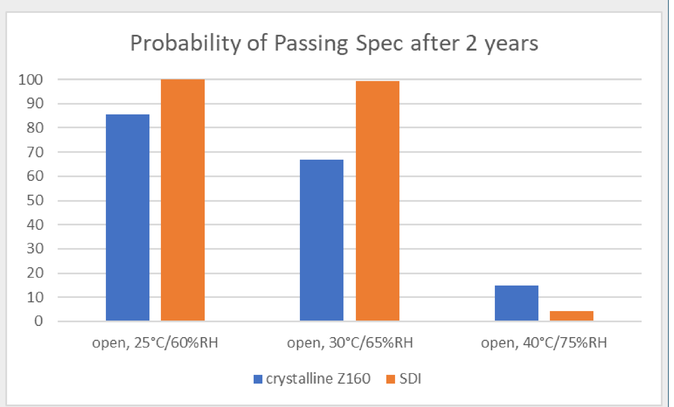
(b)

ASAP study design summary for (a) crystalline Z160 and (b) 40:60 Z160:PVP-VA64 SDI

Formulation	Lot Number	Spec. limit (%)	ln A	E_a (kcal/mol)	B	R^2	Q^2
Crystalline Z160	CMLW-243/13-ZA2	0.5	18.04 ± 6.65	16.35 ± 4.57	0.027 ± 0.01	0.848	0.689
40:60 Z160:PVP-VA64	A4-976-71	0.5	38.11 ± 8.31	28.13 ± 5.70	0.012 ± 0.02	0.992	0906



Plots of calculated %degradation vs time for (a) crystalline Z160 and (b) 40:60 Z160:PVP-VA64 SDI open packaging configurations. Blue curve is the mean, green and red curves and plus and minus two standard deviations.



Probabilities of passing the specification limit of 0.5% total degradation after 2 years for the crystalline Z160 API and 40:60 Z160:PVP-VA64 SDI.

RESULTS

- Calculated activation energy, E_a, for the isoconversion of crystalline Z160 is lower than the 40:60 Z160:PVP-VA64 SDI indicating the energetic barrier to isoconversion is higher for the SDI.
- The moisture sensitivity parameter, B, is higher in the crystalline API than for the SDI indicating degradant growth in the crystalline API could be more easily controlled via packaging than in the SDI.
- Probability of passing the specification were higher for the SDI at $25°C/60\%RH$ and $30°C/65\%RH$ in open packaging, but lower for the SDI at $40°C/75\%RH$ open. This result indicates favorable conditions in the SDI at $40°C/75\%RH$ for degradant growth.
- Lower R^2 and Q^2 values observed for the crystalline Z160 API, hypothesized to be due to low degradant growth in the API. The low conversion module in the ASAPprime® software was utilized for this sample which provides more conservative predictions.

CONCLUSIONS

- The predicted shelf-life for the SDI in open packaging configurations is longer than for the neat crystalline API.
- Packaging the bulk material with desiccant increases the probability of passing the specification, and specific packaging configurations will be assessed for the final dosage form.
- An ASAP study enabled us to quickly predict product shelf-life for a range of packaging configurations. A typical long-term stability can take up to 12 months, while an ASAP study can be completed within 21 to 28 days.

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