Accelerated Stability Assessment Study for Nicorette® Lozenge

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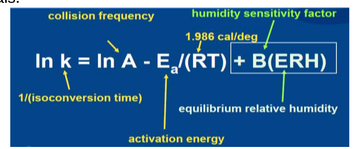
Introduction

It is crucial to develop a pharmaceutical product with good stability performance in order to gain approval from regulatory agency, maintain the quality throughout its shelf life and ensure its efficacy and safety. It is essential to determine which factors affect stability performance during early stage of product development. However, the traditional stability study is very time-consuming and costly as multiple formulations in various packaging options are typically evaluated during product development. It is a lengthy, expensive, labor-intensive and uncertain task for R&D.

In order to improve the product understanding, identify the potential stability trend, select the most cost effective packaging material, predict the product shelf life and reduce the uncertainty and risk during product development, GSK evaluated Accelerated Stability Assessment Program and ASAP*prime*™ stability modeling software marketed by FreeThink Technology Inc. The accelerated stability data can be collected within two to four weeks and used for shelf-life projection, stability trend detection and packaging selection.

ASAP*prime*™ factors in humidity sensitivity factor (B) into the traditional Arrhenius equation for solid dosage forms. ASAP study is normally conducted in five to six conditions in two weeks. Either potency and/or degradant level can be used to calculate LnA (collision frequency), Ea (activation energy) and B (humidity sensitivity factor) using ASAP*prime*™ stability software. Then, those three constants are used to predict the shelf life of the product , project the stability trend, and select the most cost effective packaging materials.



Objective

To evaluate the accelerated stability assessment program and ASAP*prime*™ stability software for Nicorette® lozenge

Methods

- Tested samples – Nicorette® peppermint lozenge
- ASAP study –

T (°C)	%RH (open)	Time points (days)
50	50	5, 10, 14
60	30	5, 10, 14
70	0	5, 10, 14
70	75	3, 7, 14
80	50	3, 7, 14
80	11	5, 10, 14
5	--	14

- Saturated salt solutions were used to create the humidity –
  - NaBr/50%RH
  - $MgCl_2$/30%RH
  - NaCl/75%RH
  - LiCl/11% RH
  - $CaSO_4$/0%RH
- MicroRH Temp data loggers were used to record the actual temperature and humidity
- 40 lozenges were taken for each sampling time point and stored in a refrigerator after sampling
- All samples were analyzed for composite assay for each time point at the end
- Moisture sorption isotherm of the whole Nicorette® lozenge was obtained using AquaLab Vapor Analyzer
- ASAP*prime*™ stability software was used to calculate iso-conversion point (time required to reach 90% potency) for each condition, to fit to the moisture-modified Arrhenius equation and to obtain collision frequency (LnA), activation energy (E_a) and humidity factor (B)

- The actual shelf life at PVdC blister was used for validation of the predicted shelf lives

Results

Figure 1 – difference between designed and actual conditions

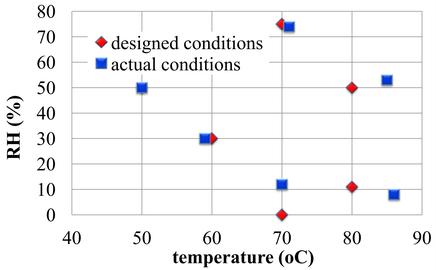


Figure 2 – Accelerated stability

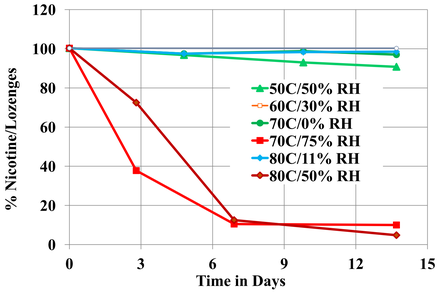


Figure 3 – Moisture sorption isotherm

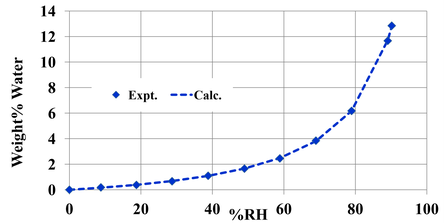


Table 1 – Isoconversion points

Temperature (°C)	RH %	Isoconversion (Days)	SD (Days)
50	50	14.6	1.2
59	30	56.4	18.4
70	12	55.0	17.5
71	74	0.3	0.1
85	53	1.0	0.0
86	8	95.6	44.8

Table 2 – Arrhenius constants

ln A	18.7±3.1
E_a	15.6±2.0 kcal/mol (65.3±8.4 kJ/mol)
B	0.103±0.008
R^2	1.00

Table 3 – Validation of ASAP predicted shelf life

Conditions	Actual Shelf-life (mos.) PVdC blister	ASAP*prime*™ Shelf-life (mos.) PVdC blister
25°C/60%RH	18	18
30°C/65%RH	8	7
30°C/75%RH	5	6
40°C/75%RH	1	1

Conclusions

- Moisture sorption isotherm indicates a significant moisture uptake at high relative humidity which contributes to the loss of nicotine from lozenges.
- Significant browning and discoloration is also observed at high humidity conditions and temperature.
- The potency loss from the lozenge follows the first order kinetic which is used to calculate the isoconversion points for all six ASAP conditions.
- A fitting coefficient of $r^2 = 1$ is obtained for all three modified Arrhenius constants
- High humidity sensitivity factor (B) indicates that the potency of Nicorette® lozenge is highly sensitive to the humidity. The absorbed moisture dissolves buffers in the lozenge and allows ionic nicotine to dissociate from polyacrilex and convert from ionic nicotine to base nicotine which is known to be volatile and escape along with moisture during sorption process.
- The single unit container closure system with high barrier function (i.e. foil-foil) and the multiple doses container with desiccant are required to protect Nicorette® lozenge from moisture and to achieve the desired shelf life.
- Validation of ASAP*prime*™ predicted shelf life could only be achieved when MVTR value of formed blister at given condition was available.