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Uniformity of weight test: a non-destructive test compared to the European Pharmacopoeia test

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The test for uniformity of weight as stipulated in the European Pharmacopoeia (Ph. Eur) is a complicated and time consuming method. The aim of the present project was to prove, that a new method developed in the Pharmacy Department of the University Hospital of Heidelberg is in principle equivalent to the Ph. Eur. method. Six lots of capsules were produced with a hand operated capsule filling machine. They were filled with mannitol and Aerosil®. Three lots of capsules contained 0.5% Aerosil and the other three lots contained 5% Aerosil. Before filling the capsules, the lot specific empty capsule weight was defined in order to determine the real weight of contents. According to the Ph. Eur. method and our method the filling weight was calculated in two different ways. The results of both methods were compared always in relation to the real weight of contents of the capsules. The results suggested that the average filling weight of the Ph. Eur. method could never be well-defined because there is always substance left in the capsules when they are emptied in order to determine the empty weight. These findings demonstrated that our approach can be considered at least as good as the European Pharmacopoeia method. Furthermore the average filling weight of our method was more accurate which raises the question if the Ph. Eur. should be revised in this regard.

1. Introduction

The uniformity of weight is an assay for capsules mentioned in the European Pharmacopoeia (Ph. Eur. 5th edition).
According to the characterised method, the single weight of 20 filled capsules selected at random was measured as follows: The entire capsule was weighed, then the capsules were emptied and the shell of each capsule was weighed in order to define the weight of the content. In the following the sub- and the upper limit of the weight of contents of the capsules were determined in order to verify that all capsules are in the limits given by the European Pharmacopoeia.
This method implicates some disadvantages. It represents a destructive method, especially in case of small lots which might end up in economic problems. Furthermore, if the capsules are containing drugs with a high risk potential (e.g. CMR drugs) emptying the capsules bears a risk to the working person. In order to overcome these problems, we developed a new method (called HD Method).
Before producing capsules the average weight of 20 empty hard gelatine capsules selected at random is defined for a lot of 1000 empty capsules. This lot specific "empty capsule weight" is used for measuring the weight. After filling the capsules, 20 filled capsules selected at random were weighed. The mass of content is the difference between the average empty weight and the weight of full capsules.
In the following the average filling weight of both methods were compared with the real weight of contents of the capsules. In order to obtain a broad database, we did not only consider the 20 samples of a lot in our calculations but the complete lot containing 100 capsules.
The objective of the present study was to show that the HD method is at least as accurate as the EP method.

2. Investigations and results

In general the findings indicate that both methods show the same result.
In reference to the Table, the average weight of contents of the HD method was closer to the real average weight of contents than the results of the EP method (see Fig. 1).
The discrepancy of average values of EP and HD method was more significant in capsules containing 5% Aerosil® than in capsules containing 0.5% Aerosil®.
The standard deviation (S.D.) of both methods was similar to each other.
The Fig. 1 shows that the measured weight of the EP method is always below the real weight of content.
Moreover, the averages of deviation of the HD method were more close to the real weight of contents than the averages of the EP method. While emptying the capsules,

Table: Average filling weight and standard deviation of capsules

Filling material Mannitol and Aerosil (99.5 : 0.5)	Aver. weight of contents of capsules		EP method		HD method	
			(Difference between measured content weight and real content weight [mg])			
	Aver. [mg]	S.D. [mg] (%)	Aver. [mg]	S.D. [mg] (%)	Aver. [mg]	S.D. [mg] (%)
Lot 1	285.9	9.8 (3.43)	285.4 (−0.5)	9.8 (3.43)	285.5 (−0.4)	9.6 (3.36)
Lot 2	297.2	8.9 (2.99)	296.3 (−0.9)	9.0 (3.03)	296.8 (−0.4)	8.9 (2.99)
Lot 3	295.0	8.1 (2.74)	294.5 (−0.5)	8.1 (2.75)	294.8 (−0.2)	8.0 (2.71)
Filling material Mannitol and Aerosil (95 : 5)						
Lot 1	200.0	5.9 (2.95)	199.6 (−0.4)	5.8 (2.90)	199.7 (−0.3)	6.0 (3.00)
Lot 2	200.3	5.4 (2.69)	198.9 (−1.4)	5.3 (2.66)	199.7 (−0.6)	5.5 (2.75)
Lot 3	202.0	4.9 (2.42)	200.8 (−1.2)	5.1 (2.53)	201.9 (−0.1)	5.0 (2.47)

The measured content via EP method is always lower as with the HD method

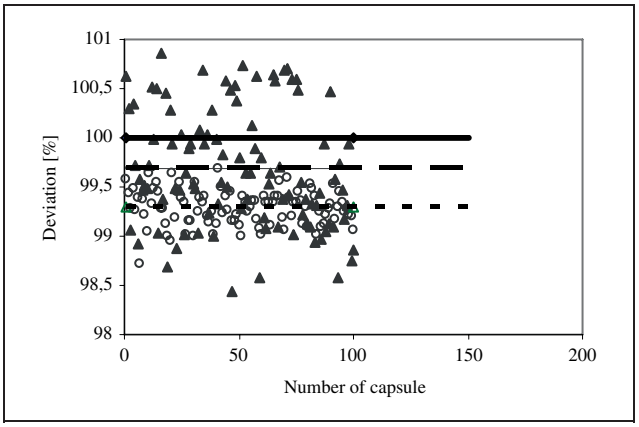

Fig.: Deviation of average filling weight of the EP method and the HD method compared with the average mass of content of capsules (e.g. Lot 2: Capsules were filled with a mixture of mannitol (95) and Aerosil (5)).
▲ HD method
○ EP method
——— Real weight of contents of capsule (= 100%)
— — — Aver. filling weight of HD method
------- Aver. filling weight of EP method

as stipulated by the EP method, substance is always left in the dosage forms. This bias always existed in all 6 lots and could not be compensated.
The deviation of the EP method increased in case of working with drugs which were more difficult to handle (e.g. capsules containing 5% Aerosil). In these cases the HD method can be established as a method with smaller rates of deviation.
The deviation of the average filling weight of our method was sometimes more or less the real filling weight. Consequently the average filling weight of the HD method was much closer to the real weight of contents of the capsules than the average filling weight of the EP method.

3. Discussion

The results of the EP method were always lower than the real filling weight, whereas the deviation of our method could be slightly higher or lower than the real filling weight.

According to the EP method, the weight of contents could not be well-defined in all produced lots due to the method of calculating the weight of the emptied capsule. There was always substance remaining in the capsules after they had been emptied. This bias existed in all 6 lots. Nevertheless the S.D. of both methods is equal. These findings indicate that the HD method is as precise as the directive characterised in the European Pharmacopoeia in terms of uniformity of weight test.
Nevertheless the real weight of the capsule content is better characterised by our method due to the problems of completely clearing the capsule.

- According to the EP method, a loss of content is obligatory because in the European Pharmacopoeia it is stipulated that the capsules should be emptied in order to define the weight of content of the capsule. This represents a destructive method.
- Another problem of the EP method is capsules containing drugs with a high risk potential. In these cases the procedure of emptying the capsules bears a risk for the operating person.
- In case of filling capsules with substances that are very electrostatic, the filling substance is adsorbed by the capsule when emptying it.
- In addition the EP method is a time-consuming method, because the capsules have to be emptied entirely.

Therefore the EP method should be changed to a more convenient, precise and save method like the HD method which reflects, furthermore, the real weight of the capsule more accurately.

4. Experimental

4.1. Materials

Hard gelatine capsules (size 1, filling volume 0.5 ml) were obtained from WEPA Apothekenbedarf GmbH & Co. KG (Hillscheid, Germany).
Filling material according to DAC 2006 (99.5% mannitol; 0.5% Aerosil®) (DAC 2006) and filling material (95% mannitol and 5% Aerosil) were obtained from the Pharmacy Department of the University Hospital of Heidelberg (Germany). Mannitol and Aerosil were both obtained from Caesar & Loretz GmbH (Hilden, Germany). The materials were of reagent grade and were used as received.
A Mettler AE 200 (e = 1 mg) precision balance was used to measure the weights.
Capsules were filled in a hand operated capsule filling machine Aponorm 100 capsules from WEPA.

4.2. Methods

The mean empty capsule weight was established by weighing of 20 randomly selected capsules.
Six lots of capsules – 100 capsules per lot – were produced using two different kinds of filling material. The filling material differed in the amount of Aerosil. Every 3 lots were filled with a mixture of 99.5% mannitol and 0.5% Aerosil or 95% and 5%, respectively. 50 ml of the aforementioned filling material was filled vibration-free in a graduated cylinder. Subsequently the substance was evenly dispersed on the capsule filling machine and "brushed" into the empty capsules.
Every empty capsule was weighed and then positioned in the hand operated capsule filling machine. After filling every capsule was reweighed and the real content was calculated as the difference of filled and empty capsule weight.

According to the EP method the weight of the content was measured by weighing the entire capsule, emptying the capsule, reweighing the capsule shell and calculating the difference. For the HD method we calculated the difference between the filled capsule and the mean empty capsule weight of the empty capsule lot.
Afterwards the deviation of the measured weight of the content from the real weight was calculated for both methods.

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