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Dosage uniformity problems which occur due to technological errors in extemporaneously prepared suppositories in hospitals and pharmacies

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Abstract The availability of suppositories in Hungary, especially in clinical pharmacy practice, is usually provided by extemporaneous preparations. Due to the known advantages of rectal drug administration, its benefits are frequently utilized in pediatrics. However, errors during the extemporaneous manufacturing process can lead to non-homogenous drug distribution within the dosage units. To determine the root cause of these errors and provide corrective actions, we studied suppository samples prepared with exactly known errors using both cerimetric titration and HPLC technique. Our results show that the most frequent technological error occurs when the pharmacist fails to use the correct displacement factor in the calculations which could lead to a 4.6% increase/decrease in the assay in individual dosage units. The second most important source of error can occur when the molding excess is calculated solely for the suppository base. This can further dilute the final suppository drug concentration causing the assay to be as low as 80%. As a conclusion we emphasize that the application of predetermined displacement factors in calculations for the formu-

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lation of suppositories is highly important, which enables the pharmacist to produce a final product containing exactly the determined dose of an active substance despite the different densities of the components.

1. Introduction

Drugs used for rectal administration are frequently supplied by independent pharmacies and especially clinical pharmacies. This route of administration is very important in pediatrics. Pharmaceuticals used for the treatment of fever, pain, spasms, asthmatic symptoms and vomiting can be administrated rectally (Abd-el-Maeboud et al., 1991; Dahl et al., 2000; Fumoleau et al., 1997; Kauss et al., 2012; Okabayashi et al., 2012; Richter et al., 2012; Sabchareon et al., 1998; Shiohira et al., 2009; Tinner et al., 2013). Approximately 80% of the suppositories used in Central Europe are produced extemporaneously using the molding technique. In clinical pharmacies quantities of 100–300 and in independent pharmacies 10–12 suppositories are generally molded as one batch. Suspension suppositories, in particular, are formulated with a solid fatty vehicle ("e.g." Witepsol 35) or a combination of this suppository base with surfactants (Rowe et al., 2003). The core of this technology is the dispersion of the finely powdered drug with the molten suppository base. After which, the suspension is molded under continuous stirring. Fatty suppository bases have very low viscosities, which decrease still further with an increase in temperature, causing rapid sedimentation of the suspended particles and leading to a non-homogeneous product. When the liquid mass is molded at around the solidification point, solidification occurs immediately as the mass enters the mold, making further additions of the base and drug impossible. In the calculation of the suppository base weight, the following formula must be applied (Eq. (1)):

$$T_m = E - \sum_{i=1}^{n} f_i \cdot s_i \qquad (1)$$

where T_m is the suppository base to be weighed, E is the calibration constant of the mold, f_i is the displacement factor of the ith component and s_i is the weight of the ith component. During the calculation of a correct formula, it is not sufficient to subtract the weight of the solid components from the final weight of the suppository to obtain the required amount of the suppository base. We must also know the value of E for the specific mold and specific suppository base, which can be determined through independent measurements. Ten suppositories are usually prepared with the mold, using the pure base, and after cooling they are weighed and the average suppository weight is calculated. This average value will be used as the calibration constant for the mold for any specific base. Since the density of the active ingredient (hereinafter referred to as "API") incorporated into the suppository base can differ from that of the base itself, the displacement factor (f) is required to compensate for the difference in densities. The value of f, which shows how much base will be displaced by a unit weight of an API, can be calculated from the following equation (Eq. (2)):

$$f = \frac{100 \cdot (E - G)}{G \cdot x} + 1 \qquad (2)$$

where E is the weight of the blank suppository containing only base, G is the weight of the suppository containing an API in a known concentration, and x is the API content of the suppository in weight percentage.

If the pharmacist fails to carry out the steps in strict accordance with these rules, significant deviations will be observed in the results for the homogeneity of the batch and in the total drug content of the batch. In this research we report on an investigation of samples prepared in pharmacies, with a special emphasis on the homogeneity and the total API content of the batches. The circumstances of the preparation of the suppositories were known in all cases and are presented. In pharmacies, the f-values of the most frequent APIs in the most common bases are not generally available. According to a good manufacturing practice pharmacists apply the participle of overage during the calculation of the batch composition, but an incorrect calculation for the amount of vehicle required and other technological errors may lead to serious deviations in the final dosage for the individual suppositories (Allen, 2007; Miseta and Soós-Csányi, 2011; Rácz and Selmeczi, 1991).

2. Materials and methods

2.1. Materials

HPLC grade solvents and triple-distilled water were used during the chromatographic measurements. For the preparation of the HPLC mobile phases and sample preparation solvents, the following materials were used: 4-dimethylaminoantipyrine (Sigma–Aldrich, St. Louis, MO, USA), methanol (Chromasolv for HPLC, Sigma–Aldrich, St. Louis, MO, USA), sodium acetate (Reanal, Budapest, Hungary), acetic acid 96% (Molar Chemicals, Budapest, Hungary), sodium hydroxide (Reanal, Budapest, Hungary) and sodium chloride (VWR, Prolabo, Leuven, Belgium). Volumetric solutions for the cerimetric titrations were prepared with the following materials: cerium(IV) sulfate tetrahydrate (Panreac, Barcelona, Spain), sulfuric acid 96% (Farmitalia Carlo Erba, Milano, Italy) and ferroin-solution, 1/40 M (Reanal, Budapest, Hungary).

Commercially-made suppositories were used during the comparisons for the analytical methods. The reference product was *Suppositorium antipyreticum pro parvulo* FoNo VII. Naturland (Naturland Magyarország Kft., Budapest, Hungary), which contained 150 mg of aminophenazone per suppository in a solid fatty suppository base. One box contains six suppositories (Paál, 2003).

Samples were also prepared in regular pharmacies by the molding technique, according to the following procedure. Ten suppositories were obtained from 15 independent pharmacies with a labeled claim of 100 mg of aminophenazone in each suppository. The choice of vehicle for the suppository was left to the responsibility of the pharmacist at the site. Practically all of the samples were prepared with a solid fatty base. In each

case, predetermined technological errors (known to us) were made during the sample preparation.

2.2. Test methods

2.2.1. Cerimetric titration

The basis of the drug content determination is the use of a cerimetric redox titration method (Rózsa, 1953), During this assay the nascent oxygen evolved from the reaction of Ce(IV) with water oxidizes aminophenazone. The end-point of the titration is observed by the change in color of ferroin added as the indicator. During the sample preparation, whether from the commercially prepared suppository or the extemporaneously prepared ones, one suppository is melted over a 40 °C water bath and 3 replicate samples of 0.20–0.30 g are weighed from the molten mass into titration flasks. A 10.0 ml portion of 15% sulfuric acid is added to each sample and the mixture is heated to 40 °C to extract the API from the suppository base. The mixture is then cooled to room temperature. A 15 ml portion of distilled water is added, and after mixing, one drop of ferroin as indicator is added. This is then titrated with 0.05 M cerium(IV) sulfate volumetric solution until the color of the solution changes from orange to green and remains green for at least 1 min (Paulenova et al., 2002; Townshend, 2005).

2.2.2. Assay of aminophenazone by HPLC

HPLC measurements were carried out on a Shimadzu Prominence UHPLC system (Shimadzu Corp., Kyoto, Japan) equipped with an LC-20AD pump, a four port solenoid mixing valve, a CTO-20A column oven, a DGU-20ASR degasser, and an SPD-M20A UV/VIS PDA detector with a 10 mm optical path length flow cell. Sample injection was performed with a Rheodyne six port manual injector valve fitted with a 20 μl sample loop. Separation was achieved on a Hypersil ODS (C18) 150 × 4.6 mm, 5 μm column (Thermo Scientific, Keystone, UK). Data acquisition and peak integration were carried out with the LC Solution (Shimadzu Corp., Kyoto, Japan) chromatographic data acquisition and processing software.

The mobile phase was methanol:sodium acetate (pH 5.5; 0.05 M) (60:40, v/v). The pH of the sodium acetate buffer solution was adjusted to the desired value with acetic acid. The flow rate of the reversed-phase isocratic eluent was 1.5 ml/min and the run time was 5 min. The chromatographic column was thermostated at 30 °C throughout the separation. The chromatograms were recorded at 243 nm. The retention time

of aminophenazone was found to be 1.8 min. The applied method was validated. The samples were prepared with a technique elaborated previously by our research group. The exactly weighed suppository was melted over a 40 °C water bath in a 50:50 (v/v) methanol:water mixture. After identification of the suppository base on the basis of its physicochemical properties, the base was separated from the solution if necessary. The sample solution was then filtered through a 0.45 μm pore size nylon membrane filter. The solution was injected onto the HPLC through the Rheodyne injector valve.

3. Results and discussion

3.1. Comparison of the cerimetric titration and the HPLC method

We compared the two analytical methods by measuring two sets of six commercially-made suppositories from the same batch having the exact lot number. The individual assays for the suppositories were carried out by either the volumetric or the chromatographic technique. All of the final results (the averages of the three replicates for each of the six suppositories in the case of the titrimetric method, and the individual suppository assay value in the case of the chromatographic determination) fell within the range 95–105%, which conforms to the strictest requirements of the European Pharmacopoeia. The individual content data are presented in Table 1.

It should be noted that the volumetric results exhibit a larger standard deviation than that of the chromatographic results, but the preparation of samples for titration (one total of 18 replicate samples prepared from the molten suppository) involves a higher level of uncertainty, and this can therefore be considered acceptable. A comparison of the two methods reveals that both can be used for the analysis of suppositories containing aminophenazone.

3.2. Dosage uniformity study of extemporaneously prepared suppositories

We additionally studied pediatric suppositories with the composition described in Section 2.1. All samples were from different Hungarian independent pharmacies, and each sample consisted of 10 individual suppositories. The manufacturing technology for each of the samples was known to us with the pharmacists committing intentional technological errors during the preparation of the suppositories. The extemporane-

Table 1 Assay results for factory-produced suppository samples, measured by cerimetric titration or the HPLC method.

| Sample | Cerimetric titration | | | | Sample | HPLC |
	Replicates%			Average cont.%		Content%
S1	101.6	107.2	103.5	104.1	S7	103.9
S2	98.9	99.3	97.5	98.5	S8	104.9
S3	106.3	100.7	100.3	102.4	S9	102.8
S4	96.1	100.7	97.1	98.0	S10	102.3
S5	100.9	110.4	102.1	104.5	S11	103.9
S6	103.6	104.0	104.7	104.1	S12	104.6
Average				101.9		103.7
SD				2.93		1.01
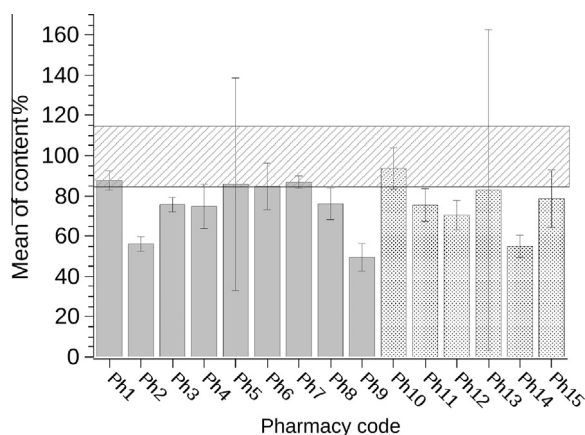
Figure 1 Mean API content for the samples, with the standard deviations. An API content in the interval 85–115% is satisfactory. Samples Ph1–Ph9: HPLC results; Samples Ph10–Ph15: cerimetric titration results.

ously prepared samples (containing 10 suppositories) from pharmacies Ph1–Ph9 were measured with the HPLC technique described in Section 2.2.2. The extemporaneously prepared samples (containing 10 suppositories) from pharmacies Ph10–Ph15 were tested for dosage uniformity with the titrimetric method presented in Section 2.2.1. All of the findings (see Fig. 1) were compared on the basis of the results given in Section 3.1. It can be stated that two samples conformed to the specifications of Ph. Eur. 7.8, "i.e." the individual assay values fell within the range 85–115% at level 1, and one further sample would probably have conformed to the level 2 specification of 75–125% (Ph Eur 7.8). For the remaining samples, generally either lower individual assay results or (in 2 samples) significant non-homogeneity was found, which are justified by standard deviation values visible in Table 2.

3.3. Effects of f-value on the assay results

The possible consequences of the most common errors can be illustrated utilizing a theoretical example. If the pharmacist produced suppositories on the basis of the following parameters: $E = 1.7$ g; $f = 0.78$ and $s = 0.1$ g then, according to Eq. (1), $T_m = 15.22$ g for the 10 suppositories. If f-value is not applied, but only the weight of the API is subtracted from the value of E, then we have $T_m = 16.0$, which will result in an assay which is 4.6% lower than the required value. If this error is superimposed with the one when the calculated molding excess is taken solely from the suppository base (taking the required base for 12 dosage units instead of 10) then the concentration of one suppository is diluted even further, to 80.3% of the intended theoretical value.

3.4. Effects of stirring on the homogeneity and total assay of the samples

The suppository mass can be well homogenized by choosing an appropriate rate of manual stirring or machine-based mixing. Stirring during the molding process can help avoid the sedimentation of the API in the container. Too slow a stirring rate is not effective, however too fast a stirring rate may also lead to errors: since air bubbles may be formed in the mass, which will decrease the weight of the suppositories. Foam can be formed from the surfactant-containing bases, or shearing forces may appear, which decrease the viscosity of the suppository mass by rheodestruction, causing the rapid sedimentation of the API. The ideal machine stirring speed for fat-based suppositories is recommended as 150 rpm.

The results demonstrate that the stirring technique for extemporaneously prepared pharmacist suppositories before and during the molding procedure was appropriate, with the exception of a small number of serious cases. Those samples can be considered homogeneous which gave SD ⩽ 10 with respect to the individual suppository assays. A larger deviation can originate from the lack of stirring during molding, as may be seen for samples 5, 7 and 16. Extremely large deviations result when both thorough homogenization and stirring during the molding process are omitted, which maybe observed for samples 6 and 13. If (f) is not applied and the suppository base is used in an excess amount, the assays for the samples will fall below the lower limit of acceptance. If the molten mass is not stirred during molding process, the decrease in the API content becomes more serious since the suspended material is sedimented, and the mold will contain an API – which is depleted from the mixture.

4. Conclusions

The results for pediatric suppositories produced extemporaneously under predefined conditions in Hungarian independent pharmacies revealed that serious errors may arise if the rules used in the pharmaceutical technology for preparing such suppositories are not strictly adhered to, and the assay results on the individual dosage units may be affected. On the other hand, suppositories prepared with strict adherence to the correct manufacturing practices conform to the specifications described in Ph. Eur. 7.8. Since extemporaneously prepared suppository preparations are frequently compounded and supplied in central European clinical pharmaceutical practice because of the low costs involved, we would encourage the use of and the inclusion of the f-values for the most common APIs and for the most common suppository bases into the European or national pharmacopoeias. To our knowledge the paucity of this information prohibits the preparation of the "right" dose for the "right" patient and may even do harm. Calibration of

Table 2 Average assay results on the samples and standard deviations in the homogeneity study. Ph in the sample raw stands for pharmacy.

Sample	Ph1	Ph2	Ph3	Ph4	Ph5	Ph6	Ph7	Ph8	Ph9	Ph10	Ph11	Ph12	Ph13	Ph14	Ph15
Average%	87.7	56.1	75.6	74.8	85.8	84.7	86.9	76.2	49.5	93.7	75.5	70.4	82.9	54.9	78.6
SD	4.8	3.6	3.6	11.1	52.8	11.6	3.0	7.8	7.0	10.2	8.0	7.4	79.7	5.5	14.3

the mold and the determination of the *f*-value for these basic common suppository bases can be accomplished very simply.

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