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ORIGINAL ARTICLE

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.

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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)):

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

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)):

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

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

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