Hospital Pharmacy

Evaluation of the Quantos® powder dosing system for capsule manufacturing in a hospital pharmacy.

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Background

The Quantos® powder dosing system (Mettler Toledo, Germany) offers the filling of small amounts of powders and liquids into different containers. Although it is already used for handling of hazardous substances and/or preclinical drug development, very few experience exist for the routine manufacturing of capsules in a hospital pharmacy.

Therefore, accuracy and practicability of Quantos® as compared to the manual capsule filling according to the German drug codex (DAC, Deutscher Arzneimittel-Codex) in a hospital pharmacy was evaluated.

Questions and examinations

1) Accuracy/uniformity of mass and content	Comparison of Ph.Eur.-assays of DAC and Quantos® methods
2) Dosing process of Quantos®	Does the homogenity of the powder change over time?
3) Time taken	Which method is less time consuming?
4) Alternative filling methods (Quantos®)	Impact of „Sandwich" and pure active agent filling

Experimental setup

Investigated drugs and dosages:

Hydrochlorothiazide capsules (HCT) with 0.5 mg, 2.0 mg und 5.0 mg each

Spironolacton capsules (SL) with 2.0 mg, 6.0 mg und 12.,5 mg each

DAC method: 2 x 100 capsules → sample size: 10 random capsules per batch

Quantos®: 1 x 200 capsules → sample size: 4 consecutive capsules according the following design:

Methods

a) Ph.Eur.-assays for capsules

- *2.9.5 Uniformity of mass for single-dose preparations*
  - ✓ Weight of 20 random samples (intact and emptied)
  - ✓ Calculation of average mass and deviation from average mass
  - ✓ Limits: max. 2 caps. > 10 % and none > 20 %
- *2.9.6 Uniformity of content for single-dose preparations*
  - ✓ Quantitative analysis of 10 random samples
  - ✓ Calculation of average content and deviation from average amount
  - ✓ Limits max. 1 caps. > 85-115 % and none > 75-125 %
- *2.9.40 Uniformity of dosage units*
  - ✓ Calculation of acceptance value (AV) including the content of active substance as percentage of the label claim
  - ✓ Maximum allowed AV: 15

b) Time taken

- Determination of the duration of all processes of capsule manufacturing in [min:s]

c) Quantitative analyses

- UV/Vis-spectroscopy at 273 nm (HCT) or 242 nm (SL)
- Linearity HCT: 0,3-0,7 mg in NaOH (0.1 N)
- Linearity SL: 3,0-7,0 mg in HCl (0.1 N)

Results*

* as example for HCT, results for SL are similar

Quantitative analyses

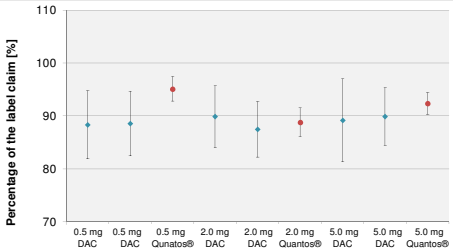

Fig.1: Content of HCT as percentage of the label claim (mean ± standard deviation)
blue = DAC method (Batch of 100 capsules)
red = Quantos® (Batch of 200 capsules)

- ✓ Triturations used as bases for both methods contain the expected content (table1)
- ✓ All batches irrespective of the manufacuring process contain only about 90% of the label claim (figure 1)
- ✓ Standard deviations of the DAC method are higher compared with the Quantos® method (table 2)

	Quantos®			DAC method
Trituration	0.5 mg	2.0 mg	5.0 mg	Raw trituration
Content [%]	**99.79**	**99.39**	**104.65**	**99.00**

Table1: Contents of the triturations used as bases for capsule manufacturing [% of label claim]

	Dosages (batch)					
	0.5 mg	0.5 mg	2.0 mg	2.0 mg	5.0 mg	5.0 mg
Standard deviation [%] DAC method (n=100)	**6.44**	**6.11**	**5.83**	**5.25**	**7.84**	**5.46**
Standard deviation [%] Quantos® (N=200)	**2.33**		**2.69**		**2.07**	

Table 2: Overview of the contents' relative standard deviations[%].

1) Ph.Eur. assays

Ph.Eur. 2.9.5: : Uniformity of mass

- DAC method: 5/6 batches (100 caps.) comply
- Quantos®: 3/3 batches (à 200 caps.) comply

Ph.Eur. 2.9.6: Uniformity of content

- DAC method: 0/6 batches comply
- Quantos®: 3/3 batches comply

Ph.Eur.: 2.9.40: Uniformity of dosage units

- DAC method: 0/6 batches comply
- Quantos®: 2/3 batches comply

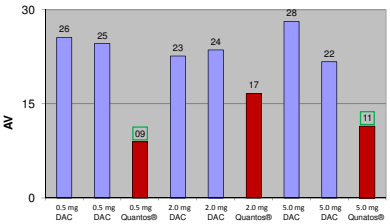

Fig. 2: Acceptance value (AV) of Ph.Eur. 2.9.40
blue = DAC method
red = Quantos®
Green square = AV <15

2) Dosing process of Quantos®

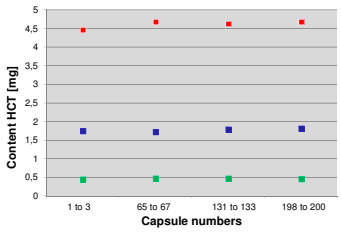

Fig.3: Mean values of four dosing groups during the Quantos dosing process.
red = 5.0 mg
blue = 2.0 mg
green = 0.5 mg

- ✓ The rocking motions of the dosing head does not have any impact on the homogeneity of the active substance within the filler.

3) Expenditure of time

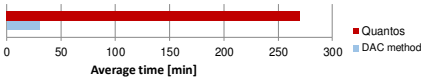

Fig.4: Average cumulative time for the manufacturing of 200 capsules with both methods.
DAC method contains: trituration, manufacturing
Quantos® contains: trituration, preparation of the dosing head, preparation of the maschine, filling, cleaning of the maschine

4) Alternative filling methods with Quantos®

Analysis of 30 capsules each (label claim: 2.0 mg HCT)

Normal procedure: Filling with a trituration. All results shown above refer to this method

„Sandwich capsules": Preparation in 3 steps (filler/ active substance/ filler)

- content: 2.14 mg (standard dev. 8.40 %)
- Ph.Eur. analyses: all fulfil the requirements
- Time per batch (30 caps.): 01:05:49

Filling with active substance (without filler).

- content: 2.39 mg (standard dev. 8.26 %)
- Emptying efficiency*: 35-68 %
- Time per batch (30 caps.): 00:31:39

Fig. 5: Illustration of the different analysed filling methods: normal procedure: filling of a trituration (A), „sandwich filling" (B) and filling of pure active substance (C); **Light blue**= active substance; **dark blue**= filler (Mannitol/Aerosil: 99,5/0,5)

* Measured as percentage of emptied mass in relation to filled mass (usually, capsules are emptied and the powder is solved or suspended immediately before application on the ward)

Conclusion

Both methods offer the opportunity to produce capsules that comply with the Ph.Eur. Requirements. The Quantos® system is able to fill the capsules more precisely and allows a GMP-conform documentation. However, in respect of a day-to-day work the handling of Quantos is still open to improvements. The recovery rate of about 90% might be due to an incomplete emptying of the capsules before quantification. This finding also has major implications for the common practice of emptying capsules on the wards and needs further investigation. Due to the poor flow characteristics of the pure active substance, the evaluated alternative filling methods are less accurate and slower compared with the filling of the trituration

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