The Effect of Temperature Changes on the Quality of Pharmaceutical Products During International Transportation

H. Farrugia, R. Brincat, MC. Zammit, F. Wirth, A. Serracino Inglott, LM. Azzopardi, M. Zarb Adami
University of Malta, Department of Pharmacy, Msida Malta
E-mail: hfar0002@um.edu.mt
University of Malta

Introduction

During shipment of temperature sensitive pharmaceuticals it is imperative to sustain an unbroken cold chain to ensure drug quality. A malfunction in the cold chain transportation can result in a decreased shelf life, which will have negative economical repercussions on the pharmaceutical industry.[1] Although storage conditions are fairly constant, the distribution environment can show greater fluctuations especially if transportation occurs through different climatic zones. Seasonal changes and mode of transportation are parameters that should be monitored during shipment.[2]

Aim

To establish the effect of temperature change on the quality of cold storage pharmaceutical products during international transportation, using oxytocin injections and fluvastatin active pharmaceutical ingredient (API) as specific examples.

Methodology

Oxytocin Study

- An analytical method for the rapid and efficient detection of oxytocin using High Performance Liquid Chromatography (HPLC) was developed.
- A stability study was carried out over a period of 96 days using different storage temperatures; 2-8°C, 25°C, 30°C, 40°C and 50°C. From the degradation kinetics an Arrhenius plot was sketched.
- Oxytocin injections were sent together with a miniature data logger from Malta to Amsterdam on a monthly basis between May 2001-April 2002.
- The temperature readings were compared to the stability study results to estimate the extent of degradation; expressed as the percent of oxytocin degraded in relation to the initial assay concentration (10.29 IU/mL) of oxytocin in the vials.

Fluvastatin API Study

- API in amber vials together with temperature data loggers where shipped to the chosen destinations.
- No temperature control was used during shipment when sending raw fluvastatin to six European countries during winter 2008/2009 and spring 2009.
- Initially the destinations were France, Italy, Germany, Holland, Hungary and England.During second shipment, Hungary and Italy were exchanged with Denmark and Portugal, as there was a shift in the pharmaceutical demand.
- The increase in percentage impurity was measured using a validated HPLC method. Paired sample t-test and Pearson correlation were used to analyse the increase in percentage impurity of 5-oxofluvastatin.

Results And Discussion

Oxytocin Study

Temperature (°C)	Rate of Degradation (k) (min^{-1})	Time to degrade to 90% potency (days)
2-8	0.4606×10^{-4}	159
25	0.4606×10^{-4}	159
30	1.1515×10^{-4}	64
40	1.3818×10^{-4}	35
50	4.6060×10^{-4}	16

Table 1: Rate of Oxytocin degradation at different temperatures.

1. Oxytocin injection is fairly stable at temperatures below 25°C however it degrades exponentially at temperatures above 30°C.
2. Highest degradation was observed in June (0.61%) whereas, lowest degradation was observed in December (0.24%).

Fluvastatin API Study

Winter 2008-2009

Destination	Mean Temperature(°C)	Increase in % impurity (Limit=0.15)	Duration of Transport (days)
Malta-Italy-Malta	35.16	0.0012	12
Malta-Germany-Malta	16.83	0.0008	12
Malta-England-Malta	16.17	0.0001	15
Malta-Hungary-Malta	18.02	0.0001	40
Malta-Holland-Malta	16.89	0.0011	39
Malta-France-Malta	No data due to loss of data logger and sample		

Table 2: Mean temperatures recorded during shipment and the increase in 5-oxofluvastatin impurity after shipment to the corresponding countries.

Spring 2009

Destination	Mean Temperature(°C)	Increase in % impurity (Limit=0.15)	Duration of Transport (days)
Malta-Portugal-Malta	24.40	0.0029	28
Malta-Germany-Malta	21.16	0.0024	12
Malta-England-Malta	25.92	0.0037	16
Malta-Denmark-Malta	21.68	0.0050	12
Malta-Holland-Malta	20.95	0.0035	25
Malta-France-Malta	22.25	0.0038	14

Table 3: Mean temperatures recorded during shipment and the increase in 5-oxofluvastatin impurity after shipment to the corresponding countries.

1. The highest mean temperatures were recorded in spring 2009 during shipment to England and Denmark.
2. The level of 5-oxofluvastatin was always less than 0.15% limit.
3. A statistically significant increase in impurity level was observed during winter and spring ($p<0.05$).

Conclusion

Both studies indicate that an increase in temperature leads to an increase in degradation of temperature sensitive products. For the oxytocin study, the transportation period was always constant (5 days), whereas for the fluvastatin API study, transportation duration varied (Table 2 and 3). This shows that the rise in temperature is the major contributor to instability when compared to the length of transportation.

References

[1] Geraint, T., Developing cold chain solutions. Pharm. Technol. Eur. 20, 51-55 (2008)
[2] Lucas, T., et al. A stability program for the distribution of drug products. Pharm. Technol. 68-73 (2004)