Accelerated Stability Modeling of Gelatin Capsule Disintegration Time

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Introduction

Gelatin capsule drug product shelf life can be limited by crosslinking, resulting in slower disintegration/dissolution. The literature suggests this is related to excipient aldehydes.

- ASAP*prime*® approach for accelerated aging:
  - Time-to-fail specification (isoconversion)
  - Moisture-modified Arrhenius equation:

$$\ln(k) = \ln(A) - E_a/(RT) + B(RH)$$

k = (change to specification limit)/(isoconversion time),

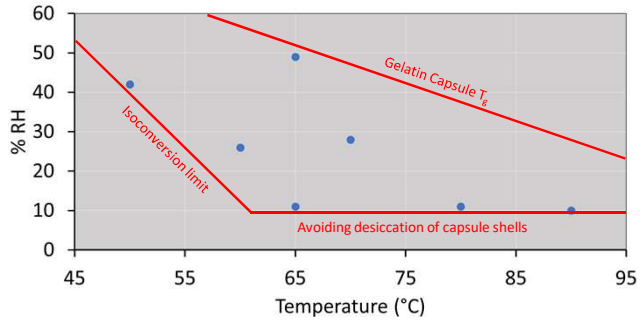
A = collision frequency, E_a = activation energy, R = gas constant,

T = temperature, B = humidity sensitivity factor,

RH = equilibrium relative humidity

Study Design

T (°C)	% RH (Saturated Salt)	Days (Repeats)
Control		0 (3)
50	42 (Potassium Carbonate)	7 (1); 20 (1); 27 (1); 38 (1)
60	26 (Sodium Iodide)	7 (1); 20 (1); 37 (1)
65	11 (Lithium Chloride)	9 (1); 16 (1); 22 (1); 37 (1)
65	49 (Sodium Bromide)	2 (1); 6 (1); 15 (1); 20 (1)
70	28 (Magnesium Chloride)	3 (1); 9 (1); 16 (1); 22 (1); 27 (1)
80	11 (Lithium Chloride)	2 (1); 6 (1); 15 (1)
90	10 (Lithium Chloride)	1 (1); 2 (1); 5 (1); 9 (1)



Method

Disintegration Testing

- SOTAX DT2 unit: capsules moved in/out of water bath (37 ± 2°C)
- Disintegration time = moment capsule shell deforms + air/excipient visibly released

Screening of excipient-containing gelatin capsule disintegration times after aging

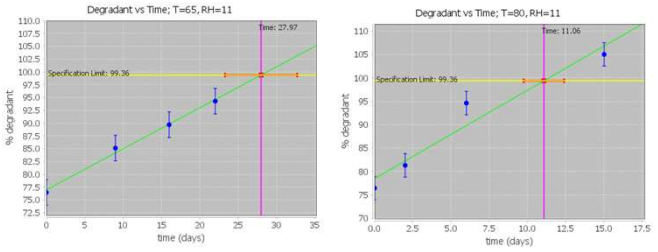
Excipient	Disintegration Time (s)	
	Initial	80°C/ 41% RH/12 d
Empty	73	90
Lactose (GranuLac® 200)	84	110
MCC (Avicel® PH-102)	85	109
PVP (Plasdone™ K-29/32)	120	151
Pregelatinized Starch (Starch 1500®)	92	145

- Quali-G™ 00 gelatin capsules (n = 10), empty or with ~600 mg of Starch 1500® (selected as model), sealed in canning jars with saturated salt solutions
- Placed in ovens for different durations

Results

- Isoconversion times at all conditions used to generate stability model with ASAP*prime*®

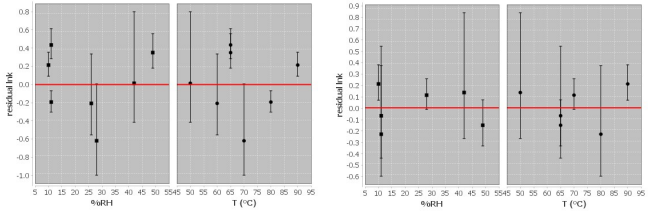
Example data of empty capsule disintegration times after storage at 65°C/11% RH (left) and 80°C/11% RH (right)



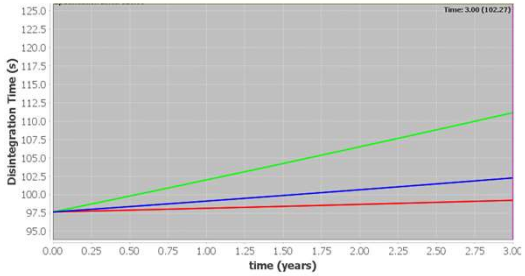
ASAP*prime® *fitting of isoconversion times to moisture-modified Arrhenius equation showing overlapping behavior with and without starch

Fill	ln A	E_a(kcal/mol)	B	R^2
Empty	36.2 ± 8.4	24.9 ± 5.9	0.016 ± 0.018	0.91
Starch	41.0 ± 7.6	28.3 ± 5.4	0.034 ± 0.017	0.98

Residuals plots of isoconversion times, relative to temperature and RH, showing good fit to model



ASAP*prime® *predictions for disintegration time stability of starch-filled capsules



Conclusions

- Disintegration slowdown of gelatin capsules modeled effectively using ASAP*prime*®
- Excipient does not significantly impact capsule disintegration stability, implicating crosslinking is intrinsic to gelatin

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