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Original Research Article

Formulation of ketotifen child-friendly chewing gums for pediatric administration

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Abstract

Purpose: *To formulate ketotifen fumarate (KTF) in the form of an oral chewing gum to enhance patient compliance, particularly among children.*
Methods: *Six KTF gums were prepared using gelatin alone or in combination with sodium carboxymethylcellulose (NaCMC) at 68 ºC and at 75 ºC. The six batches prepared were code-labeled, F1 to F6. The prepared KTF gums were characterized with respect to appearance, thickness, weight variation, moisture loss, and in vitro drug release.*
Results: *Temperature did not significantly affect the properties of the formulated gums ($p > 0.05$). However, the addition of a second polymer affected the properties of the gums. Two KTF gums (F2 and F4), which had NaCMC as a second polymer, showed maximum release in 2 h (100 % and 87.25 %, respectively). The moisture content for F2 was 15.20 %, suggesting better mechanical properties.*
Conclusion: *Ketotifen fumarate may be formulated into a chewing gum as an alternative method for pediatric administration, aiming to improve compliance.*

Keywords: *Ketotifen fumarate, Chewing gum, Sodium carboxymethylcellulose*

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INTRODUCTION

Children often have distinct preferences for taste, texture, and ease of swallowing of medications. These preferences significantly affect their willingness to follow prescribed treatments. The recognition of these preferences is essential for healthcare professionals, caregivers, and pharmaceutical developers. Therefore, there is increasing focus on creating oral solid dosage forms tailored to the specific needs of pediatric patients so as to enhance their drug acceptability and adherence. Innovations in formulation technology are being explored to enhance the acceptability of the oral solid dosage forms. The innovations involve the development of chewable tablets, gums, dispersible formulations, and flavored options that appeal to children. Additionally, considerations surrounding age-specific developmental stages are critical: younger children may require more palatable and easily-administered forms, while older children may be more amenable to conventional tablets if they are appropriately sized and flavored [1].

Chewing formulations have appeared as a popular dosage form in the pharmaceutical industry, particularly for pediatric patients and

individuals who may have difficulty swallowing traditional tablets or capsules [2]. These gums combine the appeal of candy-like textures and flavors with the therapeutic benefits of active principles, thereby making them an attractive option due to palatability and ease of administration. Gums may be used to improve adherence and ensure that patients receive necessary treatments. From a formulation perspective, creating effective chewy gum involves careful consideration of various factors such as the selection of suitable excipients, stability of the active drug, and the desired release profile [3]. Gums are typically made from a gelatin or pectin base, which provides the chewy texture, while sweeteners and flavoring agents contribute to taste. The incorporation of vitamins, minerals, herbal extracts, or pharmaceutical compounds into these formulations requires precise formulation techniques to ensure proper dosing and bioavailability [4]. Ketotifen fumarate (KTF) is a histamine (H1) receptor antagonist. The chemical formula is 4-(1-methylpiperidin-4-ylidene)-4H-benzo-4,5-cyclohepta-1,2-b-thiophen-10(9H)-one monofumarate, which is usually represented by its structural formula. The drug appears as a white-to-pale, yellowish-white crystalline powder with limited solubility in methanol and acetic acid, and minimal solubility in water, ethanol, and acetic anhydride. The melting point of KTF ranges from 191 to 195 ºC, and the pKa and Log P (octanol/water) values are 8.75 and 4.99, respectively. After oral administration, KTF is almost fully absorbed from the gastrointestinal tract, achieving peak plasma concentrations within 2 to 4 h. It is primarily excreted in urine as an inactive metabolite, with a small fraction as unchanged drug, and a terminal elimination half-life of about 21 h. However, the bioavailability of KTF is approximately 50 %, due to extensive hepatic first-pass metabolism [5]. Given these properties, there is need for more child-friendly dosage forms of the drug. This study was aimed at developing a novel chewable formulation of KTF in order to improve its suitability for pediatric use.

EXPERIMENTAL

Materials

Ketotifen fumarate (KTF) was purchased from Zhejiang Shenzhou Pharmaceutical Co., Ltd., China. Hydrochloric acid (HCl) was purchased from British Drug House Chemicals lab-England, while gelatin was a product of BASF, Germany. Sodium carboxymethyl cellulose was bought from Hyper Chem, China. Sorbitol was obtained from Central Drug House, India. Coloring agents (green, orange, and red) were products of L.M. Chemical Industries, India. All other chemicals were of analytical grade.

Pre-formulation studies

Preparation of 0.1 M HCl

The HCl solution (0.1 M) was prepared by diluting 8.176 mL of 37.5 % HCl to 1000 mL with distilled water.

Determination of wavelength for maximum absorption (λ_{max})

The UV absorbance for KTF was scanned in 0.1 M HCl solution, and in distilled water in the wavelength (λ) range of 200 - 400 nm using Shimadzu UV-1800 spectrophotometer (Kyoto, Japan), and the λ for maximum absorption (λ_{max}) of KTF was determined [6].

Preparation of a KTF standard calibration curve

Calibration curves of KTF in 0.1M HCl solution and in distilled water were constructed using serial dilutions of KTF stock solution (1 mg/mL). The absorbance values of the serial dilutions were read spectrophotometrically at the wavelength of maximum absorbance of KTF. To generate the standard calibration curves, the measured absorbance values were recorded and plotted against the respective concentrations of KTF.

Determination of melting point of KTF

The melting point of KTF was determined using the capillary tube method. A capillary tube sealed at one end was filled with the drug powder and inserted into a melting point apparatus. The temperature was incrementally raised, and the point at which the powder transitioned into a liquid state was noted as the melting point [6].

Determination of saturation solubility

An excess amount of KTF was added to 20 mL of 0.1 M HCl solution and also to 20 mL of distilled water. Each mixture was shaken for 48 h at 37◦C in a water bath, to attain equilibrium. Then, each mixture was filtered through a 0.45-µm Millipore filter, and after suitable dilution, the filtrate was analyzed spectrophotometrically at the wavelength of maximum absorbance of KTF, and the readings were used to calculate the solubility of KTF [6]. Three determinations were carried out for each solvent (distilled water and 0.1 M HCl).

Preparation of KTF-chewable gum

The main components of the prepared gum consisted of gelatin (5 – 8 %) as gelling agent, 30 % sucrose solution as a sweetener, sorbitol (to prevent crystallization), and 0.5 % citric acid. The formulation was prepared at two different temperatures, i.e., 68° and 75°C. Gelatin was hydrated in 20 mL of water (20 %) at either 68 or 75 °C, with mixing. The temperature was maintained using a water bath and checked using a thermometer. The procedure used in the formulation was as follows: CMC was added with gelatin powder as viscosity enhancer. Then, sorbitol was added to the gelatin dispersion. The dispersion was allowed to stand for 10-15 min until clear, after which the foam formed was skimmed off. Then, sucrose solution was added to the dispersion, with gentle blending, and the mixture was placed in the water bath again. The mixture was removed from the water and allowed to cool down at room temperature. Thereafter, using hand mixing, the other components were added, i.e., the drug (KTF), citric acid (acidifier), and the colors and flavors. The mixture was poured into molds and placed in a refrigerator for 4 h. Six formulas were prepared (F1-F6), as listed in Table 1 [7].

Physical evaluation of the gums

Visual appearance

All the gums were visually inspected for color, clarity, transparency, homogeneity, smoothness, and taste.

Thickness and pH measurement

The thickness of each gum was measured using an electronic digital caliper for diameter determination. A pH meter was used to determine the pH of each of the gums. After calibrating the pH meter electrode, 1.0 g of each gum was suspended in 25 mL of distilled water. Then, the pH of the sticky mixture was read using the pH meter. The mean pH and standard deviation values were calculated [7].

Weight uniformity

The gums were subjected to determination of weight variation by individually weighing three randomly selected samples using a digital balance. Using the data obtained, the mean and standard deviation values were calculated [7].

Drug content

Each gum was placed in a beaker with 50 mL of 0.1 M HCl solution and stirred using a magnetic stirrer for 2 h. The mixture was then filtered through a 0.45-µm Millipore filter, and the filtrate was analyzed for drug content using a UV-visible spectrophotometer, with a reference solution of blank gum as the control. This procedure was performed on three gums per formulation, with results reported as mean ± standard deviation [8].

Percentage moisture content

Each gum was precisely weighed and placed in a desiccator containing 1.0 g of anhydrous calcium chloride. After 72 h, the gum was removed and reweighed. The moisture content (M) was determined as indicated in Eq 1.

$$M (\%) = (Wi-Wf/W1)100 \quad \ldots\ldots\ldots\ldots\ldots (1)$$

Where Wi is the initial weight, and Wf is the final weight

Surface pH

Each formulation was cut into four pieces and placed in 50 mL of purified water, and pH was recorded after 10 min using a pH meter [9].

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra of pristine KTF and the chosen formulations (F2 and F4) were obtained using a Fourier transform infrared analyzer (FTIR-8300 Shimadzu, Japan).

Table 1: Compositions of the 6 KTF chewable gummy formulations

Code	KTF (mg)	Sucrose solution (mL)	Sorbitol (g)	Stevia (g)	Gelatin (g)	CMC (g)	Citric acid (%w/w)	Temperature (°C)	Final weight (g)
F1	0.5	5	0.5		1.5		0.5	65	2
F2	0.5	5			1.0	0.5	0.5	65	2
F3	0.5	5	0.5		1.5		0.5	75	2
F4	0.5	5			1.0	0.5	0.5	75	2
F5	0.5	5	0.5			1.5	0.5	65	2
F6	0.5			0.5	1.5		0.5	65	2

Each medication was pulverized and mixed with potassium bromide (KBr), and the mixture was compressed into a thin tablet disc using a hand tablet press, followed by scanning at a wavelength range of 4000 - 400 cm^{-1}. The goal of the FTIR procedure was to identify any possible interactions or complexations between KTF and the excipients used in the formulation [10].

Dissolution study

To mimic teeth crushing, each gum was sliced into four pieces with a knife and placed at the bottom of the USP apparatus type II paddle-type dissolving vessel. Then, 900 mL of 0.1 M HCl was used as the dissolution medium, and the device was run at a speed of 50 rpm and adjusted to a temperature of 37 ± 0.5°C. Samples were taken out at 10-min intervals over a duration of 3 h.

The collected samples were filtered through a Millipore filter (0.45µ), and the absorbance of each sample was read at λ_{max} of KTF in a UV-Visible spectrophotometer. The percentage of drug release was plotted against time [11].

Gelatin hardness study

The study was focused on evaluating the hardness, chewiness, and firmness of the formulations developed. The hardness of each gum was determined using TA.XT PlusC Texture Analyzer (Stable Micro Systems Technology Ltd., London, UK).

The compression test was conducted using a 25-mm cylindrical or spherical probe with a load cell capacity of 50 N so as to ensure accurate force measurement. The test began with a trigger force of 100 g applied at a controlled speed of 0.8 mm/sec until a target distance of 2.5 mm was reached, representing the depth of compression and a return speed of approximately 1.0 mm/sec.

This setup allowed for precise evaluation of the mechanical response of the sample under compression, thereby ensuring reproducibility and reliability of the measurements. The probe was lowered until it contacted the gummy surface and was forced to compress the gum. Then, the hardness value was recorded based on resistance to deformation [12].

RESULTS

Maximum wavelength (λ_{max})

The λ_{max} of KTF in 0.1 M HCl was 288 nm.

Calibration curve of KTF

The calibration curve for KTF in 0.1 M HCl solution resulting from plotting absorbance against KTF concentration yielded a linear relationship (*y = 0.0546+ 0.0115; R2 = 0.9993*).

Physical properties of KTF

Melting point

The melting point range of KTF was 193 – 195 °C.

Solubility

The results obtained showed that the measured saturated solubility of KTF in 0.1 M HCl, pH 1.2, was 0.205 mg/mL, while in distilled water, it was 0.11 mg/mL.

Physical properties of the gums

Visual appearance and taste

All the KTF gums appeared homogenous, each with a smooth surface and even distribution of color. Volunteer students who tasted the gums indicated that the formulations had acceptable taste and odor [6].

Thickness and pH

The average thickness of each of the gums in all formulations is shown in Table 2. The thickness was found to vary from 4.6 ± 0.021 to 4.8 ± 0.058 mm. Results of pH measurements showed values of 3.8 - 5.5.

Weight uniformity

The gums showed good uniformity in weight, with values ranging from 1.99 to 2.53 g. The results indicated minimal variability in gum weight, as shown in Table 2.

Drug content

All the formulations exhibited consistent KTF content ranging from 92 to 100 %, demonstrating the reliability of the preparation method. The formulations complied with the British Pharmacopoeia content uniformity standards (85 – 115 %), which is an indication that KTF was evenly distributed within the gums.

Percentage moisture content

Moisture content has a major impact on product quality and shelf life, stability, and the capacity of a gum to retain its physicochemical properties under normal storage conditions, since water content influences microbial growth, which will in turn affect gummy stability. The moisture contents of the formulations are presented in Table 3. The values obtained were in the range of 9.5 - 17.3. These values were almost uniform, indicating little moisture loss and stable formulations.

Gelatin hardness

Table 3 and Figure 1 exhibit hardness of gelatin in the selected formulation (F2).

FTIR spectroscopic analysis

The infrared spectrum of pure KTF powder displayed distinct peaks at 2979.48 cm^{-1} corresponding to C-H stretching of the thiophene ring; at 3448.1 cm^{-1} for aromatic C-H stretching; at 1648 cm^{-1} for the carbonyl C=O group, and at 1257.36/1317.14 cm^{-1} for in-plane C-H stretching [13]. In contrast, the physical mixture of KTF, gelatin, and sorbitol powder in the specified equal ratio (1:1:1) displayed characteristic KTF peaks at 2929.87 cm^{-1}, 3417.86 cm^{-1}, 1651.04 cm^{-1}, and 1255.66/1313.52 cm^{-1}. These peaks are shown in Figure 2.

Table 2: Physical properties of KTF Gums

Code	Thickness (mm)	pH	Drug content (mg)	Weight (g)
F1	4.8±0.055	3.8±0.023	0.46±0.013	2.116±0.035
F2	4.7±0.010	5.1±0.102	0.54±0.024	2.039±0.101
F3	4.8±0.033	5.3±0.067	0.52±0.036	2.267±0.072
F4	4.6±0.018	5.5±0.033	0.48±0.052	2.239±0.048
F5	4.77±0.040	4.8±0.013	0.49±0.010	2.53±0.017
F6	3.94±0.120	5±0.050	0.51±0.020	1.99±0.100

Values are expressed as mean ± SD, n=3

Table 3: Percent moisture loss from KTF formulations

Code	Initial wt (W_o; g)	Final wt (g)	Moisture content (%)	Hardness (N)
F1	2.116±0.035	1.839	13.09	30±0.4
F2	2.039±0.101	1.729	15.20	32.5±0.5
F3	2.267±0.072	1.047	17.30	29.5±0.2
F4	2.239±0.045	1.990	11.10	30.8±0.1
F5	2.53±0.017	2.290	9.50	6.7±0.3
F6	1.99±0.100	1.780	10.55	3.42±0.1

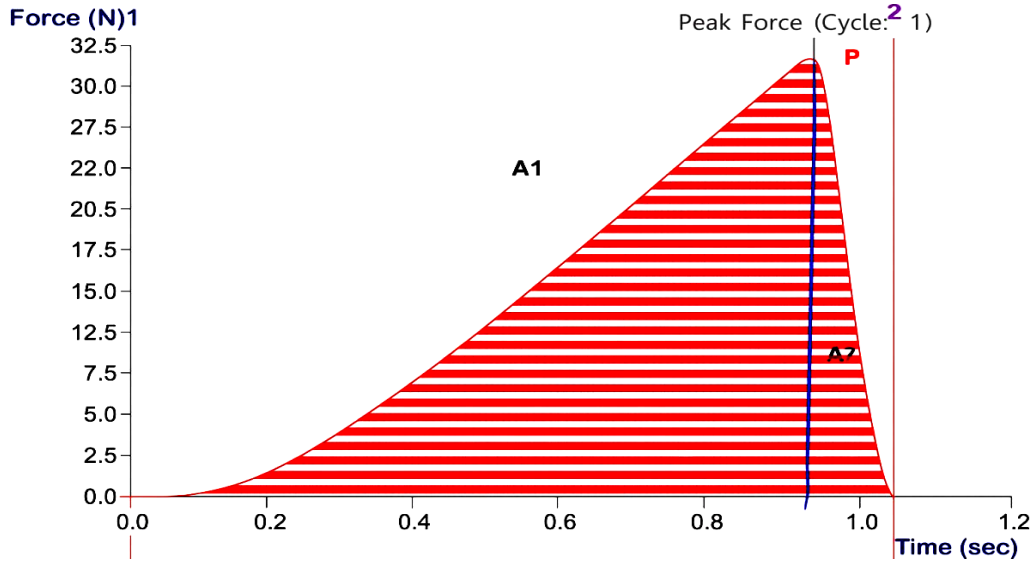

Figure 1: Texture profile analysis of the selected formulation (F2)

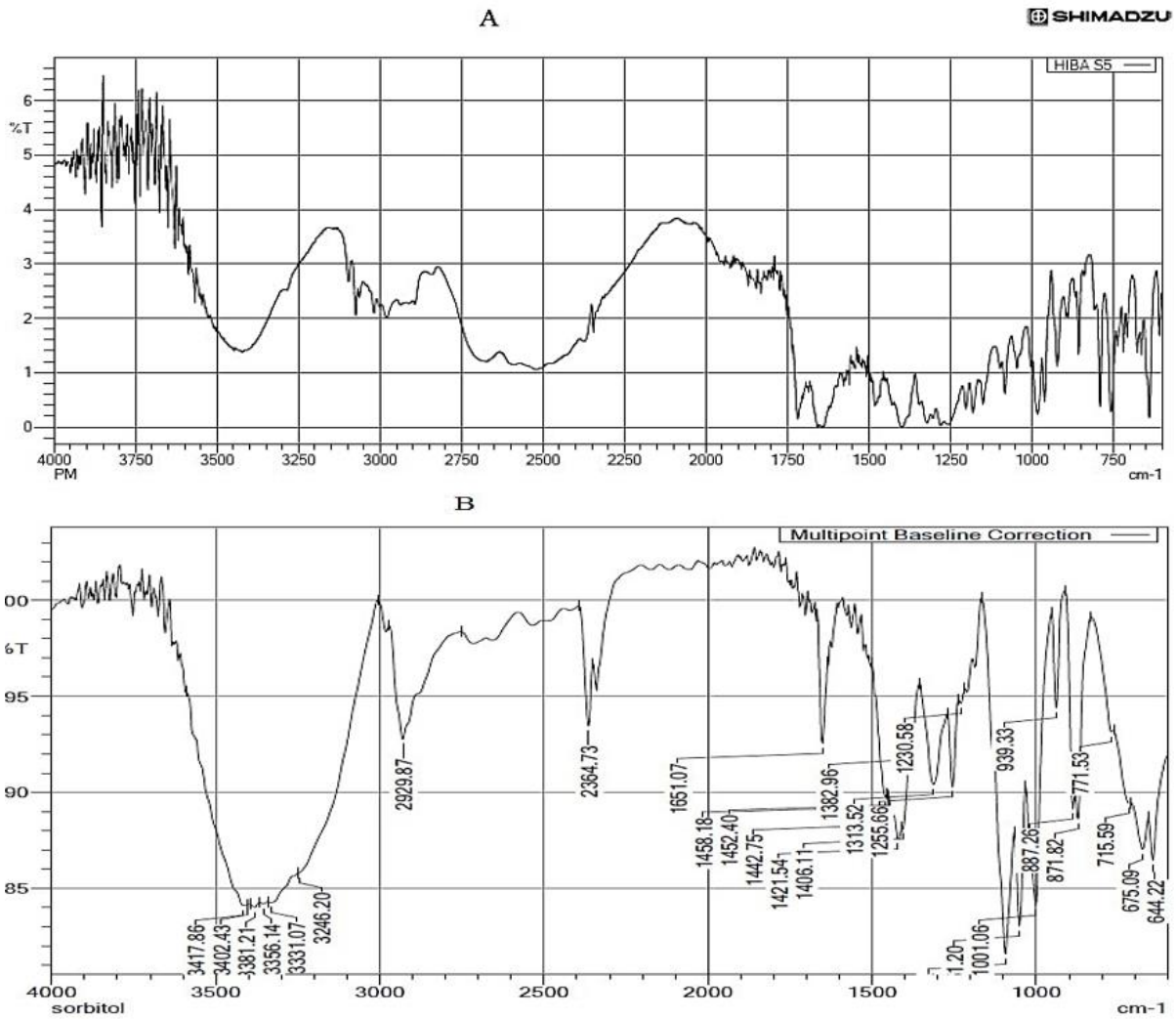

Figure 2: FTIR of (a) pure KTF, and (b) physical mixture of selected formula F2

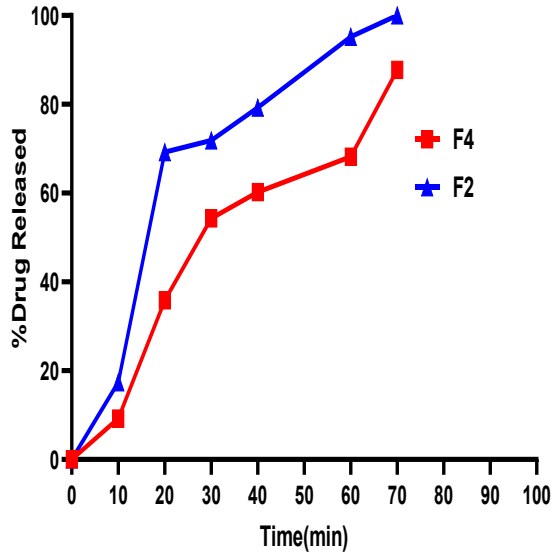

Figure 3: The dissolution of KTF gums in 0.1 M HCl at 37 °C

Dissolution properties

The amounts of KTF released within 1 h from F2 and F4 (gelatin with CMC) were found to be very high. Usually, CMC forms a thick dispersion upon contact with water. This may impede further movement of water, which may account for the slightly lower KTF release from F4 (87.25%) than from F2 (100%) within 70 min, as shown in Figure 3.

DISCUSSION

The λ_{max} obtained for KTF is similar to values reported in the literature. The calibration curve in 0.1 M HCl yielded a linear relationship that demonstrated compliance with the Beer-Lambert law within the concentration range tested [14]. Results of melting point determination for KTF are consistent with values reported in the literature, thereby confirming the purity of the drug powder used [13], while solubility

measurements revealed the poor aqueous solubility of KTF is consistent with reported solubility profiles in aqueous media [15].

The data on thickness showing very low standard deviation value indicated that the method used for the formulation yielded a uniform thickness. Additionally, the gums showed good uniformity in weight, with acceptable drug contents. The results of pH measurement suggest that the composition of the preparation and the pH of the medium affected the swelling index. Carboxymethyl cellulose (CMC) and gelatin (a natural polymer) form a three-dimensional structure with the capacity to swell in water due to the presence of hydrophilic groups (-NH_2 and -COOH) and the formation of new hydrogen bonds [12].

Hardness measurements revealed firmer, stable gums as a result of mixing gelatin with CMC. The effect of temperature was not significant. Hardness may vary, depending on the formulation and storage conditions, which affect firmness over time. Temperature had no significant effect on hardness. The results obtained from FTIR indicate no chemical interaction between pure KTF and the polymers used in the formulation. Data from dissolution studies showed that CMC enhanced the release of KTF due to its swelling properties. When CMC swells, it creates a more porous structure, which facilitates drug release [16]. However, the increase in temperature reduced the amount of KTF released, as higher temperatures lead to a softer gelatin texture, reduction in gelatin strength, and lower gelling power, resulting in a weaker gel [17].

CONCLUSION

Ketotifen fumarate (KTF) may be effectively formulated into oral pediatric gum gels. Optimal results were achieved using gelatin as the gelling agent in combination with carboxymethyl cellulose as a viscosity enhancer. Complete drug release was attained within 70 min. Thus, formulation represents a promising alternative for pediatric drug delivery and enhanced compliance, especially in pediatric patients.

DECLARATIONS

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Ethical approval

None provided.

Use of Artificial intelligence/Large language models

We also declare that we did not use generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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