Development of method and process validation for quantitative analysis of ibuprofen suppositories

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Background

Ibuprofen suppositories are produced as bulk ware by the hospital pharmacy. According to the recently amended German regulation, “Apothekenbetriebsordnung”, supplementary quality controls regarding bulk ware have been requested in § 8: For non-validated manufacturing processes, each batch of bulk ware has to be analyzed for uniformity of content. Neither the German nor the European Pharmacopoeia (Ph.Eur.) provides instructions for the quantitative analysis of formulations.

Purpose

Since only validated methods and processes must be used for manufacturing and analysis, the purposes of this study were

(1) to develop and validate an appropriate method for the quantitative analysis of ibuprofen suppositories, which fulfills the demand of the European Pharmacopoeia as well as the Good Manufacturing Practice Guidelines

and

(2) to validate the manufacturing process.

Methods

Leading Question

- Literature research + solution attempts → What kind of method is suitable for the quantitative analysis?
- Method validation → Evaluation of the validation parameters (according to ICH guidelines)
- Risk analysis → What critical parameters must be considered during the production process?
- Process validation
- Quantitative analysis of the suppositories → using the developed and validated titration method
- Quantitative analysis of the suppositories → Test for uniformity of content (according to Ph.Eur.)

Results

Method for quantitative analysis

(A) For the method validation, a procedure for the dissolution with dichloromethane and methanol and quantification of ibuprofen using an acidimetric titration was developed and successfully validated according to the requirements of ICH Guidelines.

Method validation

(B) Validation of the titration method by determining the validation parameters

	Consumption of NaOH [ml] (Person A)	Consumption of NaOH [ml] (Person B)
	2013-02-08	2013-04-12
1	4,55	4,54
2	4,55	4,56
3	4,55	4,56
4	4,55	4,55
5	4,55	4,56
6	4,55	4,54

Table 1:
Results of repeatability and reproducibility (s = 0.0067)

	Consumption of NaOH [ml]
Pure agent solution	12,40
Agent and excipient solution	12,35

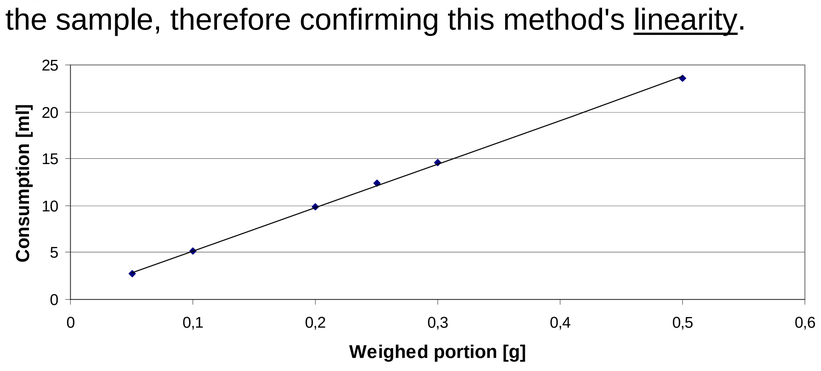
Table 2:
Consumption of NaOH solution for pure ibuprofen, compared to a solution also containing additional components of the suppository (specificity; s = 0.0354)

	Consumption of NaOH [ml] (Person A)		Consumption of NaOH [ml] (Person B)	
	2013-02-14	2013-02-15	2013-04-10	2013-04-12
1	11,05	11,05	11,00	11,00
2	11,05	11,05	11,00	11,00
3	11,05	11,05	11,00	11,00

Table 3:
Results of robustness determination (s = 0.0261)

The minor deviations of the results in tables 1 – 3 confirm the repeatability and reproducibility, the specificity and robustness of this titration method.

Figure 1 shows the proportionality between test results and analyte concentration in the sample, therefore confirming this method's linearity.



y = 48,05x

R^2 = 0,9982

Figure 1:
Consumption of NaOH vs. weighed portion of ibuprofen, creating a calibration line (linearity)

The determination of accuracy was provided by a plausibility consideration; the positive results of precision, linearity and specificity confirm the accuracy.

All requirements for the validation parameters have been fulfilled. The titration method is validated accordingly and thus can be used for process validation.

Process validation

(C) Risk analysis

Three important parameters must be considered in the production of suppositories and appropriate measures need to be taken when necessary:

1. Manufacturing personnel
2. Cross-contamination
3. Reliability of the analytical method

(D) Implementation of process validation – Testing for uniformity of content for single-dose preparations

By including all individual measurements of content, the distribution of results within a batch can be seen. The uniformity of content is provided for the range between 85 and 115 %. Figure 2 shows that this fact does not apply to 2 batches. Therefore these had to be validated again. This resulted in a significant improvement of the uniformity of content (figure 3), which shows that further training of the staff members provides a great benefit.

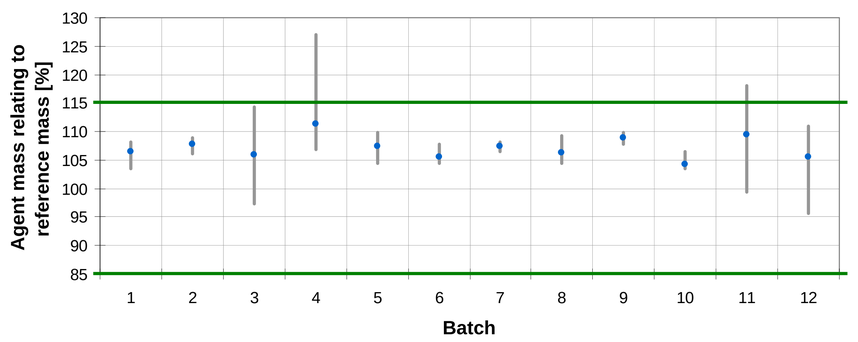


Figure 2:
Maximum and minimum values of each batch (executed by four staff members)

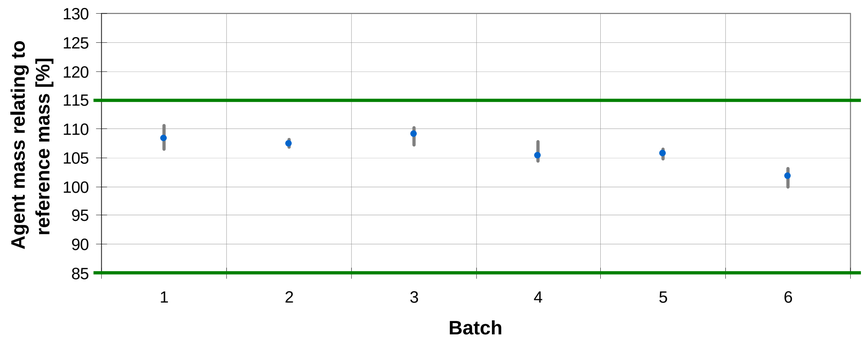


Figure 3:
Results after Revalidation

The validation process has been successfully carried out under routine conditions, which guarantees that it can be applied to routine production.

Conclusion

The developed method and process validation are suitable to ensure the quality control of the manufacturing process of ibuprofen suppositories. The implementation of this project has contributed to the improvement of drug safety as well as to the simplification of operational processes. Furthermore, this approach can be adopted by other hospital pharmacies and may serve as an example for the development of further method and process validations in the future.

19th EAHP Congress, Barcelona, Spain, 26 – 28 March 2014, Abstract number: PP-001

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