ASAP Case Study of a Tablet Drug Product

Helen Williams

Science of Stability, 3rd Annual Conference, Dublin

3rd October 2017

Introduction

- 200 mg tablet formulation, phase III
- Manufacturing change from wet granulation to roller compaction
- Chemically stable product, 2 years long term stability data on wet granulation product
- Reduction in dissolution rate observed when exposed to high humidity, so packed with desiccant in bottle

Needed to quickly determine stability characteristics of the new roller compaction formulation ……. ASAP study

ASAP Study

Previous product knowledge

- No chemical degradation after 4 weeks at 70°C/75% RH during forced degradation study
- No significant risk of API under going a form change when exposed to the typical temperatures or humidities of an ASAP study
- Standard tablet excipients, no significant risk of excipient form change.
- Potential reduction in dissolution rate at high humidities

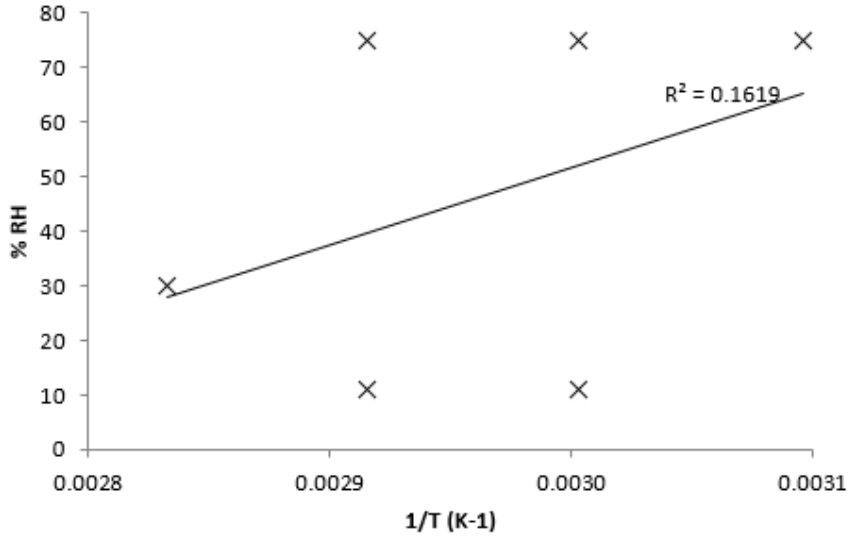
ASAP Study Protocol

Temperature (°C)	Humidity (% RH)	Storage Time (weeks)
Initial	Initial	0 (3 repeats), X
50	75	4, 8, S
60	11	4, 8, S
60	75	4, 8 (5 repeats), S
70	11	4, 8, S, X
70	75	4, 8, S, X
80	30	4, 8, S, X

Impurities analysis by LC at all time points
S = spare sample, as optional additional time point
X = XRPD sample

ASAP Study Protocol

Temperature (°C)	Humidity (% RH)
Initial	Initial
50	75
60	11
60	75
70	11
70	75
80	30



ASAP Study – Dissolution Protocol

Temperature (°C)	Humidity (% RH)	Storage Time (weeks)
Initial	Initial	0
40	30	6, S
40	55	6, S
40	75	6, S

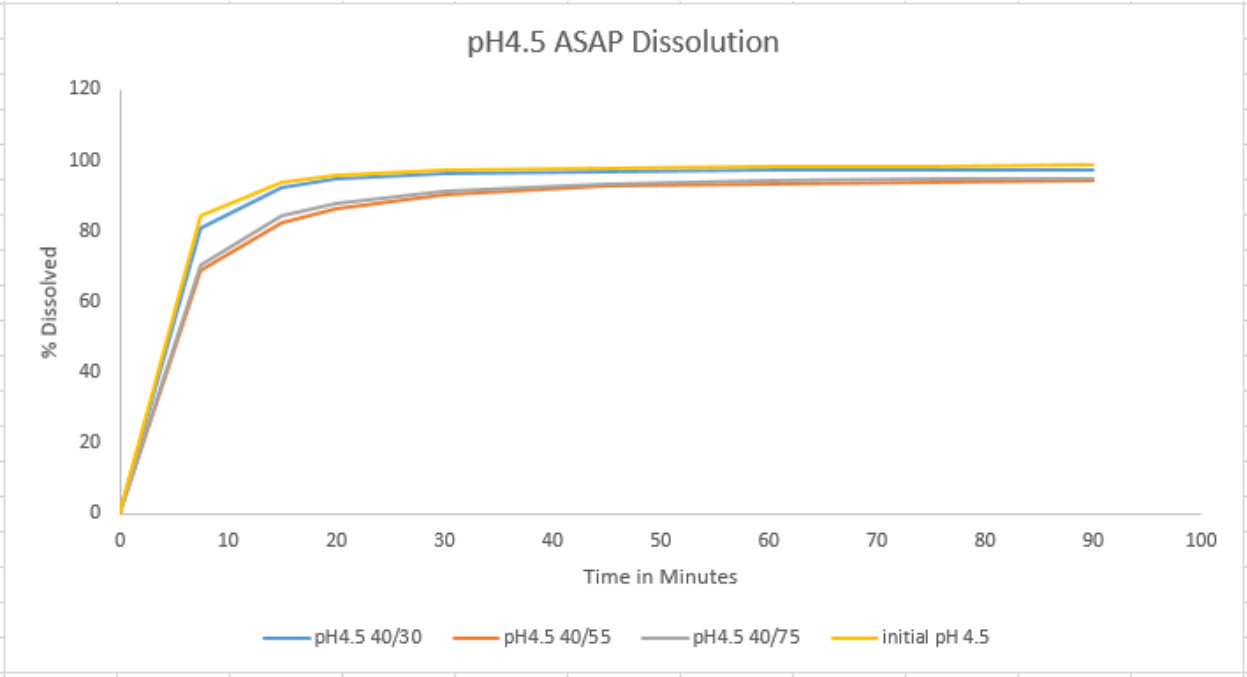
24 tablets set down for each time point
(n=6, two dissolution methods pH 1.2 and 4.5, and spares)

ASAP Study – Set down

- The tablets were set down in glass jars, with inserts containing the tablets and a further insert containing the relevant salt solution.
- Salt solutions were used to control the humidity - lithium chloride 11% RH, magnesium chloride 30% RH, sodium chloride 75% RH and Amebis humidity capsule (U036) for 55% RH.
- Coated tablets are usually allowed to pre-equilibrate with humidity for at least 24 hours before exposure to high temperatures
- The jars were then placed in ovens
- 44 tablets for the initial analysis were placed in the fridge, also stored in the same inserts.

ASAP Study - Results

- No degradants detected during the 8 week ASAP study
- No change in physical form of API detected (XRPD)
- No change in dissolution profile of tablets stored at 40°C/30% RH
- Evidence of dissolution rate slowing in tablets stored exposed to higher humidities
- All still pass specification (>75% dissolved at 30 minutes)



ASAP Study - Conclusions

- Roller compacted tablets are chemically stable
- The tablets should be packed with desiccant to minimise the risk of a reduction in dissolution rate on storage
- Demonstrated equivalence with wet granulation tablet formulation

ASAP data (impurities and dissolution) was included in the Phase III IND and IMPD submissions, as supporting information.

Regulatory submission

- ASAP study on 200 mg roller compaction batch
- At time of IND submission 1 month stability data on 200 mg roller compaction development batch
- At time of IMPD submission 3 months stability data on 200 mg roller compaction development batch and 1 month on clinical batch
- Alongside 2 years stability data on 200 mg wet granulation batch

- Claimed a 12 month initial shelf for new 200 mg roller compaction formulation in the bottle packed with desiccant
- Submitted in Canada, US, Ukraine, Russia, Taiwan and Poland
- Accepted with no regulatory questions

Further ASAP study

- Six months later, a lower dose tablet was required for a different clinical trial (100 mg, roller compaction, common granule)
- No real time stability data on 100 mg formulation
- Performed a second, very similar ASAP study on 100 mg tablets

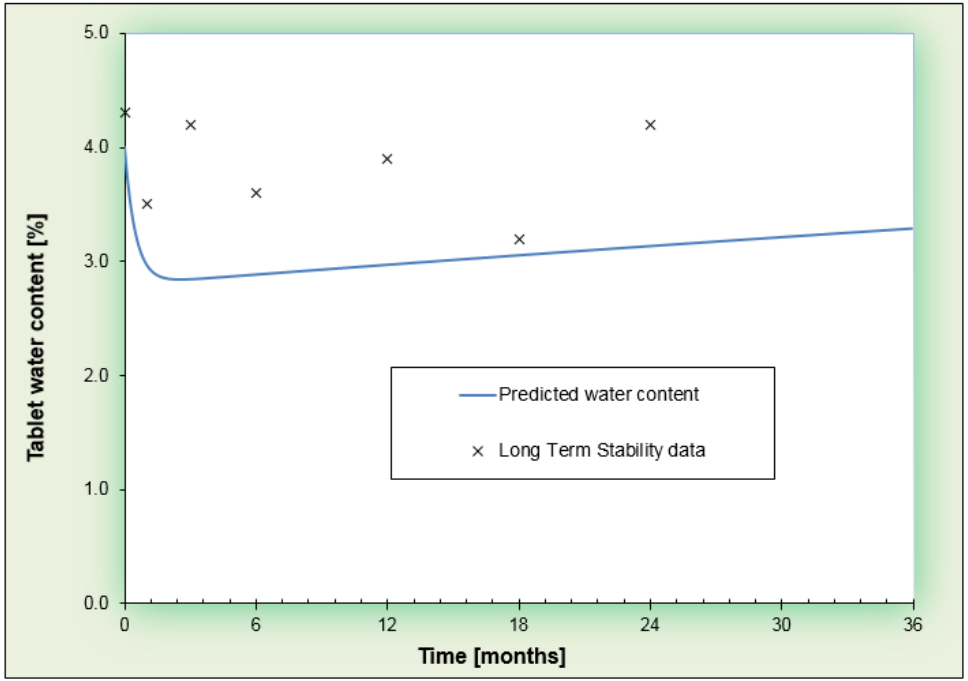
- Again no degradation was observed during the study and a small reduction in the dissolution rate was observed at 40°C/75% RH.
- Demonstrated equivalence between the 100 mg and 200 mg roller compaction formulations in terms of stability characteristics

Further Regulatory submission

- No long term stability data on new 100 mg roller compaction tablets, ASAP study data only was presented for this formulation
- Alongside 2 years stability data on 100 mg wet granulation batch and 6 months stability data on two 200 mg batches roller compaction tablets.
- Claimed a 18 month initial shelf for new 100 mg roller compaction formulation in bottle pack with desiccant, based on equivalence with 200 mg roller compaction formulation.
- Committed to setting down ICH stability for 100 mg roller compaction formulation
- Recently submitted to Ukraine, Russia, Canada, US, Taiwan, Poland and Japan
- Currently waiting on responses……

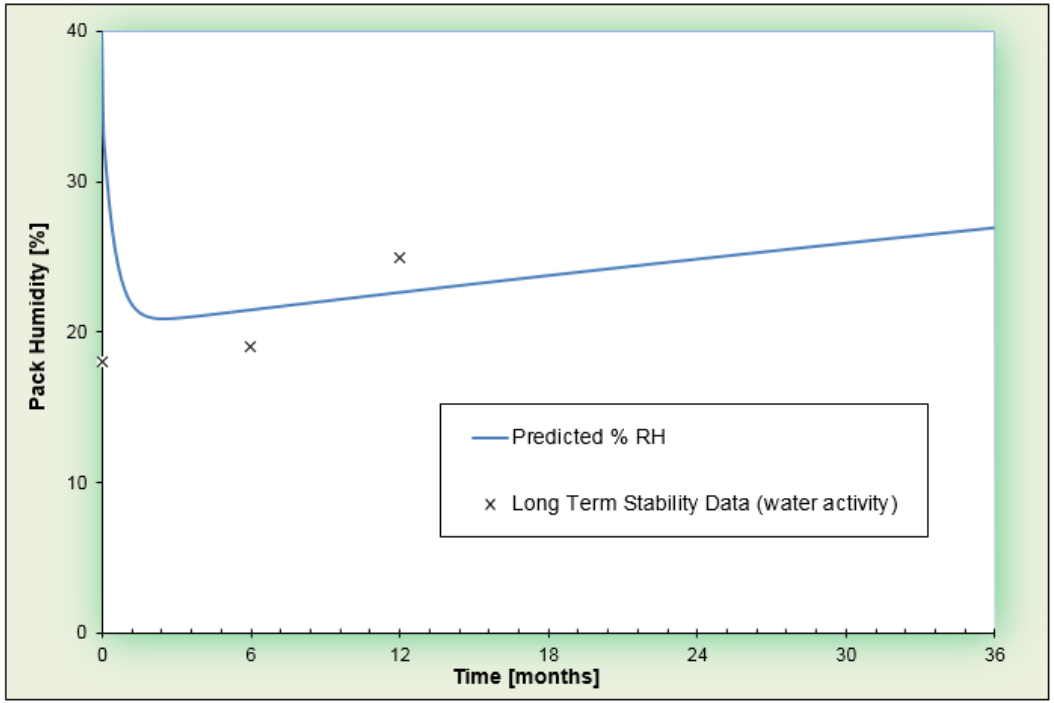
Packaging Predictions

Predictions were also performed to determine the tablet water content and humidity inside the pack on storage at 25°C/60% RH for 3 years



Packaging Predictions

Predictions suggest that the humidity in the bottle will remain below 30% RH over 3 years stored at 25°C/60% RH.



Conclusions

- ASAP studies used to demonstrate equivalence of a new tablet formulation with the existing formulation, even though no degradation occurred in the ASAP study and no shelf life predictions could be performed.

- ASAP data was used in phase III regulatory submission to support a shelf life claim in the absence of long term stability data, waiting regulatory questions.

Acknowledgements

Debbie Lane
Edward Griffin
Emily Roddy
Faye Turner
Emily MacDougall
Andrew Brookes
James Mann
Nadim Akhtar

Thank you for your attention