SHORT CHARACTERIZATION OF RECTAL SUPPOSITORIES CONTAINING DROTAVERINE HYDROCHLORIDE

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SHORT CHARACTERIZATION OF RECTAL SUPPOSITORIES CONTAINING DROTAVERINE HYDROCHLORIDE (Abstract): In Romania, drotaverine formulations are only available orally or by injection. Improvements in bioavailability led to the development of rectal suppositories using three lipophilic bases. This study aimed to develop and analyze 40 mg drotaverine suppositories using semi-synthetic glycerides. The goal was to enable atraumatic administration to patients with gastrointestinal obstructions that are unsuitable for oral treatment. **Materials and methods:** Suppositories were cast in adult moulds using S1 (Witepsol), S2 (Lipex), and S3 (Suppocire). For the developed suppositories, the average mass and melting time (through two different methods) were measured. Drotaverine hydrochloride content was quantified using UV-Vis spectrophotometry, which had previously been checked for linearity and selectivity. **Results:** The unloaded suppositories were white, while those with drotaverine hydrochloride were pale yellow; all six were crack-free and weighed 1.9523-1.9884 g. Content ranged from 40.62 mg (S2) to 42.89 mg (S3). Melting time showed the same behavior for both methods, yielding values < 15 minutes in accordance with the pharmacopoeial stipulations. **Conclusions:** Lipophilic drotaverine suppositories were successfully produced, with physical parameters within acceptable limits. Melting time was under 30 min, meeting the recommendations of the Romanian Pharmacopeia, 10th edition. Drotaverine content was within ±7.5% of the limit. **Keywords:** DROTAVERINE, SUPPOSITORIES, MELTING POINT, UV-VIS SPECTROPHOTOMETRY.

INTRODUCTION

The contemporary therapeutic strategy for managing spastic pain syndromes requires continual optimization of pharmaceutical formulations to enhance bioavailability, rapid onset of action, and patient adherence. In this regard, the development and assessment of rectal suppositories containing drotaverine hydrochloride present a practical alternative to traditional routes of administration, such as oral and parenteral routes. Suppositories are solid pharmaceutical forms that comprise drugs at room temperature, formulated in unit doses for rectal, vaginal, or urethral insertion, aimed at eliciting local or systemic effects (1). They are designed to melt or dissolve at body temperature, thereby releasing the

active pharmacological agent (2). The rectal route offers distinct physiological advantages, including partial circumvention of the hepatic first-pass metabolism and protection of the gastric mucosa from chemical irritation, as well as the option for use in conditions where oral administration is unsuitable, such as certain pathological states, or when the patient exhibits intolerance to specific preparations (e.g., idiosyncrasy, nausea, vomiting) (3, 4). The therapeutic efficacy of this pharmaceutical form relies on the interplay between the physicochemical properties of the active substance and the technological characteristics of the excipients employed as carriers. These factors critically influence the drug's release kinetics and absorption within the rectal mucosa (4, 5).

It has been established that medicinal substances from different pharmacological groups (analgesics, sedatives, antispasmodics, antirheumatics, vasodilators) are well absorbed when incorporated into a suppository matrix (6, 7).

Drotaverine hydrochloride, a chemical derivative of isoquinoline (1-(4-dietoxibenzyl)-6,7-dietoxi-3,4-dihydroisoquinoline hydrochloride), is a synthetic musculotropic anti-spasmodic extensively utilized to alleviate smooth muscle spasms associated with biliary, gastrointestinal, and urological disorders (8, 9). Drotaverine is swiftly absorbed and undergoes hepatic biotransformation to produce an active metabolite, desethyl-drotaverine. Its diffusion across the placenta is limited due to its prolonged activity following oral administration (10, 11). The antispasmodic efficacy of drotaverine exceeds that of papaverine, another naturally occurring musculotropic antispasmodic, by a factor of 2 to 5 (10, 12, 13). Notably, drotaverine's advantage lies in its lack of anticholinergic activity. Its mechanism of action involves the selective inhibition of phosphodiesterase type IV (PDE4), which elevates cyclic adenosine monophosphate (cAMP) levels and subsequently inactivates myosin light chain kinase, thereby inducing smooth muscle relaxation. Additionally, drotaverine allosterically inhibits voltage-dependent L-type calcium channels, specifically the α–1C subunit (10).

From a physicochemical perspective, the substance is a yellow or greenish-yellow crystalline powder, soluble in water and acidic in aqueous solution (9). This acidity requires rigorous selection of the polymer or lipid matrix to prevent degradation or formulation incompatibilities during thermal production.

Excipients used as bases for suppositories play a decisive role not only as mechanical support but also as modulators of the active substance's release kinetics (14). In the formulation of rectal preparations, two major categories of excipients are usually used: lipophilic bases (synthetic solid fats such as Witepsol series or cocoa butter) and hydrophilic bases (PEG 400, 1000, 4000, and 6000) (15). Witepsol or Imhausen meal is a blend of triglycerides derived from saturated natural fatty acids (C18-C16) containing varying amounts of mono- and diglycerides. This category includes several Witepsol W types known for their excellent malleability. The excipient is used in medicinal formulations that require a lower melting point. Witepsol S acts locally and is used in anti-hemorrhoidal suppositories, while Witepsol ES is suitable for hot climates (16). Currently, Witepsol H is more commonly used than other types because it contains a certain amount of aluminum stearate, which

provides high viscosity. Its properties include an arc density of 0.970-0.990 g/cm³, a melting point between 33.5 and 35.5°C, a solidification point of 32.5-33.5°C, an acidity index below 0.2, a saponification value of 230-240, an iodine index below 10, and a water index of 100 (17). It is well-suited for developing suppositories through pressing, melting, and molding. The product is physiologically well-tolerated, pharmacologically inert, non-irritating, and effectively delivers medicinal substances, thereby enhancing therapeutic effects shortly after administration (18).

TABLE I.
Advantages of the rectal administration compared to the oral route and the parenteral pathway

Comparison Criterion	Rectal suppositories	The Oral Route	Parenteral pathway
Hepatic First Pass Effect	**Partially avoided (50-70%)**; The inferior and middle hemorrhoidal veins drain directly into the inferior vena cava.	**It undergoes a complete first hepatic passage**; Partially reducing the amount of intact drotaverine that reaches the systemic circulation.	**Avoided completely**; The substance enters the systemic circulation directly.
Gastrointestinal tolerability	**Excellent**; Avoid direct contact with the gastric mucosa to eliminate the risk of irritation, nausea, or vomiting.	**Moderate**; may cause epigastric discomfort or irritation in patients with gastric sensitivity or ulcers.	**Excellent**; It totally bypasses the gastrointestinal tract.
Compliance in critical states	**Elevated**; Ideal for patients with vomiting, severe nausea, acute spasms, or pediatric/geriatric patients.	**Null or low** in case of dysphagia, intestinal obstructions, pronounced nausea, or unconsciousness.	**Low** due to fear of needles (anxiety) and local physical discomfort associated with the injection.
Level of invasiveness and pain	**Non-invasive**; completely painless; requires only minimal training for proper administration.	**Non-invasive**; completely painless but conditioned by the functional swallowing reflex.	**Invasive and painful**, they are at risk of bruising, local infections, or nerve damage at the injection site.
Need for medical personnel	**It is not necessary**; allows easy self-administration by the patient at home.	**It is not necessary**; the pharmaceutical form is intended exclusively for self-administration.	**Mandatory**; requires qualified medical personnel and rigorous aseptic conditions (for i.v. approach).
Effect installation	**Fast to moderate**; superior to the oral tract due to the rich vascularization of the hemorrhoidal plexus.	**Slow**; it depends on the timing of gastric emptying, tablet dissolution, and intestinal transit.	**Ultra-fast** (in the case of i. v. administration) but exposes the patient to the risk of hypotension.

In the contemporary pharmaceutical market (9), drotaverine is available in oral and injectable solution forms (parenteral, including intravenous and intramuscular administration) (19). Table I delineates the strategic advantages of the suppository form relative to these two options.

On the Romanian pharmaceutical market, none of the preparations designated for rectal administration contain drotaverine (9). The absence of suppositories comprising active substances with musculotropic antispasmodic effects (drotaverine) served as the motivation for this study. Considering the physical and chemical properties of drotaverine, formulating a lipophilic base suspension suppository was considered a plausible approach. This study aimed to evaluate the influence of the suppository base type on the properties specific to this pharmaceutical formulation.

MATERIALS AND METHODS

Materials. To develop the suppositories, the following were used:

- bases for suppositories: Suppocire NAI 25 (Gattefosse SAS, Saint-Priest, France), Witepsol W 35 (Condea Chemie GmbH, Marl, Germany), Lipex (Vitamar Import Export, Bucharest, Romania), drotaverine (DROT);
- molds for adults.

Development process of unloaded suppositories and drotaverine hydrochloride suppositories

To determine the capacity of the molds, suppositories were prepared using only the selected fat-soluble bases: Lipex, Suppocire, and Witepsol, by the "melting and molding" method. To obtain 20 suppositories for each base, the formulations are presented in second table. The quantity of suppository base, 42.0000 g, was measured precisely using an analytical balance and then melted in a water bath within an enameled vessel. Subsequently, the mixture was molded to ensure a slight excess in each well. The following procedures involved cooling and solidifying the base at ambient temperature, opening the molds, removing any excess material as required, and carefully detaching the obtained suppositories.

TABLE II.

The amount of base and excess considered for the evaluation of the mold capacity

	Suppository base	Amount of base / 1 supp. (g)	Excess / 1 supp. (g)
S01	Witepsol W35	2	0.1
S02	Lipex	2	0.1
S03	Suppocire NAI 25	2	0.1

The suppository base was melted by heating it to 60°C, and the active ingredient was then added (by suspending it in the selected lipophilic excipient). The melted mixture to which DROT was added was poured into the mold once the temperature reached 40°C, and it was left to solidify until volume contraction occurred. The composition of the suppositories is shown in table III.

TABLE III.
The composition of the DROT suppositories

Code	Suppository base	Amount of base / 1 supp. (g)	Amount of active pharmaceutical ingredient (API) / 1 supp. (g)
S1	Witepsol	2	0.04
S2	Lipex	2	0.04
S3	Suppocire	2	0.04

Melting point assessment–method A

To evaluate this parameter, the Pharmatest PTZ Auto 1EZ device was utilized. For this determination, the official method described in the 10th edition of the Romanian Pharmacopoeia for quality control was used (2). The results were obtained on six suppositories, followed by the calculation of the average melting point ± SD. The medium used to assess this parameter was ultrapure water thermostated at 37 ± 1°C.

Melting behavior assessment–method B

Three suppositories, one for each of the three bases (S01-S03), were examined individually using a standardized procedure. Initially, 50 mL of thermostated water at 37°C was introduced into a 100 mL Berzelius beaker. Subsequently, the test sample was placed in the beaker, and the time required for the suppository to melt was observed and recorded, with a maximum permissible duration of 30 minutes. The beaker was gently rotated every five minutes to ensure uniform exposure. Upon complete melting of the suppository (and in the absence of pressure-resistant cores when using a glass rod), the exact melting time was recorded for analysis. Conclusions regarding the suppository's compliance were then drawn based on these observations. The results were systematically documented in tabular form.

Evaluation of the active ingredient content using a UV-Vis spectrophotometric method

0.1003 g of drotaverine hydrochloride was weighed on the analytical balance. The powder was dissolved in 96° ethanol (% V/V) and diluted with the same solvent. Thus, a stock solution with a concentration of 0.1% (% m/m) was obtained.

The stock solution was diluted to obtain the following dilutions: 0.001%, 0.002%, 0.0025%, 0.005%, and 0.010%, which were analyzed spectrophotometrically using a Shimadzu UV-Vis spectrophotometer (Shimadzu, Japan). The specific wavelength for this active ingredient is 364.2 nm. Prior to each measurement, the cuvettes were rinsed with 96° ethyl alcohol to ensure accuracy.

The suppository is placed in a 50 mL Berzelius beaker and then covered with approximately 20 mL of 96% ethyl alcohol (%V/V). The beaker is then heated in a water bath maintained at 37°C until the suppository is completely melted. After melting, the mixture is gently homogenized with a glass rod and then filtered into a clean beaker. It is then transferred to a 50 mL volumetric flask and diluted to the mark with ethyl alcohol, then filtered again. The solution is aspirated into a syringe, filtered into an alternative flask, and a 1:20 dilution is prepared. The flask is stirred thoroughly to ensure homogeneity and to prevent solidi-

fication. Ethanol has been employed as a blank. The method underwent verification for linearity and selectivity.

Statistical analysis

A statistical analysis was performed using GraphPad Prism 11 software (Dotmatics, Boston, MA, USA). The ROUT test was used to identify one or more outliers with Q=1%, followed by a normality test (Shapiro-Wilk test) to assess whether the data distribution was/was not Gaussian. If the distribution was Gaussian, ANOVA-derived tests were used, assuming unequal SDs (Brown-Forsythe ANOVA, Welch one-way ANOVA, and Dunnett's T3 multiple comparisons test). If the residuals exhibited a non-Gaussian distribution, a non-parametric test was performed – Kruskal-Wallis and Dunn's multiple comparisons test. The results are presented as mean ± SD. The significance level was set to 0.05 (p).

RESULTS

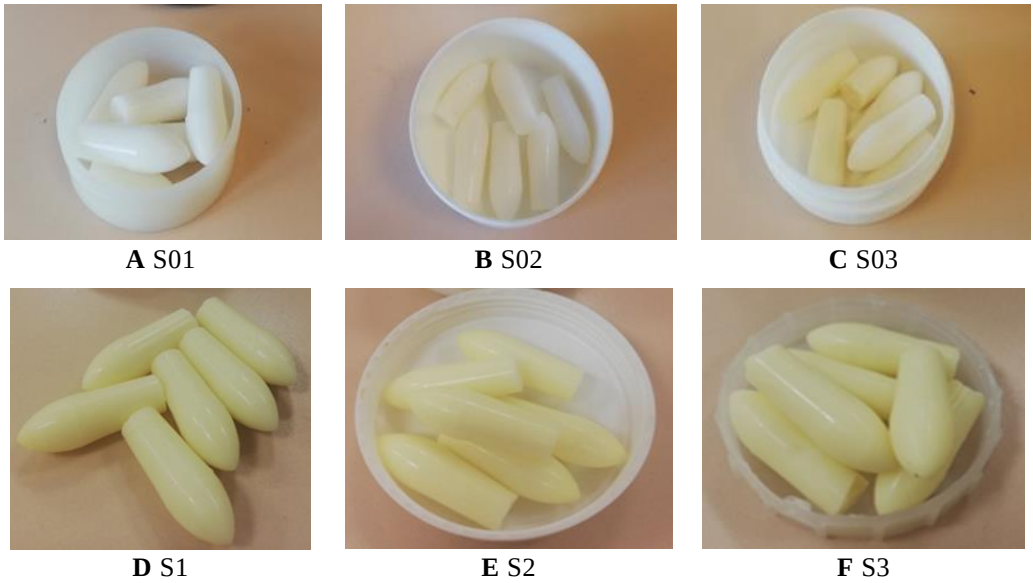
Visual aspect. Following this determination, suppositories were prepared using the selected excipients and characterized as glossy, homogeneous, and torpedo-shaped. As shown in first figure, the unloaded suppositories were white, whereas those containing the active ingredient were yellow, consistent with the active ingredient's properties. No differences were observed in the homogeneity of the active ingredient (S1-S3), which appeared homogeneous and yellow, and the suppositories showed no signs of cracking or rupture.

The capacity of molds and the average weight of DROT-suppositories assessment

Given the amount of active substance used to prepare a suppository (below 100 mg/suppository), the displacement factor is negligible when formulating these suppositories. The capacity of the molds is close to 2 g in both cases (unloaded suppositories and the ones containing active ingredient) (fig. 2).

For a better evaluation, the results from the suppositories that did not contain any active ingredients were included in second figure, since introducing suppositories without an active pharmaceutical ingredient allows the influence of the presence/absence of DROT to be underscored. The results can be compared as follows: the first three (S01-S03), in which the type of lipophilic excipient was considered, or S1-S3, in which DROT was incorporated. Furthermore, comparing S01 with S1 shows the influence of the active ingredient incorporated into the suppository base. The average mass values for the proposed suppositories ranged from 1.8983 (S03) to 1.9883 g (S1).

In all cases, incorporating the active ingredient into the suppository matrix yields a statistically significant difference. In conclusion, adding the active ingredient produces statistically significant differences in S01-S1 ($p<0.0001$), S02-S2 ($p=0.0439$), and S03-S3 ($p<0.0001$). For the unloaded suppositories, only one statistically significant difference was observed between S02 and S03 ($p = 0.0498$), which may be attributable to differences in the suppository bases. When evaluating the suppositories containing the selected active ingredient, no differences were observed, and in all cases the results were very close to the proposed limit of 2 g. In all cases, the SD was lower than the average value obtained.



A S01 **B** S02 **C** S03

D S1 **E** S2 **F** S3

Fig. 1. Visual aspect for the blank suppositories (white color: S01-S03) and for the DROT suppositories (yellow color: S1-S3).

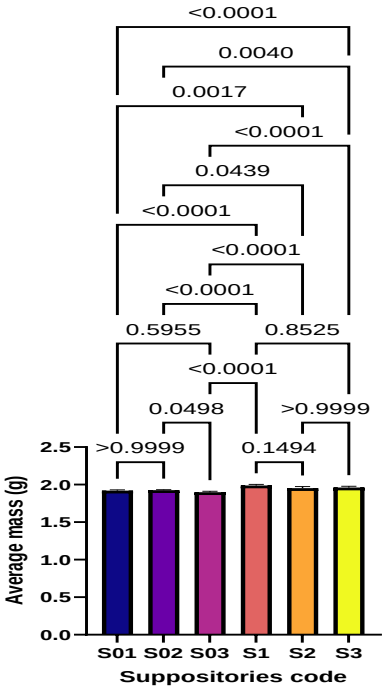


Fig. 2. The average mass assays and its comparison using Dunnett's T3 multiple comparison test ($p<0.05$)

Suppositories' melting behavior by means of two different evaluation methods

Since the developed suppositories were based on a lipophilic base, the maximum melting time was set to 30 minutes, as is usually recommended in pharmacopoeias (2, 5). In all cases and across both methods, the melting time was less than 30 minutes, indicating compliance with the pharmacopoeial requirements (2, 5). This test is important because it serves as a precursor to dissolution behavior and can indicate the release behavior of the active ingredient from the developed suppository. Since the active ingredient is suspended in the lipophilic base, it is expected to be released quickly considering the excipients used and the low melting times achieved.

Most comparisons of melting time showed no statistically significant differences ($p>0.05$); the only exception was S1-S2 ($p=0.0086$) (fig. 3), where method A from the Romanian Pharmacopoeia, 10th Edition, was utilized (2).

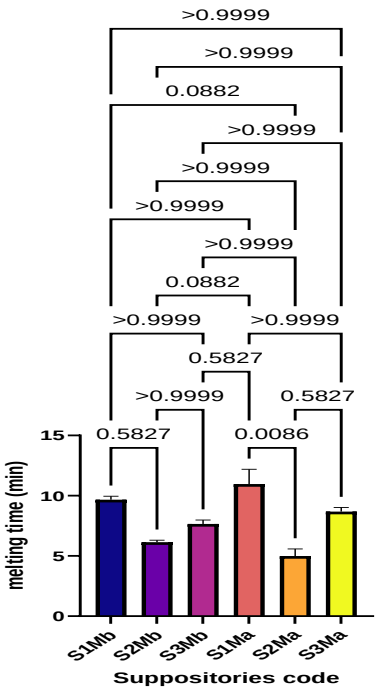


Fig. 3. The melting time of the three suppository formulations using two different pharmacopoeial methods (2)
(Ma = method A, Mb = method B stipulated in the Romanian Pharmacopeia)

The evaluation of the dimensional parameters (basal / maximum circumference and the length of the suppositories)

For the dimensional parameters, the basal and maximum circumferences (fig. 4) were assessed along with the length of the suppository. The length and other dimensions evaluated need to be correlated with the anatomical region of administration.

Romanian Pharmacopoeia stipulates a length of 2-3 cm (2).

The length of the torpedo-shaped suppositories was very close to the upper limit imposed by the pharmacopoeias (2, 5), with a small margin of error (3.1 cm - S3 and 3.16 cm - S2 (fig. 5.c). For this parameter and for the maximum circumference (fig. 5.b), no statistically significant differences were observed. In contrast, the basal circumference showed significant statistical differences between the S1-S2 (p=0.0011) and S2-S3 (p=0.031) (fig. 5.a). These differences can be explained by the use of different lipophilic excipients (Lipex, Witepsol, Suppocire).

The torpedo-shaped form was selected because it facilitates insertion, minimizes patient discomfort, and enhances retention after administration.

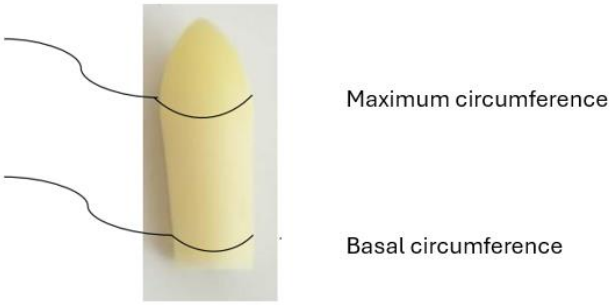
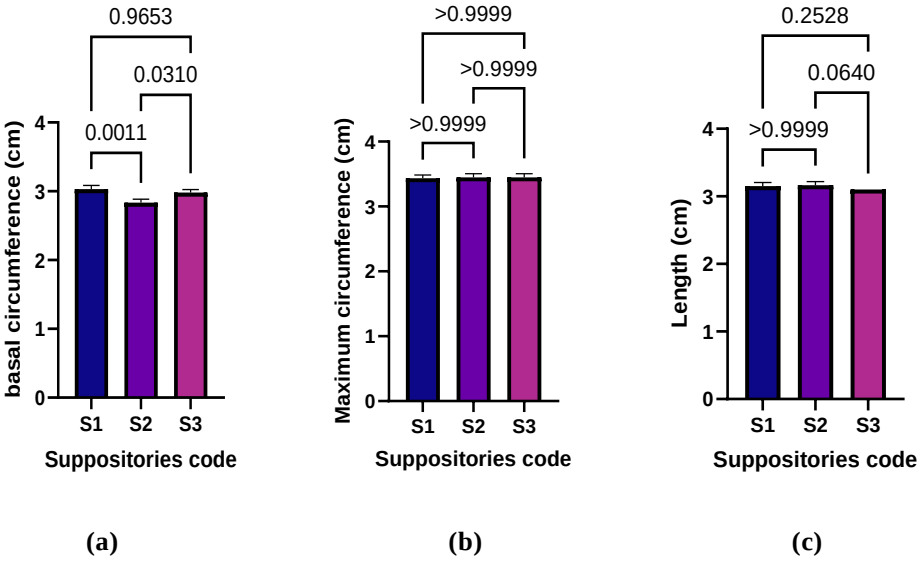


Fig. 4. Marking the maximum and basal circumference on the suppository-samples



(a) **(b)** **(c)**

Fig. 5. The evaluation of the dimensional parameters for the suppositories in which the active ingredient was incorporated (S1-S3), (a -basal circumference), (b-maximum circumference), (c-length)

The evaluation of the DROT content

To evaluate the DROT content, the spectrophotometric method was verified for linearity (R^2=0.9979) and selectivity. The wavelength used in the evaluation was 364.2 nm. Since the selected wavelength is not in the 200-250 nm range, a lower interference risk is observed. Also, since the formulations are simple and, in this study, few excipients were used, the risk of interference is reduced. Values close to the declared amount were obtained using this spectrophotometric method, ranging from 40.62 mg (S1) to 42.89 mg (S3). The standard deviation was within the range recommended by the Romanian Pharmacopoeia (±7.5%) (2). Only one statistically significant difference was noticed between the S1-S3 formulation (p=0.0211) (fig. 6).

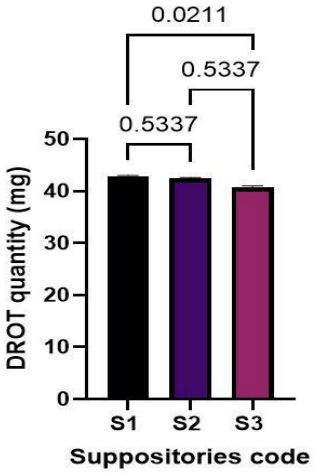


Fig. 6. The statistical evaluation for the S1-S3 DROT suppositories

CONCLUSIONS

In situations where oral medication isn't feasible, the rectal route is the preferred alternative, allowing for both systemic and local drug effects.

Suppositories containing drotaverine hydrochloride in lipophilic bases were developed, each containing 40 mg of active ingredient and meeting the specified physical parameters (no cracks or ruptures, homogeneous pale yellow or yellow color).

At present, there are still no suppositories containing musculotropic antispasmodics on the Romanian pharmaceutical market; the only pharmaceutical forms in which these substances are available are capsules, tablets, film-coated tablets, and injectable ampoules. The developed suppositories comply with the stipulations regarding melting time and declared content.

CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest, and they received no specific funding regarding this scientific research.

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