DruQuaR

FACULTY OF PHARMACEUTICAL SCIENCES

Influence of variability in starting material quality on stability of finished drug products: A quality-by-design factor and response

Matthias D'Hondt[1], Evelien Wynendaele[1], Tiene Bauters[2], Johan Vandenbroucke[2], Hugo Robays[2] and Bart De Spiegeleer[1,*]

[1] **Drug Quality and Registration (DruQuaR) group, Faculty of Pharmaceutical Sciences, Ghent University, Harelbekestraat 72, B-9000 Ghent, Belgium.**

[2] **Department of Pharmacy, Ghent University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium.**

* Corresponding author: bart.despiegeleer@ugent.be (O. Ref.: 2012-132e)

INTRODUCTION

The use of poorly selected excipients in drug formulations can have a significant influence on the overall stability of the finished drug product. Therefore, evaluation of chemical and physical excipient compatibility with the active pharmaceutical ingredient (API) has become a major part in the development of new drug products. Moreover, while general and individual limits for excipient impurities have been set by the Ph. Eur. and USP, batch to batch variability of these excipient impurities, although still Ph. Eur. / USP compliant, can cause significant variability in the stability profile (= response) of a finished drug product. Although currently often overlooked, the excipient quality (= factor) should be an important consideration of the Quality-by-Design (QbD) approach [1], as a consistent stability profile is a highly desired quality attribute, as recently demonstrated by β-artemether-containing antimalarial products [2].

We demonstrated the influence of the quality of the starting materials, *i.e.* methylprednisolone (21) sodium succinate, on the variability in the stability profile of an *in-situ ex-tempore* prepared drug solution for intrathecal use (Triple IT), used in pedratric oncology [3].

EXPERIMENTAL

Objective: short-term stability evaluation of *ex-tempore* Triple IT solution (n=3)

Storage conditions:
5 C / 50% relative humidity
25 C / 60% relative humidity (ICH storage rooms)
40 C / 75% relative humidity (ICH storage rooms)

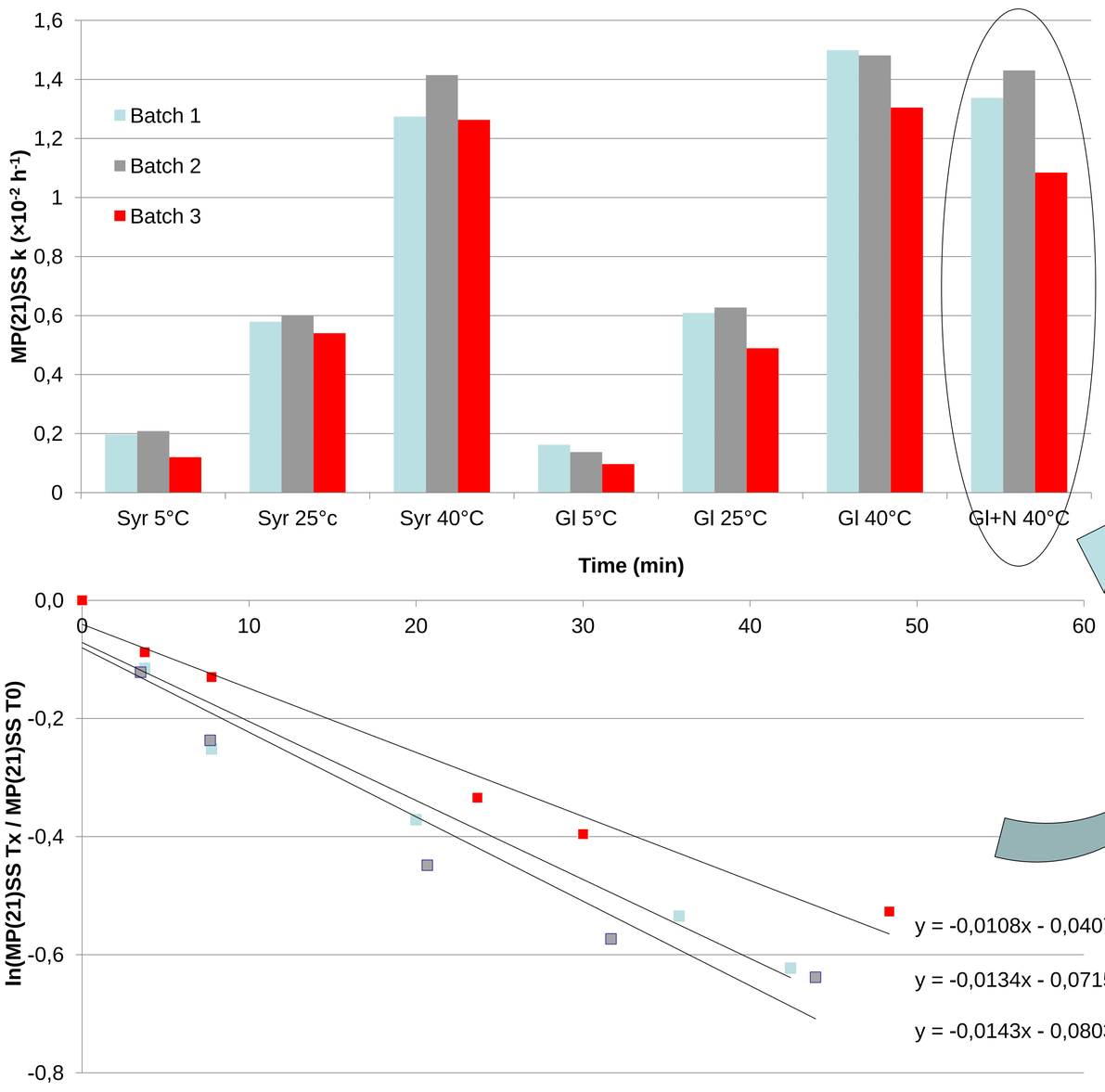
Packaging materials:
Plastic syringes (PhaSeal® system) [Syr]
Brown glass vials with rubber stopper [Gl]
Brown glass vials with rubber stopper + metal needles [Gl+N]

Ingredient	Lot number starting material	Concentration in Triple IT sol (%m/V)
Solu-medrol (methylprednisolone (21) sodium succinate)	X06014 (Batch 1)	0.0510
	X06014 (Batch 2)	
	X02490 (Batch 3)	
Emthexate (methotrexate)	10A25LB (all)	0.1538
Cytosar (cytarabine)	EK74F (all)	0.385

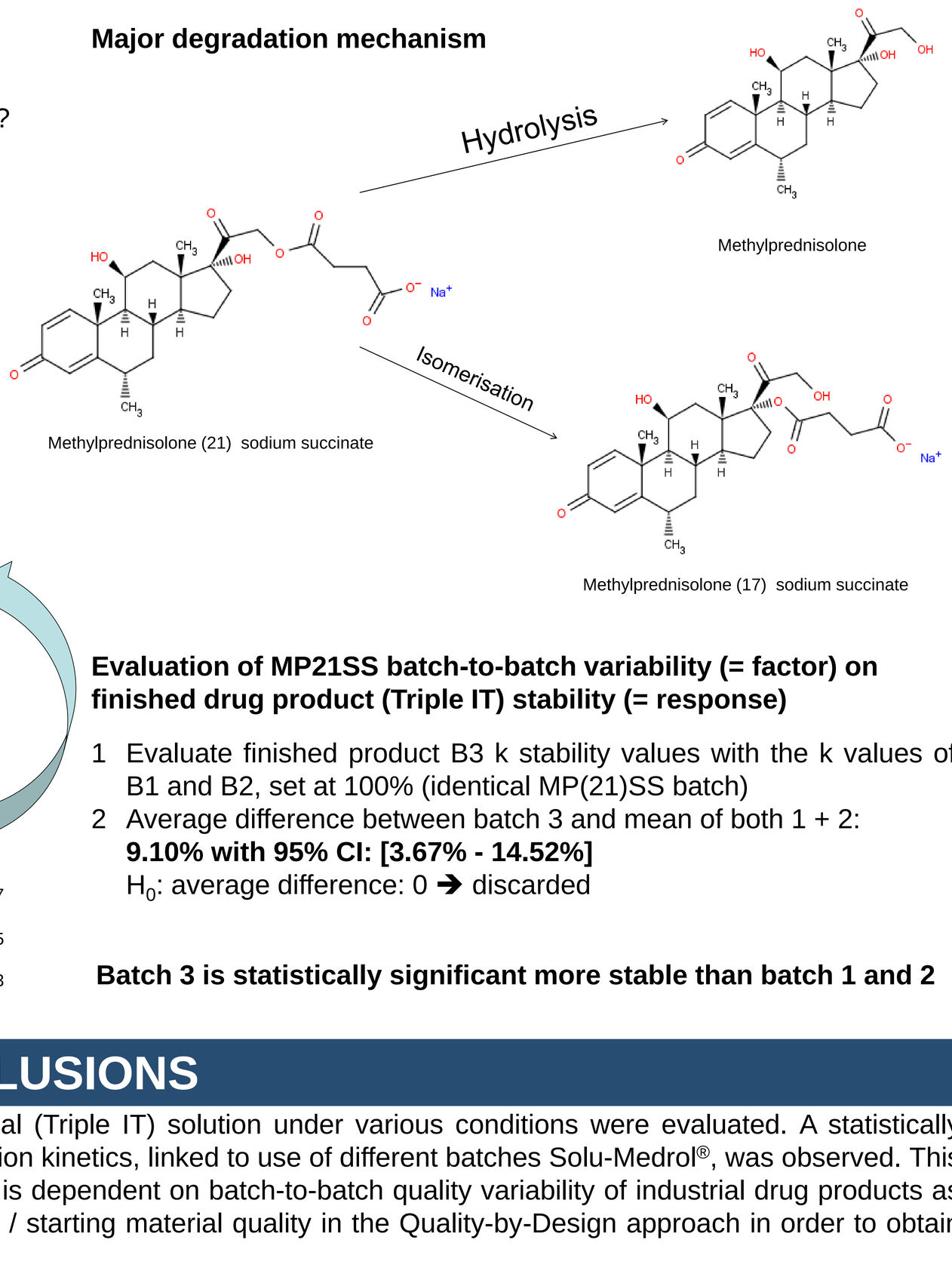
RESULTS and DISCUSSION

Methotrexate: stable
Cytarabine: stable
Methylprednisolone (21) sodium succinate: degradation

- Temperature
- Time
- Batch (B)???



Major degradation mechanism



Evaluation of MP21SS batch-to-batch variability (= factor) on finished drug product (Triple IT) stability (= response)

1 Evaluate finished product B3 k stability values with the k values of B1 and B2, set at 100% (identical MP(21)SS batch)
2 Average difference between batch 3 and mean of both 1 + 2:
9.10% with 95% CI: [3.67% - 14.52%]
H_0: average difference: 0 ➔ discarded

Batch 3 is statistically significant more stable than batch 1 and 2

CONCLUSIONS

The short-term (48 hrs.) storage stability of three batches triple intrathecal (Triple IT) solution under various conditions were evaluated. A statistically significant variability in methylprednisolone (21) sodium succinate degradation kinetics, linked to use of different batches Solu-Medrol®, was observed. This is a case where the stability of an *in-situ ex-tempore* prepared formulation is dependent on batch-to-batch quality variability of industrial drug products as starting material and further underlines the need of incorporating excipient / starting material quality in the Quality-by-Design approach in order to obtain consistent stability profiles.

REFERENCES

[1] M. D'Hondt, B. De Spiegeleer. *manuscript in preparation.*
[2] B. Baert, B. De Spiegeleer. Analytical and Bioanalytical Chemistry, *2010; 398*: 125-136
[3] M. D'Hondt, E. Vangheluwe, S. Van Dorpe, J. Boonen, T. Bauters, B. Pelfrene, J. Vandenbroucke, H. Robays, B. De Spiegeleer. American Journal of Health-System Pharmacy, *2012; 69: 232-240*.