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Mass uniformity of nasal sprays

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Abstract

The uniformity of nasal spray dose delivery was investigated. Four selected nasal sprays commercially available on the European market were checked for their mass uniformity according to the guidelines of the European Pharmacopoeia and recent draft guidelines of the Food and Drug Administration (FDA). Mass uniformity was also determined with simulation of a patient's use daily, and at 3- and 7- day intervals. The influence of the degree of filling and different storage positions on mass uniformity were also investigated.

At first usage, all preparations fulfilled the specifications of the Ph.Eur. and the FDA draft guidelines. When patient application was simulated, however, the dose accuracy decreased significantly with some of the preparations with increasing time of non-usage, presumably due to evaporation of liquid in the application system. This is indicated by a loss of weight of the nasal spray flasks observed during simulated weekly usage. Under these conditions (6 days' storage without use, same demands for uniformity of mass of the delivered dose), one of the preparations even failed to meet the Ph.Eur. and FDA limits.

Key words

Nasal sprays, Mass uniformity

1. Introduction

Nasal sprays are pharmaceutical preparations which are applied to the nasal cavity to produce local or systemic effects. In contrast to nasal drops, the microbiological burden of the aqueous drug solution or suspension is minimized and dose accuracy improved [1,2]. Additionally, nasal sprays are a useful option for many compounds that cannot be administered orally. For these reasons, nasal sprays have become increasingly significant in recent years.

Since highly potent drugs are often given as nasal sprays, control of content uniformity and mass uniformity is of great importance. The authorities demand precise controls on dose accuracy and content or mass uniformity. The European pharmacopoeia gives mandatory guidelines for the control of nasal sprays [3]. The delivered masses of 10 samples have to be determined by difference weighing. A preparation meets the specification if not more than 2 single values deviate by more than 25% and none by more than 35% from the mean value. Recently, the FDA published draft guidelines for nasal sprays [4] which propose a maximum deviation of ±15% from the target weight for the individual sprays and ±10% deviation of the mean weight from the target weight. These guidelines, however, are only recommendations and it remains to be determined whether these limits are realistic and practicable.

The importance of dose accuracy of nasal sprays has already been noted in the literature [5], but little is actually known about it, especially with respect to simulation of patient's use. We aimed to investigate the delivery technique with regard to mass uniformity of some selected nasal sprays available on the European market.
As examples for locally acting preparations, two products containing the anti-allergic drug cromoglicinic acid were chosen (Prep.A, Prep.B). The effect of the locally acting drug is restricted to the nasal cavity.

Prep.B is a preservative-free, multiple-dose preparation. To comply with the microbiological demands of the Pharmacopoeia, a patented delivery device is used. Studies demonstrating the drug safety of such preservative-free preparations have focused on microbiological safety [6,7]. Since there is no literature on spray mass uniformity during usage, a comparison to a drug product of similar composition and usage, but with a conventional delivery device was of interest.

To investigate nasal sprays for systemic use, desmopressin nasal sprays were chosen, since there are two comparable products available on the market (Prep.C, Prep. D). Since the drug is poorly absorbed after oral application, the nasal route is used for systemic application [8,9]. A prerequisite to the safe application of this highly potent drug is accurate mass uniformity, which we tested.

The studies followed the instructions for use of the drug products. Usually nasal sprays are applied with 2 puffs, one in each nostril. There are studies that demonstrate the superior effectiveness and bioavailability of 2 puffs compared to the application of the same drug amount with 1 puff [10]. The volume of one single puff is restricted to the capacity of the nostril. Current dispensing systems offer a broad range from 25 µl to 1000 µl [1], but the dosage volume usually lies between 50 µl and 150 µl. For systemic resorption smaller volumes should be preferred [11].

In this study the target volumes for 1 puff were 140 µl for the cromoglicinic acid nasal sprays and 100 µl for the desmopressin nasal sprays.

2. Experimental

2.1. Apparatus:

A SCALTEC balance (SCALTEC INSTRUMENTS, Heiligenstadt, Germany) with an accuracy of ± 0.01mg was used.

2.2. Materials

Two nasal sprays containing cromoglicinic acid (Preparations A and B) and two nasal sprays containing desmopressin (Preparations C and D) were investigated. The preparations were purchased from German or Austrian pharmacies.

2.3. Procedure:

Before measurements were made, the pumps were operated 5 times at 5 s intervals until the spray stream was constant ("priming"), according to the Ph.Eur. guidelines and manufacturers' operating instructions. Subsequently 2 puffs (corresponding to a single dose) were delivered and their masses individually determined by difference weighing of the flasks. To determine the mass uniformity of the different preparations at different intervals of use, this procedure was also carried out at 3- and 7-day intervals (i.e. 2 and 6 days' interruption), but without repeated priming.

Full and half-full spray flasks were investigated to determine the influence of the filling level. The influence of different storage positions such as upright, horizontal and upside down was also investigated. In the case of Prep.C, horizontal storage involved keeping the end of the supply tube aligned upward (out of the liquid) or downward (immersed in the liquid). Furthermore, the flasks were stored with and without their caps.

Ten samples each were investigated for the different investigations.

3. Results and Discussion

3.1. Daily use:

After priming, 2 puffs were delivered and the masses of each puff determined. This procedure was repeated daily over a period of 5 days, but without priming.

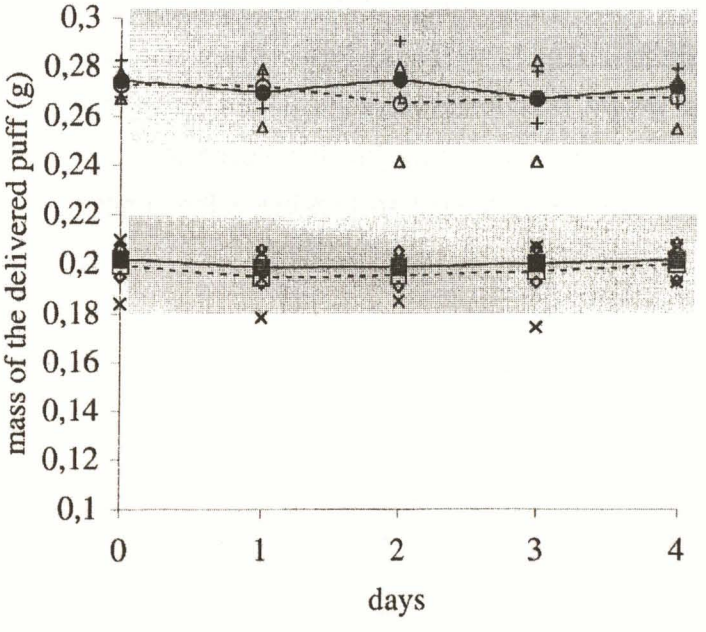

Fig.1 : Mass uniformity of 2 puffs at daily use.
Mean values :○--------- Prep.A
●----------Prep.B
□-------- Prep.D
■------- Prep.C
Extreme values :
△----------Prep.A
+----------Prep.B
x---------- Prep.D
◇---------- Prep.C
The gray area indicates ±10% deviation from the target weight.

Fig. 1 shows the results of the spray uniformity tests. While the deviations of the mean values from the target values (according to the draft guidelines of the FDA) remained below 3% for Prep.D and 1% for Prep.C; Prep. A and B showed deviations of up to 5%. These deviations, however, are still in accordance with the Ph.Eur. and the FDA draft guidelines.

3.2. Use every 3 days (2 days without actuation):

After priming on the first day, 2 puffs were delivered every 3rd day (without additional priming). The mass of each puff was determined.

As can be seen from Fig.2 for Prep.B and D the mean values of the single dose (corresponding to two puffs) deviated less than about 5% from the target weight. Prep.A showed some fluctuations with deviations of about 7% from the target weight. In the case of Preparation C mean values were more than 11% below the target weight.

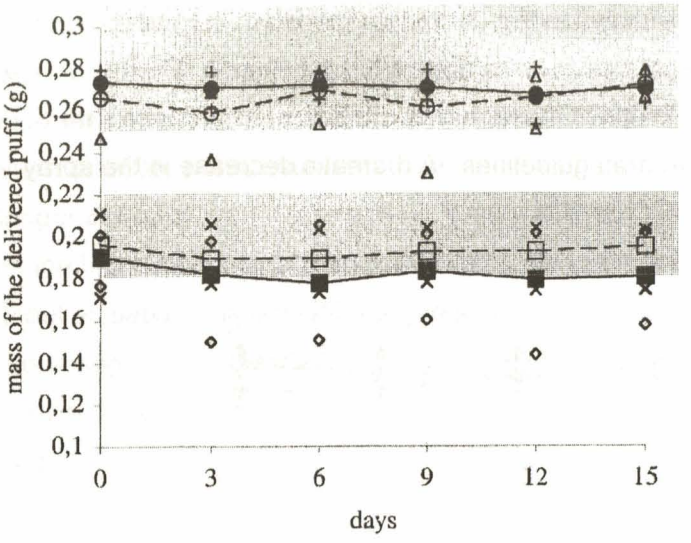

Fig.2 : Mass uniformity of 2 puffs at 3 days interval use.
Mean values :○--------- Prep.A
●----------Prep.B
□-------- Prep.D
-■------- Prep.C
Extreme values :
△----------Prep.A
+----------Prep.B
x---------- Prep.D
◇---------- Prep.C
The gray area indicates ±10% deviation from the target weight.

3.3. Use every 7 days (6 days without actuation):

Following priming on the first day, 2 puffs were delivered at 7-day intervals (without additional priming), simulating weekly use of the product. Use after a 6-day interruption without the need of additional priming still corresponds to the manufacturers' instructions for all the products. Especially for Prep.A,B and D, priming is required only the first time the nasal spray is used; Prep. C requires repeated priming after 7 days of non-usage.

The results are shown in Fig. 3. The deviations of the mean values from the target values were up to 4.5% for Prep.D, 8% for Prep.A and 9% for Prep.B. These results are still in accordance with the Ph.Eur and FDA draft guidelines . A dramatic decrease in the spray

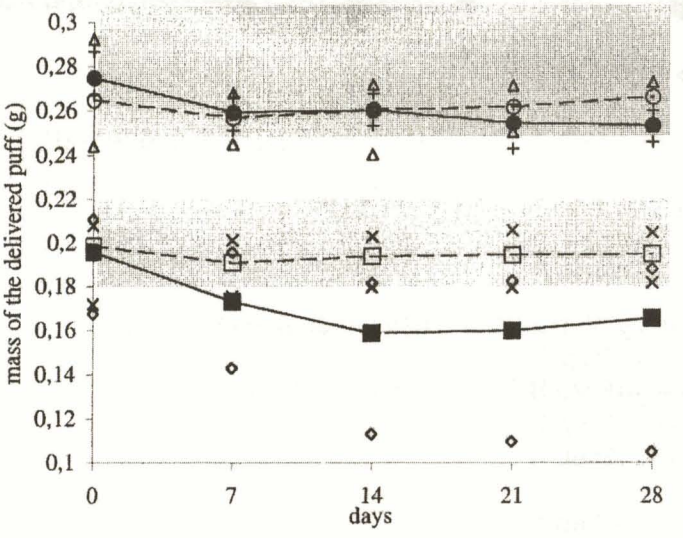

Fig.3 : Mass uniformity of 2 puffs at 7 days interval use.
Mean values :○--------- Prep.A
●----------Prep.B
□-------- Prep.D
■------- Prep.C
Extreme values :
△----------Prep.A
+----------Prep.B
x---------- Prep.D
◇---------- Prep.C
The gray area indicates ±10% deviation from the target weight.

mass was noticed for Prep.C. The mean values deviated by as much as 20%. Single values deviated by more than 40% from the target weight and up to 37% from the mean value. These values fail to meet both the Ph.Eur guidelines and FDA recommendations. To clarify this surprising result, the change of weight of the nasal sprays during storage without actuation was investigated. As Table 1 clearly shows, the nasal sprays lose weight during storage at room temperature. The

degree of weight loss was different for all tested preparations and was lowest for Prep.D. These data suggest that the weight loss is due to evaporation of the solvent. This in turn appears to influence the mass uniformity of the puffs, especially when the nasal spray is not used for a longer period of time. Mass puff uniformity of Prep.C, the nasal spray with the highest weight loss during storage, suffers most from storage without actuation and only for that product is a re-priming after 7 days of non-usage recommended [12]. As the results clearly show, the recommended period of re-priming does not, however, suffice to guarantee the puff mass uniformity.

Week	Prep.D	Prep.C	Prep.A	Prep.B
1	7.55	31.11	36.18	16.43
2	6.70	30.67	21.36	18.99
3	8.24	28.08	26.26	26.53
4	7.22	33.41	23.72	24.00
Average loss	**7.43**	**30.82**	**26.88**	**21.49**

Table 1: Average loss in weight with weekly activation (weight in mg)

3.4. Investigation of the application devices

We were very much interested in finding out why the dose accuracy of some preparations is strongly effected by the storing period, whereas this was not the case with Prep D to the same extent. To this end, the application devices of all products were taken apart and studied.

Single doses of all the nasal sprays under consideration here are delivered by a pump system connected to a nasal applicator that also atomizes the liquid.

The pump systems are all similar, with a piston pump with a dosing valve. Scrutiny of the pump systems did not explain why the delivered mass of some of the nasal sprays declined after storage.

In contrast to the pumps, the applicators of the various nasal sprays have one obvious difference, which could be decisive for the maintenance of the delivered mass. The applicator in Prep.D contains an elastic insert which shuts the hollow core of the application system. This could hinder the decrease by evaporation of the delivered mass of drug solution and permit longer storage periods without actuation. The lack of this kind of seal might explain the higher weight loss of the other nasal sprays compared to Prep.D. The fact that the values of the second puffs were generally somewhat better than those of the first puffs can be explained by the action of the first puff as a short priming. These results indicate that nasal sprays, especially Prep.C, should be primed repeatedly when they are not used daily. Prep.B uses a special application system, which allows a preservative-free application of nasal solutions [6,7]. However, as Table 1 shows, there is also some loss of weight with this system during storage; this may be due to evaporation of liquid residues in the upper part of the applicator.

3.5. Influence of the degree of filling

The FDA draft guidelines propose testing the influence of the degree of filling on mass uniformity. To this end, 5 full and 5 half-full spray flasks of each product were investigated. The degree of filling was never found to have any significant influence on the uniformity of dose delivery.

3.6. Influence of the mode of storage

Ten flasks each were stored upright, horizontal and upside down. As the supply tube in Prep.C is bent at the bottom, 5 flasks each were stored in the horizontal position with the tube orientated upwards or downwards. It turned out that the results are only marginally affected

by the mode of storage. The same trends were observed for all preparations as under upright storage. With Prep.B, the decrease in spray volume with weekly use was slightly lower in the horizontal position. Evaporation might be reduced with horizontal storage. Surprisingly, the values were slightly higher for flasks whose supply tubes were oriented upward.

3.7. Influence of storage with and without closing caps

Five flasks each were stored with and without closing caps. No significant differences between storing with and without caps were observed for any of the products.

3.8. Accordance with the guidelines of the European Pharmacopeia and the FDA draft guidelines

According to the guidelines of the Ph.Eur., not more than 2 values may deviate more than 25% and none more than 35% from the mean value. Recent draft guidelines from the FDA propose that the weight of the individual sprays should remain within ± 15%of the target weight and their mean weight within ±10% of the target weight.
In our opinion, these specifications should apply not only to the first usage, but throughout the application period.

Upon first usage, all preparations met both the Ph.Eur. guidelines and the FDA draft guidelines. In the case of usage at 7-day intervals, only Prep. C failed to meet these specifications (Tab.2).

Specification	Prep.D	Prep.C	Prep.A	Prep.B
First usage with priming				
Ph.Eur.	+	+	+	+
FDA	+	+	+	+
Usage at 7 days intervals (without repeated priming)				
Ph.Eur.	+	-	+	+
FDA	+	-	+	+

Table 2: Accordance with the guidelines of the European Pharmacopoeia and the draft guidelines of FDA

4. Conclusion

The dose accuracy of nasal sprays was tested for four products commercially available on the European market. The uniformity of mass was chosen as the parameter for dose accuracy. All the nasal sprays fulfilled the demands of the European Pharmacopoeia and the FDA draft guidelines for the first usage. When patient's usage was simulated, however, the dose accuracy changed depending on the intervals of non-usage and in the case of Prep.C failed to meet the specifications. These deviations seem to depend on the application systems but the results also demonstrate the importance of priming, which has already been stressed in literature. The recommended number of actuations prior to first usage differ; at least 4 actuations [Instructions for use of Prep.C], 5 actuations [12] or 10 actuations [13] are mentioned, or it is suggested that the spray should be actuated until the spray beam is uniform [Instructions for use of Prep.D]. Our results suggest that re-priming might be of similar importance when dose accuracy cannot be maintained over the period of the patient's use. In these cases the operating instructions should be adapted, and

the periods of non-usage for re-priming should be shortened. This is also confirmed by the observation that the second puff always showed better values. It can be assumed that the first puff acts as a kind of priming. It is especially important that recommendations not to re-prime, as given for a certain preparation, be viewed critically until the dose accuracy during patient's use is demonstrated.

As our results have shown, the deviations from the target weight in the case of interrupted use (simulated patient's usage) are close to the limits or exceed the limits recommended by the FDA in the case of one of the preparations investigated. These guidelines, however, are only a draft and it has yet to be determined whether these guidelines are realistic and practicable. This would require more comprehensive studies of a broad spectrum of preparations to prove the feasibility of these guidelines.

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