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Optimization of HPMC K4M and Glycerin Concentration in the Formulation of Orally Disintegrating Films of Chlorpheniramine Maleate Using the Solvent Casting Method

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ABSTRACT

Chlorpheniramine Maleate (CTM) is an alkylamine derivative and antihistamine. It has a relatively short half-life and requires frequent administration, approximately four to six times per day. Ensuring patient convenience in drug consumption is essential. Therefore, CTM was formulated into an Orally Disintegrating Film (ODF), which can be administered without the need for water. This study aimed to formulate CTM into an ODF dosage form using HPMC K4M as the polymer, glycerin as the plasticizer, and stevioside as the sweetener. The ODF was prepared using the solvent casting method. Four formulations were developed: F1 (2% HPMC K4M, 0.2% glycerin), F2 (2% HPMC K4M, 0.6% glycerin), F3 (4% HPMC K4M, 0.4% glycerin), and F4 (4% HPMC K4M, 1.2% glycerin). The pre-gel pH evaluation showed that all formulations met the requirements, with a pH range of 5.743 ± 0.005 to 5.817 ± 0.011. Organoleptic evaluation revealed that F1 and F2 formed whitish, wrinkled, and non-homogeneous films, whereas F3 formed a clear, non-wrinkled, and relatively homogeneous film, and F4 formed a whitish, non-wrinkled, but non-homogeneous film. The results of the thickness and weight evaluation were only F3 qualified, with values of 0.075 ± 0.003 mm and 0.035 ± 0.001 g. Moisture content analysis showed compliance with the required range of 15.49 ± 3.35% to 21.81 ± 1.39%. The disintegration time met the requirement of being <60 seconds. The content uniformity evaluation met the required specifications, with an average content of 97.33 ± 4.63%, and an acceptance value of 12.28. Based on these results, F3 was determined to be the optimal ODF formulation for CTM.

Keywords: Orally Disintegrating Film, Chlorpheniramine Maleate, Solvent casting, HPMC, Stevioside

1. INTRODUCTION

The most used and known route of drug administration by the public is the oral route (Pimple et al., 2022). Tablets are one of the most widely used oral dosage forms. However, this tablet form has drawbacks, such as difficulty swallowing (dysphagia) in geriatric and pediatric patients, which poses a risk of choking, thus reducing patient compliance and leading to suboptimal therapeutic effects of the medication. One way to address this issue is by formulating it into a Fast Dissolving Drug Delivery System (FDDS) (Gauri and Kumar, 2012), such as Orally Disintegrating Tablets (ODT) (United State Pharmacopeia Convention, 2023) and Orodispersible films (European Directorate for the Quality of Medicine & Healthcare, 2022), also known as Orally Disintegrating Films (ODF) (Carvalho et al., 2023; Colucci & Rodrigues, 2022; Irfan et al., 2016; Lee et al., 2017; Lou et al., 2014). ODF is a thin film formulation that will disintegrate quickly (<60 seconds) upon contact with saliva without chewing and without the need for water to swallow (Kawale et al., 2023).

The selection of polymer and plasticizers is the most crucial stage in ODF formulation. A good ODF has physical properties of a transparent, strong, flexible film, and dissolves easily within <60 seconds. Generally, the polymer and plasticizer pairs used are hydrophilic. This property causes the ODF to disintegrate quickly when placed on the tongue (Ferlak et al., 2023).

Chlorpheniramine maleate (CTM) is an antihistamine medication derived from alkylamines. The bioavailability of CTM in conventional tablets is low. The half-life of CTM is 9.6 – 13.1 hours. The onset of action and frequency of use for CTM are high, which is 4 -6 times a day (American Society of Health-System Pharmacists, 2019). This may present a challenge for patients in situations where they are unable to take the medication, such as when they lack access to drinking water or are travelling, particularly when the scheduled dosing time approaches. Therefore, to address this issue, CTM has been formulated into the ODF preparation.

In previous research, glycerin was identified as a suitable plasticizer in combination with HPMC K4M (Febriyenti et al., 2025). However, the concentration obtained has not produced a good ODF shape. Therefore, further study is needed to determine the optimal concentrations of HPMC K4M and glycerin to make an effective CTM ODF.

2. MATERIALS AND METHODS

Ingredients

The materials used include CTM donated by PT. Metiska Farma, Jakarta. HPMC K4M was provided by Lawsim Zecha, Jakarta. Stevioside was obtained from PT. Tatarasa Primatama, Tangerang. Nipagin was purchased from Medchem Express, Monmouth. Glycerin was bought from PT. Palapa Muda Perkasa, Jakarta. CTM BPFI and nipagin BPFI were purchased from BPOM, Indonesia.

Formulation of pre-gel CTM ODF.

The pre-gel CTM ODF was prepared with a combination of HPMC K4M concentration as the polymer and glycerin as the plasticizer. The CTM ODF production process was carried out using the solvent casting method. The composition of each formula is explained in Table 1. HPMC K4M was dispersed in glycerin that already contains Nipagin as M1. CTM and stevioside were dissolved in distilled water until completely dissolved as M2. M2 was added to M1 to prepare the pre-gel of the CTM ODF, and the mixture was homogenized using an Ultra-Turrax for approximately 3 minutes. Then, it is allowed to stand at room temperature to eliminate air bubbles. After the air bubbles had dissipated, the pre-gel of the CTM ODF was poured into molds (petri dishes) and dried at a temperature of 25℃ for about two days. After drying, the formed CTM ODF was carefully removed from the molds and cut into pieces measuring 2 cm x 2 cm. Then, an evaluation of the preparation was conducted (Febriyenti et al., 2025).

Table 1. Pre-gel CTM ODF formula in one mold

No.	Ingredient (%)	F1	F2	F3	F4
1.	CTM	0.7546	0.7546	0.7546	0.7546
2.	HPMC K4M	2	2	4	4
3.	Glycerin	0.2	0.6	0.4	1.2
4.	Stevioside	1.5	1.5	1.5	1.5
6.	Nipagin	0.01	0.01	0.01	0.01
7.	Distilled water ad	100	100	100	100

Evaluation of ODF preparations

pH of pre-gel ODF

The pre-gel pH was measured using a pH meter (Basset et al., 1994). The obtained pH should be close to the saliva pH and should not irritate the oral mucosa (Febriyenti et al., 2025; Ferlak et al., 2023).

Organoleptic

The organoleptic evaluation of the ODF preparation was determined through visual observation, including homogeneity, color, odor, texture, and taste (Febriyenti et al., 2025; Hamza, 2017).

Measurement of the Thickness of ODF

Evaluation of ODF thickness using a digital micrometer was conducted on six ODF samples for each formulation. The average thickness value of ODF was calculated, and the coefficient of variation must be less than 5% (Febriyenti et al., 2025; Hamza, 2017). The acceptable thickness value for ODF is 0.02-0.07 mm (Jaiswal et al., 2021).

Moisture Content of ODF

The moisture content of ODF was measured using a moisture analyzer at a temperature of 105℃. The percentage of moisture content will be displayed on the device's screen (Febriyenti et al., 2025; Huanbutta et al., 2021).

Measurement of the Weight of ODF

Six ODFs from each formulation were randomly selected and weighed. The weight of each ODF should not deviate significantly from the average weight (Febriyenti et al., 2025; Irfan et al., 2016).

Disintegration time

Evaluation of ODF disintegration time using the slide frame method. The acceptance value is 30-60 seconds (Febriyenti et al., 2025; Hamza, 2017; Vlad et al., 2023).

Swelling index

The initial weight of the ODF is denoted as W_0. The ODF is allowed to swell in 15 ml of phosphate buffer at pH 6,8 in a petri dish for 5, 10, 15, and 20 seconds. Repeat the immersion process until a constant weight (W_t) is achieved. Calculate the swelling index using the following equation: $\%\ \text{Swelling index} = \frac{W_t - W_0}{W_0} \times 100$ where W_t = weight of the ODF at time t; W_0 = initial weight of the ODF at time 0 (Febriyenti et al., 2025; Sharma et al., 2020).

Preparation of standard solution and determination of the maximum absorption wavelengths of CTM (λ_1) and nipagin (λ_2)

A standard solution was prepared at a concentration of 100 µg/ml, then diluted to obtain concentrations of 35 µg/ml for CTM and 5 µg/ml for Nipagin. The absorbance was measured using a UV-Vis spectrophotometer within the wavelength range of 200-400 nm (Rivai et al., 2017).

Validation of analysis methods

The tests conducted include linearity, limit of detection (LOD), limit of quantification (LOQ), precision, and accuracy (ICH Expert Working Group, 2023).

Uniformity of content testing using multicomponent spectrophotometric analysis

Determination of the absorptivity values of CTM and nipagin at wavelengths λ_1 = 262 nm and λ_2 = 246 nm

The CTM solutions with concentrations of 10, 15, 20, 25, 30, and 35 µg/mL, and nipagin solutions with concentrations of 2, 3, 4, 5, 6, 7, and 8 µg/mL, were analyzed for their absorbance at a wavelength of $\lambda 1$. Then, the CTM solutions with concentrations of 20, 30, 40, 50,

60, and 70 and nipagin solutions with concentrations of 3, 4, 5, 6, 7, 8, and 9 had their absorbance measured at a wavelength of $\lambda 2$. The determination of the absorptivity coefficient values is done using Lambert-Beer's law (Gandjar & Rohma, 2013) :
$A = a \,.\, b.\, C$ where A = absorbance; a = molar absorptivity coefficient; b = cuvette thickness; C = solution concentration.

Preparation of the test solution for the uniformity of content of CTM ODF

The uniformity of content test was conducted for 10 sheets of ODF. One sheet of ODF 2 cm x 2 cm was dissolved with 0.1 N HCl in a 50 mL volumetric flask. Then shake and sonicate for about 60 minutes. A 1.5 mL aliquot of the solution was taken and diluted to 10 mL with 0.1 N HCl in the volumetric flask. The test solution was then measured for total absorbance ($AT^{\lambda 1}$ and $AT^{\lambda 2}$) at wavelengths $\lambda 1$ = 262 nm and $\lambda 2$ = 246 nm (Lou et al., 2014).

Calculation of CTM concentration in ODF

The concentration of CTM in ODF is calculated at each wavelength $\lambda 1$ = 262 nm and wavelength $\lambda 2$ = 246 nm. The obtained absorbance is then calculated using the formula below. The values of nipagin and CTM concentrations are then obtained through substitution and elimination mathematical operations. (Gandjar & Rohma, 2013):

$$A_T^{\lambda 1} = a_1^{\lambda 1} \,.\, C_1 + a_2^{\lambda 1} \,.\, C_2 \ldots\ldots\ldots\ldots\ldots\ldots (1)$$
$$A_T^{\lambda 2} = a_1^{\lambda 2} \,.\, C_1 + a_2^{\lambda 2} \,.\, C_2 \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Where $A_T^{\lambda 1}$ = total absorbance of CTM and nipagin at wavelength λ_1; $A_T^{\lambda 2}$ = total absorbance of CTM and nipagin at wavelength λ_2; $a_1^{\lambda 1}$ = absorptivity of CTM at wavelength λ_1; $a_1^{\lambda 2}$ = absorptivity of CTM at wavelength λ_2; $a_2^{\lambda 1}$ = absorptivity of nipagin at wavelength λ_1; $a_2^{\lambda 2}$ = absorptivity of nipagin at wavelength λ_2; C_1 = measured concentration of CTM; C_2 = measured concentration of nipagin.

3. RESULTS AND DISCUSSION

Formulation of CTM ODF using the solvent casting method. This method is chosen due to its ease of execution, relatively low cost, no requirement for specialized equipment, and the amount produced is suitable for laboratory scale. The results of the ODF evaluation are presented in Table 2.

Table 1. Results of the evaluation of the four CTM ODF formulas

Evaluation	F1	F2	F3	F4	Acceptance value
pH	5.782 ± 0.011*	5.753 ± 0.008*	5.743 ± 0.005*	5.817 ± 0.011*	5.5 – 7.6 (Baliga et al., 2013; Suresh et al., 2022)
Organoleptic	A transparent white film is formed, wrinkled, non-sticky, non-homogeneous, and easy to remove from the mold	A transparent white film is formed, wrinkled, sticky, non-homogeneous, and easy to remove from the mold	A transparent film is formed, not wrinkled, homogeneous, non-sticky, and easily removed from the mold*	A transparent film is formed, not wrinkled, not homogeneous, sticky, and easy to remove from the mold	Transparent, non-sticky, homogeneous, not wrinkled (Febriyenti et al., 2025)
Thickness (mm)	0.062 ± 0.027 CV: 43.89%	0.061 ± 0.029 CV: 47.19%	0.075 ± 0.003* CV: 3.44%.	0.105 ± 0.012 CV: 11.19%	0.01-0.35 mm dan CV <5% (Centkowska et al., 2024; Febriyenti et al., 2025; Hamza, 2017)
Moisture Content (%)	-	-	15.49 ± 3.35*	21.81 ± 1.39*	-
Weight (g)	-	-	0.035 ± 0.001 (CV: 2.16%)*	0.044 ± 0.002 (CV: 5.19%)	CV <5% (Febriyenti et al., 2025; Irfan et al., 2016)
Swelling Index (%)	-	-	388.90 ± 41.74*	430.09 ± 9.14*	-

Disintegration time (seconds)	-	-	23.00 ± 3.60*	7.33 ± 1.53*	<60 seconds (Febriyenti et al., 2025; Hamza, 2017; Vlad et al., 2023)

* = meet the requirements

The normal pH value of saliva ranges from 6.2 to 7.6. Meanwhile, the pH values that can potentially irritate the oral mucosa are 5-5.5 (Suresh et al., 2022). As shown in Table 2, the pH value ranged from 5.74 to 5.81, thus not irritating the oral mucosa. This value is also consistent with the pH value of the active ingredient CTM, which is between 4 and 5 (Ministry of Health of the Republic of Indonesia, 2020).

In the production of ODF, the use of polymers that are unsuitable for the active substance can lead to a non-homogeneous distribution of the active substance or a physical form that is not smooth and wrinkled. In addition, the concentration of the polymer influences its ability to bind other components, such as CTM, stevioside, and nipagin. This is evidenced by the film shape formed in F1 and F2, which tended to be non-homogeneous and wrinkled due to insufficient polymer concentration. Moreover, a study conducted by Liew et al., reported that a polymer concentration that is too low results in a weak film, whereas a higher concentration produces a stronger film that is easier to detach from the mold (Liew et al., 2014).

The use of a plasticizer aims to make the ODF more flexible or elastic, and the concentration used will affect whether the formed film is sticky or not. In F2 and F4, a sticky film was formed because the concentration of plasticizers used was higher compared to F1 and F3.

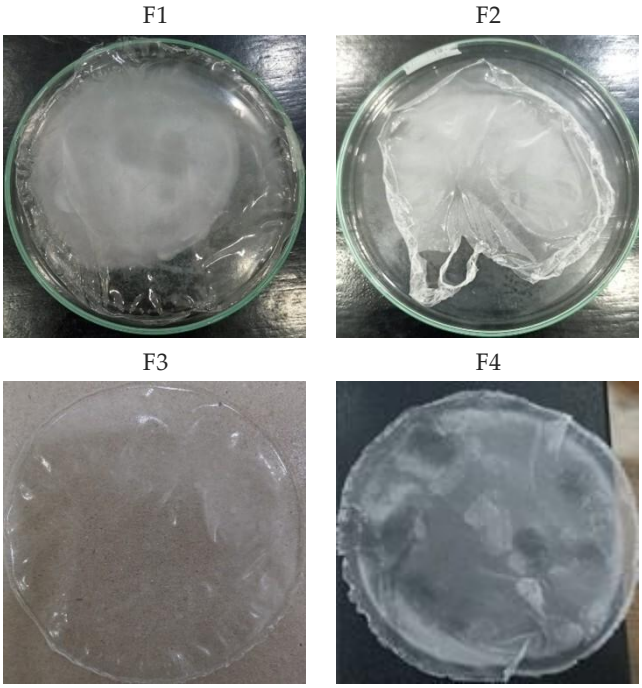

Figure 1. CTM ODF

Before the films are cut, an evaluation of the thickness of the CTM ODF is performed to determine the distribution of the active substance in each print and to control the disintegration time (Figure 1). Based on Table 2, it is shown that the higher the concentration of the polymer used, the more solids are contained, resulting in thicker films being produced. This finding is consistent with the research conducted by Chauhan et al., (2012) which reported that increasing the concentration of the polymer HPMC K4M leads to an increase in the thickness of the nicotine hydrogen tartrate ODF. In F1, F2, and F4, it visually appears to be non-homogeneous, as evidenced by the CV > 5%. In addition, based on Centkowska et al., (2024) the ideal thickness value of ODF applied to the tongue has a range of 0.01-0.35 mm. Thus, only F3 meets both thickness requirements.

The thinness and weakness of the films in F1 and F2 rendered them non-cuttable, thus preventing further evaluation. The subsequent evaluation conducted is the moisture content evaluation. This evaluation aims to determine the stability of ODF during storage. Before this evaluation is carried out, the CTM ODF preparation is placed in a desiccator first. The moisture content of F4 is higher than that of F3. This is due to the hygroscopic property of glycerin, which means that increasing its concentration enhances its capacity to bind water. The moisture content values of both formulas meet the requirements, as there are no specific moisture content range values for ODF.

The subsequent evaluation conducted is the variability of CTM ODF weight. This evaluation is carried out to assess the consistency of the CTM ODFs formed in each formula. A high variation in weight may indicate errors in the production process, such as inadequate homogeneity in mixing, insufficient water removal, or incomplete polymer expansion. F4 has a higher weight compared to F3 due to the concentration of plasticizers used. Based on the results, CV >5% indicates that F4 lacks homogeneity.

The subsequent evaluation is the swelling capacity of the film and the disintegration time. This evaluation is conducted to determine the ability of ODF to swell upon contact with saliva. The higher the swelling capacity produced by the ODF formulation, the faster the disintegration time will be. The disintegration time is evaluated using the slide frame method. This method aims to observe the disintegration time of ODF when it first comes into contact with saliva. The medium used is phosphate buffer, pH 6.8. The use of this medium is expected to provide an environment similar to saliva, which has a pH value ranging from 6.2 to 7.6 (Baliga et al., 2013).

Based on Table 2, it was found that formula F4 has a higher expansion capacity and a shorter disintegration time compared to F3. This may also be attributed to the higher concentration of plasticizer used in F4, which enhances its ability to absorb moisture. However, both formulas still have disintegration times that meet the requirement, which is less than 60 seconds. A quick disintegration of time determines the comfort of patients when consuming it. The disintegration time of ODF formulations depends on the composition of the matrix in each formula (Ferlak et al., 2023).

The selection of the optimal formula was conducted before the final evaluation of CTM ODF, specifically the determination of content uniformity. This selection is based on the results of all evaluations of the physical properties of CTM ODF obtained from each formula. The best formula is F3. This is evident in Table 2, where F3 meets the criteria in all physical property evaluations conducted.

The last evaluation of ODF is the uniformity of the dosage form in terms of content uniformity. This test is conducted on pharmaceutical preparations that have a dose of <25 mg or <25% (Ministry of Health of the Republic of Indonesia, 2020). This testing is essential to ensure the consistency of active substance content in the formulation. Additionally, it is necessary to determine the success of a formula in binding or distributing the active substance homogeneously. The amount of active substances contained in each CTM ODF formulation determines the efficacy of drug therapy in patients.

In the evaluation of content uniformity, validation of the analysis method was performed. This validation aims to assess whether the method used is accurate, specific, and robust within the range of analytes to be analyzed. The method validation includes linearity, precision, limit of detection, limit of quantification, and accuracy. A UV-Vis spectrophotometer was used for the validation of the analytical method and the test of content uniformity. Since the compound to be analyzed has a chromophore group, the UV-Vis spectrophotometry instrument is suitable for use. Based on Table 3, the method validation conducted has met the requirements.

Table 2. Validation of Analysis Method

Validation of Analysis Method	**Results**			
	CTM		**Nipagin**	
Linearity	r= 0.9997		r= 0.9995	
Precision (% RSD)	I	0.137 – 0.832	I	0.103 – 0.402
	II	0.068 – 0.432	II	0.073 – 0.506
	III	0.104 – 0.343	III	0.127 – 1.325

LOD (µg/mL)		0.93	0.22
LOQ (µg/mL)		2.81	0.66
Accuracy (%)	40% standard solution	98.61	
	80% standard solution	99.78	
	120% standard solution	101.63	

The type of analysis used is a multicomponent method of simple derivative spectrophotometry. This method is commonly used for preparations that contain more than one compound with chromophore groups (Hajian & Soltaninezhad, 2013). This is consistent with the CTM ODF, which contains two compounds with chromophore groups, namely CTM and nipagin. The number of these chromophore groups causes the maximum absorption wavelength of these compounds to be close, at 262 nm (CTM) and 253 nm (nipagin). Therefore, the first step is to determine the wavelength values of both compounds to be used as references during the measurement. Based on Figure 2, the wavelengths used for the measurement are 262 nm ($\lambda 1$) and 246 nm ($\lambda 2$).

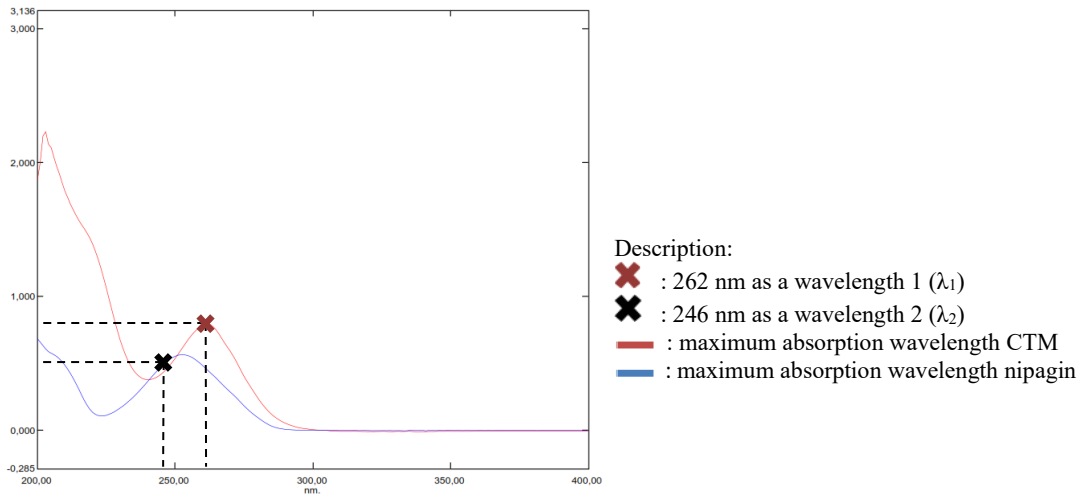

Figure 2. Selection of multicomponent wavelengths

After obtaining the wavelength value to be used, the next step is to determine the absorptivity values of each compound at the two wavelengths. As a result, two mathematical equations are obtained, as shown below. The total absorbance value entered into the equation is the absorbance value of the tested CTM ODF sample.

$$A_T^{\lambda 1} = 0.025 \,.\, C_1 + 0.103 \,.\, C_2 \ldots\ldots\ldots\ldots\ldots\ldots (1)$$
$$A_T^{\lambda 2} = 0.012 \,.\, C_1 + 0.086 \,.\, C_2 \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

In the uniformity testing of the content, the acceptable range of CTM levels in one ODF is between 90.0 – 110.0%. This value refers to the CTM content range in tablet preparations according to Pharmacopoeia VI (Ministry of Health of the Republic of Indonesia, 2020). In F3, the average % of CTM content obtained was 97.33 ± 4.63 with an acceptance value of 12.28. The obtained value is within the range, and the acceptance value is <15, thus meeting the requirements according to Indonesian Pharmacopoeia standards.

4. CONCLUSION

It can be concluded that Chlorpheniramine maleate could be formulated into an Orally Disintegrating Film (ODF) using 4% HPMC K4M as the polymer and 0.4% glycerin as the plasticizer.

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Authors' Contributions

Febriyenti: Concepts, design, definition of intellectual content, data analysis, manuscript review, guarantor

Regina Andayani: Concepts, design, definition of intellectual content, data analysis, manuscript review

Charrisca Syahyuning Kumalasari: Literature search, experimental studies, data acquisition, data analysis, manuscript preparation, manuscript editing

Ethical Approval

Not applicable. This article does not contain any studies with human participants or animals performed by any of authors.

Informed Consent

Not applicable.

Conflicts of interests

The authors declare that there are no conflicts of interests.

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Data and materials availability

All data associated with this study are present in the paper.

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