T1530-06-40

Accelerated Stability Modeling of Drug Products using ASAP*prime*®

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PURPOSE

Performing stability studies are necessary in the development of new drug products. The aim of these studies is to demonstrate chemical stability of the product, to establish expiration dating, and to aid in packaging selection. However, traditional ICH stability studies are resource intensive, costly, time-consuming, and can be the rate limiting step in the development process. In recent years the Accelerated Stability Assessment Program, ASAP*prime*®, has gained prominence as an alternative to traditional stability studies. Using a humidity corrected version of the Arrhenius equation, customizable models are created for a drug product's overall stability performance by using data obtained from short, accelerated stability studies.

OBJECTIVE(S)

The objective of Case Study # 1 was to predict stability of Cetirizine HCl containing solid dosage form drug product and compare with traditional ICH stability studies. Objective of Case Study # 2 was to determine optimal amount of desiccant for packaging of Esomeprazole Mg containing solid dosage form drug product.

METHOD(S)

Study Design

A study design is created to stress samples at a variety of humidities and elevated temperatures for varying lengths of time. The goal of the study design is to outline a set of conditions that degrade the sample by analogous degradation mechanisms to those encountered by the sample during normal product lifecycle. In some cases, feasibility testing of potentially troublesome conditions may be prudent.

Sample Storage/Stressing

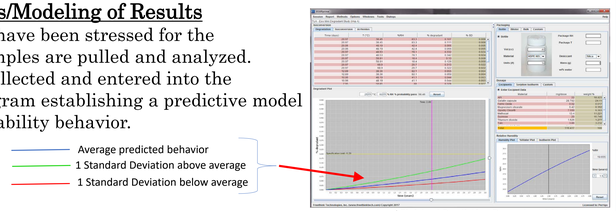
Once the design of the study has been finalized, samples are charged into chambers to be stressed at the defined accelerated conditions. For this process we use glass canning jars containing salt solutions to achieve the desired humidity. Multiple jars expressing multiple internal humidities can be placed in ovens to match the desired temperatures. Samples are stressed without packaging, corrections for packaging configurations can be applied to the product later once the predictive models have been built.

Humidity Chamber


Stability Oven Containing Multiple Stability Jars

Sample Analysis/Modeling of Results

After all samples have been stressed for the required time, samples are pulled and analyzed. The raw data is collected and entered into the ASAPprime® program establishing a predictive model of the product's stability behavior.



Example of Finished Predictive Degradant Model

METHOD(S)

Case Study # 1 – Cetirizine HCl

An accelerated predictive stability study using ASAPprime® was performed on a Cetirizine HCl containing solid dosage form drug product. The product was stressed at conditions ranging from 45-70 °C and humidities ranging from 0-80 %RH over a period of 2 weeks (see Table 1 for design).

Study Conditions

- -Two weeks duration
- -30 sample analyses
- -9 unique combinations of temperature and humidity
- -HPLC analysis of samples
- -Degradants and loss of potency modeled

Table 1: Stability Design for Cetirizine HCl Accelerated Stability Study

T (° C)	%RH	Time (repeats)
		0 (3)
45	70 (Sodium Nitrate)	9 (1); 11 (1); 12 (1); 14 (1)
50	51 (Sodium Bromide)	8 (1); 11 (1); 14 (1)
55	28 (Sodium Iodide)	9 (1); 11 (1); 14 (1)
55	81 (Potassium Chloride)	2 (1); 5 (1); 14 (1)
60	11 (Lithium Chloride)	7 (1); 10 (1); 14 (1)
60	63 (Potassium Iodide)	2 (1); 5 (1); 14 (1)
70	0 (Dessicant Pouch)	3 (1); 6 (1); 14 (1)
70	41 (Potassium Carbonate)	1 (1); 3 (1); 8 (1)
70	79 (Potassium Chloride)	1 (1); 2 (1)

Case Study # 2 – Esomeprazole Mg

An accelerated predictive stability study using ASAP*prime*® was performed on an Esomeprazole Mg containing solid dosage form drug product. The product was stressed at conditions ranging from 40-70 °C and humidities ranging from 0-80 %RH over a period of 3 weeks (see Table 2 for design). The intention of the study was to determine optimal amounts of desiccant for packaging.

Study Conditions

- -Three weeks duration
- -30 sample analyses
- -7 unique combinations of temperature and humidity
- -HPLC analysis of samples
- -Degradants and loss of potency modeled

Table 2: Stability Design for Esomeprazole Mg Accelerated Stability Study

T (° C)	%RH	Time (repeats)
		0 (2)
40	82 (Potassium Chloride)	13 (2); 21 (2)
50	42 (Potassium Carbonate)	11 (2); 21 (2)
50	81 (Potassium Chloride)	3 (2); 21 (2)
60	21 (Potassium Fluoride)	5 (2); 21 (2)
60	80 (Potassium Chloride)	1 (2); 8 (2)
70	0 (Calcium Sulfate)	3 (2); 21 (2)
70	50 (Sodium Bromide)	1 (2); 6 (2)

RESULT(S)

Case Study # 1 – Cetirizine HCl

Predictive models were constructed to model potency loss as well as the growth of 6 Cetirizine HCl impurities. Percent probabilities to pass the given specification limit at 2 years 25°C/60%RH, 3 months 40°C/75%RH, and 6 months 40°C/75%RH are given in Table 3. ASAPprime® predicted results have been confirmed by traditional ICH stability studies at 3 months 40°C/75%RH as assay and impurities are meeting acceptance criteria.

Table 3: Predictive Results of Cetirizine HCl Accelerated Stability Study

Component	2 Years 25°C/60% RH	3 months 40°C/75% RH	6 months 40°C/75% RH
Cetirizine HCl Assay	86.39	97.95	81.28
Impurity-1	96.90	99.98	99.53
Impurity-2	97.20	99.97	99.27
Impurity-3[1]	7.82	83.69	29.99
Impurity-4	90.50	99.79	97.68
Impurity-5	87.05	99.72	95.76
Impurity-6	99.43	99.99	99.57
Largest Unknown Impurity	94.07	94.22	21.51
Total Impurities	100.00	100.00	100.00

[1]No isoconversion was achieved for Impurity-3. This leads to lower confidence in the derived probabilities.

RESULT(S)

Case Study # 2 – Esomeprazole Mg

Predictive models were constructed to model the growth of 5 Esomeprazole impurities. Percent probabilities to pass the given specification limit at 2 years 25°C/60%RH (see Table 4), 3 months 40°C/75%RH (see Table 5), and 6 months 40°C/75%RH (see Table 6) were calculated at 3 different desiccant amounts, 0.5 g, 0.75 g, and 1.0 g. ASAPprime® predicted the best chance to meet all specification limits was by using 1.0 g of desiccant. Data was collected after 6 months of traditional ICH stability at 40°C/75%RH with packaging configurations containing 0.75 g and 1.0 g of desiccant. Packaging configurations with 0.75g of desiccant failed to meet acceptance criteria at 6 months 40°C/75%RH for Impurity-5. Packaging configurations using 1.0 g of desiccant were able to meet the acceptance criteria for all degradants at 6 months 40°C/75%RH. ASAPprime® results show the low probability of meeting acceptance criteria for Impurity-5 by using 0.5 g and 0.75 g of desiccant, which was confirmed by ICH stability studies.

Table 4: Predictive Results of Esomeprazole Impurities at 2 years at 25 °C/60% RH

Degradant	Desiccant Amount		
	0.5 g	0.75 g	1.0 g
Impurity-1	96.24%	97.71%	98.36%
Impurity-2	99.99%	100.00%	100.00%
Impurity-3	90.24%	91.26%	91.85%
Impurity-4	99.32%	99.75%	99.87%
Impurity-5	98.26%	99.36%	99.67%

Table 5: Predictive Results of Esomeprazole Impurities at 3 months at 40 °C/75% RH

Degradant	Desiccant Amount		
	0.5 g	0.75 g	1.0 g
Impurity-1	99.88%	99.95%	99.97%
Impurity-2	100.00%	100.00%	100.00%
Impurity-3	99.96%	99.96%	99.96%
Impurity-4	100.00%	100.00%	100.00%
Impurity-5	99.93%	99.98%	99.99%

Table 6: Predictive Results of Esomeprazole Impurities at 6 months at 40 °C/75% RH

Degradant	Desiccant Amount		
	0.5 g	0.75 g	1.0 g
Impurity-1	64.69%	81.65%	88.62%
Impurity-2	99.89%	99.96%	99.98%
Impurity-3	97.33%	97.72%	97.91%
Impurity-4	93.43%	98.63%	99.54%
Impurity-5	35.23%	71.41%	86.36%

CONCLUSION(S)

For new product development, ASAPprime® is much faster than conventional ICH stability or package screening studies at a higher accuracy. It could allow a faster clinical entry and it also could lead to fewer stability activities for post-approval changes. With ASAPprime® it is possible to link the Critical Quality Attributes of a development project more direct with long term stability effects in contrast to standard ICH accelerated studies.

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