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Optimisation of the magistral semisolid formulations with furazidine used in urogenital infections

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Abstract

Background: Urinary tract infections are the most common urogenital diseases, with an increased incidence in men and older people. Urogenital infections are caused by Gram-negative bacteria, in which *Escherichia coli* predominates with a share of 80%. The evolution of microbial resistance to preparations used in curative-prophylactic institutions, induces the need of the reintroduction of nitrofurans, noteworthy for their wide spectrum of antibacterial activity.
Material and methods: For the study, suppositories with furazidine were prepared by hand rolling and by melting and molding methods. Quantitative analysis was performed spectrophotometrically on a UV-VIS Perkin Elmer Lambda 40 spectrophotometer. All solvents and reagents had the degree of purity "pure for analysis" and "chemically pure".
Results: Duble cast method was applied to identify the exact mass of hydrophobic (cocoa butter, suppocire) and hydrophylic (polyethylene glycol mixtures) excipients. All the formulated suppositories were subjected to quality tests and showed acceptable physical characteristics and uniformity of drug contents. The UV-VIS spectrophotometric method for quantitiative determination of furazidine was developed and validated. The validation results showed that the developed method is simple, fast, accurate and robust.
Conclusions: Suppositories with furazidine were prepared by classic technological methods. Preparation of the suppositories with furazidine on cocoa butter excipient is a suitable alternative for individual medicinal prescriptions. The UV-VIS spectrophotometric dosing method for furazidine in suppositories was developed and validated.
Key words: suppositories, furazidine, PEGs, *in-vitro* dissolution test.

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Introduction

Urinary tract infections are inflammatory diseases of infectious etiology, affecting 150 million people each year worldwide [1]. Currently in the Republic of Moldova there is an increased number of people suffering from infectious diseases of the urinary tract [2], which occur in any part of the urinary system: in kidneys, ureters, bladder and urethra, more frequently infections involve the lower urinary tract – the bladder and the urethra [3]. The risk factors for its developing include urinary obstruction, renal failure, renal transplantation, immunosuppression, diabetes, obesity, genetic susceptibility, prolonged catheterization, sexual activity and older age. According to physicians the most common diseases are pyelonephritis, urolithiasis, glomerulonephritis and cystitis [4].

Most urinary tract infections are caused by Gram-negative bacteria, namely *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterococcus faecalis, Proteus mirabilis*, by Gram-positive bacteria as: *Staphylococcus aureus, Staphylococcus saprophyticus* and by yeast infections – *Candida spp.* For complicated urinary tract infections the order of prevalence for causative agents is *Enterococcus spp., K. pneumoniae, Candida spp., S. aureus* and *P. aeruginosa* [3]. Depending on the severity of the disease, the treatment for each case is complex and is selected individually.

Antibiotics are the most commonly recommended therapeutics however, increasing rates of antibiotic resistance and high recurrence rates threaten to greatly enhance the burden that these common infections place on society. Today, nitrofuran antibiotics, despite the long-term use in medicine (since the 1950) is a class of synthetic substances that are revival and reintroduced as "old" antibacterials for treating multidrug-resistant pathogens [5, 6]. Nitrofurans have a wide spectrum of antimicrobial activity, which acts by disrupting the process of cellular respiration of bacteria, inhibition the tricarboxylic acid cycle and causing disruption of nucleic acid synthesis and, ultimately, death of bacterial cells [7].

Furazidine (*furazidinum*) – is a nitrofuran derivative with properties analog to nitrofurantoin, used in the treatment of urinary tract infections. It is an imidazolidine-2.4-dione, an organonitrogen heterocyclic and an organooxygen heterocyclic antibiotic, derived from a semicarbazide [8].

Furazidine is a flavourless yellow or orange-yellow fine crystalline powder, bitter in taste. Very slightly soluble in water and ethanol, hardly soluble in dimethylformamide, slightly soluble in acetone, practically insoluble in chloroform and benzene. It is one of the most popular nitrofuran and is widely used in a large number of researches due to uses in medicine, in industrial and extemporaneous dosage forms and in cosmetology as well [9].

On Moldovan pharmaceutical market furazidine is present in industrial commercial brand names of Furasol, Furagin and Furamag in dosage forms of powder, tablets and capsules [10]. The survey of the compounding dosage forms with furazidine during the years of 2019-2021 in the production department of *Vasile Procopisin* University Pharmaceutical Center (UPhC), shows that the largest share is presented by semisolid pharmaceutical forms mostly in suppositories, followed by solid pharmaceutical forms as powders. Specialists select the rectal route of administration of drugs because it avoids the first hepatic passage, does not allow irritation of the mucosa of the gastrointestinal tract, in case of intolerance to some active substances, demonstrates good absorption of drugs, rapid therapeutic action and mostly tolerable for pediatric and geriatric patients [11, 12]. Thus, based on the importance of the study, the semisolid medicinal forms – suppositories containing furazidine only or in combination with other active components, such as benzocaine, dimexide, methylene blue and other, are frequently prescribed in the treatment of urogenital diseases [13]. Pharmaceutical forms prepared in pharmacy, whether magistral prescriptions prepared by the pharmacist on the basis of a medical prescription, or compounded dosage forms presented as stock elaborations prepared by the pharmacist on the basis of an official data from the pharmacopoeia, offer an effective alternative to industrial medicinal preparations. *Vasile Procopisin* UPhC of *Nicolae Testemitanu* SUMPh, is nowadays the leading compounding pharmacy from the Republic of Moldova and plays an important role in practic trainings of new generations of pharmacists concerning production, quality control and delivery of medicines [14].

The research was performed in order to develop the optimal composition of suppositories with furazidine prepared in the production department of *Vasile Procopisin* UPhC on hydrophilic and hydrophobic excipients using two preparation methods (hand rolling and molding), as well as to develop and validate a spectrophotometric dosing method for furazidine in suppositories. The paper aimed to highlight the comparative analysis of technological methods of suppositories prepared on water-soluble and fat-soluble excipients, quality control and quantitative determination according to the Analytical Standardization Documentation (ASD).

Material and methods

Reagents and chemicals. Furazidine – molecular formula $C_{10}H_8N_4O_5$, produced by Chengdu HuaXia Chemical Reagent Co. Ltd, 99% purity. N,N-dimethylformamide and other reagents of analytical grade have been purchased from Sigma-Aldrich Chemie GmbH and Merck (Germany). All solvents had the degree of purity "pure for analysis" and "chemically pure".

Preparation of suppositories. The preparation of the suppositories was performed in the Production Department of *Vasile Procopisin* UPhC. The elaboration of the composition and preparation of the suppositories on water-soluble excipients: PEG 400: 4000 (1:9); PEG 400: 1500 (0.5:9.5); PEG 400: 1500: 4000 (1:3:6), as well as on fat-soluble excipients: cocoa butter and suppocire was performed in accordance with the requirements of the European Pharmacopoeia [15].

Double cast technique. The amount of substance for a suppository was mixed with a part of the molten excipient and poured into the suppository mold. Calculations were made for 10 suppositories. Then the excess molten excipient was poured into each cavity, cooled and the excipient left outside the level of the mold cavities was scraped and removed. At the beginning, 10 suppositories obtained from the clean excipient were weighed, then 10 suppositories containing the excipient and each substance were weighed and the average mass was calculated for each.

Evaluation of suppositories. Visual characterization – twenty suppositories from each batch were randomly selected, longitudinally cut and examined through naked eyes for the assessment of physical characters. *Weight variation* – twenty suppositories were weighed and average weight was calculated. Each suppository was weighed individually on electronic balance (WLC 6/12 precision electronic pharmaceutical balance). No suppositories should deviate from average weight more than 7.5%. *Melting point* – melting range test was performed with the whole suppository. Suppository from each formulation was placed in a test tube with phosphate buffer pH 7.2 maintained at constant temperature 37± 0.5°C. The time required for the whole suppository to melt or disperse in the media was noted. *Penetration test* – this test was used to determine the temperature at which the suppository becomes sufficiently soft for a penetrating rod to drop through its length. Test apparatus Erweka PM 30, phosphate buffer pH 7.2 maintained at 37±0.5°C was used for this testing, the time taken for the penetration of entire suppository was recorded.

Drug content – was determined spectrophotometrically on Perkin Elmer Lambda 40 UV/VIS spectrophotometer, using solvents and reagents with a degree of purity "pure for analysis" and "chemically pure", various laboratory and pharmaceutical utensils.

In-vitro dissolution study. The study was carried out using dissolution apparatus USP Type II (Paddle) with apparatus Erweka DT6, dissolution medium – phosphate buffer, pH 7.2, the speed of paddle – 100 rpm, temperature of medium – 37 ± 0.5°C.

Validation of the UV-spectrophotometric method. The analytical parameters of linearity, accuracy, selectivity and robustness were evaluated for validation of the spectrophotometric method.

Statistical analysis. All measurements were carried out in triplicate and expressed as mean (n=3) ± standard deviation (n=3) of three replicates. Construction of curves and

graphical presentation were performed by MS Office Excel 2016, as well as identifying the differences between values. A probability value of p≤0.05 was considered to be significant.

Results and discussion

Preparation of suppositories. The active substance furazidine – a compound from the group of nitrofurans, with antimicrobial effect against specific microorganisms [16, 17], was used for the study. Due to the unwanted reactions that furazidine can manifest in the oral administration of medicinal preparations, suppositories are an effective and advantageous alternative. Furazidine – IUPAC name 1-[3-(5-nitrofuran-2-yl)prop-2-enylideneamino]imidazolidine-2.4-dione, has a pKa value of 8.23, characteristic for a substance with weak acidic properties. Calculating the percentage of non-ionized form [11] at the rectal average pH of 7.9 we can conclude that furazidine is satisfactorily absorbed at a neutral to slight basic pH, reported in adults [12].

Furazidine suppositories were prepared on a hydrophobic excipient of cocoa butter, by the method of manual modeling [18]. Subsequently the composition was developed for suppositories obtained by the melting and casting method prepared on suppocire and with polyethylene glycols (PEGs): PEG 400: 4000 (1:9); PEG 400: 1500 (0.5:9.5); PEG 400: 1500: 4000 (1:3:6). In order to efficiently and qualitatively achieve the method of preparing suppositories by melting and casting in patterns, the calculation of the displacement factors for each component of each assortment of suppositories with application of Double Casting Method was performed [13]. It is necessary to know the capacity of the forms and the value of the displacement factor, respectively the amount of displaced excipient of 1.0 g of active substance, mechanically dispersed in the excipient, according to the formula (1):

$$f = \rho \text{ excipient} / \rho \text{ active substance}, \quad (1)$$

where: *f – displacement factor; ρ – density.*

To compensate for the losses, an excess will be taken, depending on the number of suppositories to be prepared. The results obtained were used to calculate the mass of the excipients. The stages of the technological process of preparation of suppositories by the *method of melting and casting in molds*, were applied to hydrophobic base suppocire and for water-soluble excipients based on PEGs. The method consisted of pouring the mixture of active substances and excipient, hot fluidized, in forms corresponding to the subsequent cooling of suppositories. The stages of the technological flow of preparation of suppositories by the method of melting and molding in patterns are shown in fig. 1.

The preparation process depends on the properties of the active substances, so the furazidine was incorporated by suspension, in micronized form with dimensions between 50-100 μm. In the method of melting and casting into molds, melting of the excipient and mixing with the active substances is done in containers heated with water vapor, at a controlled temperature to avoid overheating [19]. Great attention has been paid to the homogeneity of the mixture when molding to avoid the tendency of sedimentation, therefore

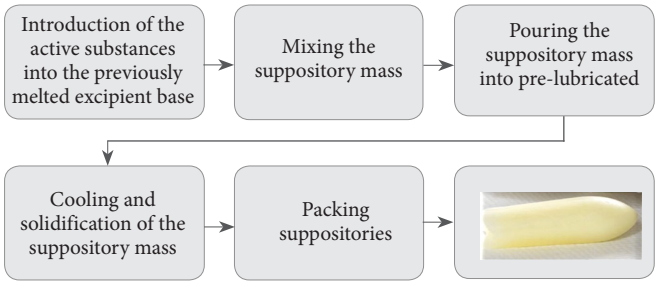

Fig. 1. Scheme of the technological flow of preparation of suppositories by the method of melting and molding in patterns

the mixture must be less fluid, stirring continuously during casting for a correct dosage. Drug has been suspended with the adjustable speed pistil, to ensure perfect homogenization in the mixture, with convenient viscosity, to maintain a homogeneous suspension of the incorporated active substance. Uniform flow in the molds was ensured.

The hand rolling method was applied for fat-soluble excipient cocoa butter. Suppositories were obtained by manual method, initially in the mortar furazidine was crushed in the presence of peach oil [20], the mixture was homogenized with cocoa butter until obtaining the appropriate consistency. Subsequently, the suppository mass was divided into appropriate doses, from which rectal suppositories were modeled, packaged in parchment paper, then in plastic boxes. The preparation was shaped, labeled according to the provisions of the ASD. The scheme of the technological process of preparation of suppositories by the method of hand rolling is presented in fig. 2.

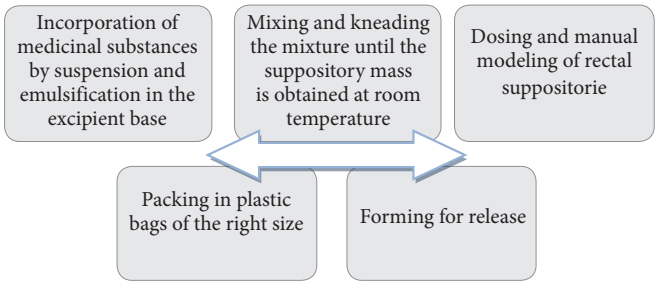

Fig. 2. The stages of the technological flow of obtaining suppositories by hand rolling method

Evaluation of suppositories. Twenty suppositories from each batch were randomly selected, longitudinally cut and examined through naked eyes for the assessment of physical characters like absence of fissuring, pitting, fat blooming, exudation and migration of active ingredients. Suppositories have a homogeneous appearance, yellowish in color, which retains its shape and consistency at room temperature.

Weight variation: twenty suppositories were weighed and average weight was calculated. Each suppository was weighed individually on WLC 6/12 electronic balance. No suppositories deviated from average weight by more than 5%, accordingly meeting the pharmacopoeia requirement [21].

Melting point: Macro melting range test was performed with the whole suppository. Suppository from each formulation was placed in a test tube with phosphate buffer pH

Table 1. Results of evaluation of furazidine suppositories for various parameters

Formulation	Weight* (average mass, gram)	Melting time** (minutes)	Penetration test** (minutes)	Drug content** (%)
Furazidine 0.1 g Cocoa butter q.s. ad 3.0 g	3.2±0.032	31.2±1.2°C	15.4±0.81	98.9% ±0.04
Furazidine 0.1 g Suppocire q.s. ad 3.0 g	3.0±0.032	36.8±0.12°C	17.25±0.73	97.14% ±0.83
Furazidine 0.1 g PEG 400: 4000 (1:9) q.s. ad 3.0 g	3.07±0.014	34.7±0.52°C	22.3±0.64	98.55%±0.112
Furazidine 0.1 g PEG 400:1500:4000 (1:3:6) q.s. ad 3.0 g	3.05±0.07	36.17±0.52°C	19.4±0.95	98.72±1.37
Furazidine 0.1 g PEG 400:1500 (0.5:9.5) q.s. ad 3.0 g	3.01±0.001	37.6±0.1°C	59.5±0.77	94.5±0.02

Note: *Average mass of 20 suppositories; **Average of 3 measurements; ± Standard Deviation.

7.2 maintained at constant temperature 37± 0.5°C. The time required by the whole suppository to melt or disperse in the media was noted. The melting time plays a crucial role in the release of active ingredient.

Penetration test: the study was carried out using apparatus Erweka PM 30, in medium of distilled water at temperature of 37±0.5°C. The average results are presented in table 1.

Quantitative determination of furazidine in suppositories was carried out by UV-VIS spectrophotometric method. Several solvents were selected for the elaboration of the technique for the extraction of medicinal substances from suppositories containing furazidine: purified water, dimethylformamide solution, acetate buffer and 96% ethyl alcohol. Repeated extraction with dimethylformamide met all the requirements for qualitative and quantitative analysis of furazidine, the extraction yield being 94%.

Extraction technique – 1 suppository (mass 3.0 g) was brought into a 100 ml beaker, 60 ml of dimethiformamide was added and mixed vigorously for 20 minutes. 30 ml of 96% ethyl alcohol was added, stirred, added 96% alcohol to the quota and mixed. The obtained mixture was filtered through filter paper; the first portions were discarded. 0.25 ml of the filtrate was placed in a volumetric flask and mixed with acetate buffer to the level.

The UV-VIS spectra of the 5 μg/ml furazidine samples recorded in the 230-450 nm region showed a maximum absorption for the standard furazidine solution at 292 nm, for the suppositories prepared on cocoa butter and suppocire at 286.11 nm, and for the suppositories with furazidine prepared on PEGs, the absorption spectrum at the wavelength of 286.04 nm was recorded, using the Perkin Elmer Lambda 40 UV/VIS spectrophotometer (fig. 3).

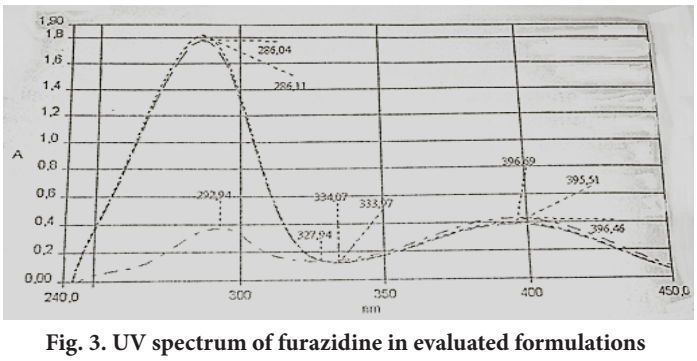

Fig. 3. UV spectrum of furazidine in evaluated formulations

The furazidine content was calculated according to the formula (2):

$$X=\frac{A_1 * 100 * 100 * a_o * 1 * C}{A_o * 1 * 1 * 100 * 100 * 100}$$

$$X=\frac{A_1 * 100 * 100 * a_o * 1 * C}{A_o * 1 * 1 * 100 * 100 * 100}, \quad (2)$$

where:

X - Furazidine content in the sample, g;

A_1 - Wavelength of the solution to be analyzed;

A_O - Wavelength of the standard furazidine solution;

a_O - mass of furazidine standard, g;

C – Amount of active substance, %.

The results for all assortments of suppositories meet the pharmacopeial requirements and are presented in table 1. All the suppositories prepared with furazidine showed acceptable physical characteristics and uniformity of drug contents.

The in-vitro drug release profile from different suppositories formulation is shown in fig. 4. The dissolution study showed that the suppositories melted in the dissolution medium maintained at 37±5^{0}C. All five formulations showed more than 50% drug release within 60 minutes.

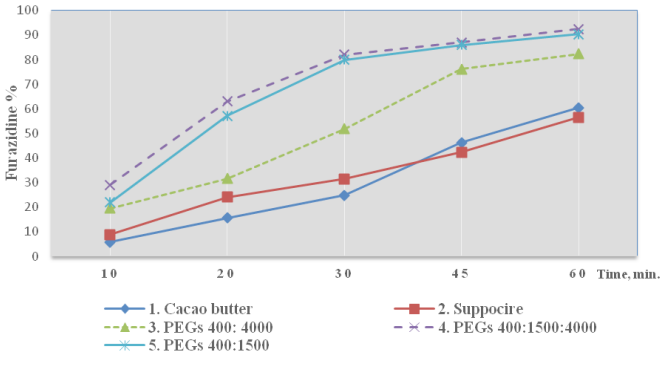

Fig. 4. Dissolution profiles of suppositories with furazidine using different types of excipients

In cocoa butter suppositories, the drug release was slightly slower due to high lipophilicity of the base and non-

Table 2. Results of validation of UV-VIS spectrophotometric dosing method for furazidine from suppositories

	Validation parameters	Suppositories with furazidine on hydrophobic base	Suppositories with furazidine on hydrophylic base
Repeatability	Substance content, g	0.108	0.989
	Coefficient of variation,%	0.550	0.467
Precision, day 1	Substance content, g	0.106	0.160
	Coefficient of variation,%	0.618	0.645
Precision, day 2	Substance content, g	0.107	0.108
	Coefficient of variation,%	0.589	0.542
Robustness	Coefficient of variation,%	286.04 nm: 0.005	286.11nm: 0.006

miscibility of the base with the dissolution media, characteristic for hydrophobic bases [22]. Furthermore, the lack of surfactants might have acted as a significant variable in the fat-based formulation in the release of furazidine [23, 24]. Suppositories prepared with the combination of PEG 400:1500:4000 (1:3:6) showed the maximum furazidine release (92.4%) within 60 minutes.

Validation of the UV-VIS dosing spectrophotometric method. UV-VIS spectrophotometric methods [25] for dosing furazidine in suppositories were developed and validated. Validation parameters were calculated according to SR ISO 8466 / 1-2016 European Pharmacopoeia Standard, Ed. 9.0 (2020) and ICH-Q2B-Validation of Analytical Procedure: Methodology (2005). The statistical parameters that were used to validate the method were: linearity, repeatability, accuracy and robustness. The first step was to select the solvent for the extraction of the active substances. Extraction technique used: a suppository (mass of 3.0 grams) was brought into a 100 ml beaker, 60 ml of dimethiformamide was added and mixed vigorously for 20 minutes, futher mixed with 30 ml of 96% alcohol and brought with 96% alcohol to the quota. The mixture obtained was filtered through filter paper, the first portions were discarded, and 0.25 ml of the filtrate was brought into a volumetric flask and mixed with acetate buffer up to 100 ml.

Preparation of the standard solution. 0.05 g (exact mass) preventively dried furazidine at a temperature of 100-105˚C, until the exact mass, is dissolved in 60 ml of dimethiformamide in a 100 ml volumetric flask, 30 ml of 96% ethyl alcohol are added, and mixed well.1 ml of solution was brought to a 100 ml volumetric flask, mixed with the acetate buffer to the level. The solutions were used ready-made.

The selectivity of the dosing method was determined by analysis of a control sample. At the wavelength of 292 nm corresponding to the furazidine determination, the control sample led to an absorbance value of 0.001. The accuracy of the developed methods was determined at 3 concentration levels: 80%, 100% and 120% by the standard addition method. The furazidine concentration was calculated using the linear regression equations established at the linearity parameter. The equation of linear regression for furazidine dosing was: $y = 0.238x + 0.014$, $R^2 – 0.999$.

The degree of accuracy, repeatability and intermediate accuracy was investigated. Repeatability was determined for 4 samples, at the concentration level of the drug substances of 100%, on the same day, respecting the same conditions. The degree of accuracy was investigated in 2 different days, under the same conditions, performing 5 determinations for each assortment of suppositories. Changes in the wavelength of absorption were performed to evaluate the robustness of the method. During the analysis of the pharmaceutical products, the levels found no significant difference and the relative standard deviation was below 0.93%, demonstrating the robustness of the proposed method, thus, furazidine in suppositories can be detected in low concentrations (tab. 2).

The UV-VIS spectrophotometric method for quantitiative determination of furazidine in evalueated suppositories was developed and validated. The validation results show that the developed method is simple, fast, accurate and robust.

Conclusions

In this paper, suppositories with furazidine were formed by hand rolling and molding methods and were subjected to physical evaluation, weight variation, content uniformity, melting point, penetration time test and *in-vitro* dissolution studies. All tests showed satisfactory results.

All five formulations showed more than 50% drug release within 60 minutes. Based on the *in-vitro* release rate studies, it can be concluded that PEG 400:1500:4000 can be used as a base which is easily soluble in aqueous medium, disperses rapidly and has higher rate of release for immediate release of furazidine and is recommended for bulk pharmaceutical elaborations.

Preparation of the suppositories with furazidine on cocoa butter excipient is a suitable alternative for individual medicinal prescriptions.

The UV-VIS spectrophotometric dosing method was developed and validated, this method could be included in the analytical procedures and documentations in the perspective of the quality evaluation of furazidine suppositories, the obtained results will serve as landmark for real-time stability studies.

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Authors' contributions

GD designed the study, performed some part of laboratory work, drafted the first manuscript; CC interpreted the data, revised the manuscript; NC conducted the laboratory work; SR conceptualized and performed a certain portion of laboratory work. All authors revised and approved the final version of the manuscript.

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Ethics approval and consent to participate

No approval was required for this study.

Conflict of Interests

No competing interests were disclosed.