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RESEARCH PAPER

Synthesis of Nanocomposite Drug Structure Containing Chitosan/ Gelatin and Its Application in Diclofenac Release Control

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ABSTRACT

In the drug delivery system, the goal is to achieve a sustained release formulation that improves the effectiveness of drugs in certain tissues by releasing the drug for a longer period of time. On the other hand, biodegradable polymers are a suitable choice in this field. There are several properties that make biodegradable polymers suitable as carriers for drug delivery: predictable biodegradation behavior, biocompatibility, ease of fabrication, availability. Nowadays, nanoparticles have received much attention due to their wide applications in various fields of biology and medicine. Nanomaterials have great potential to increase the efficiency of pharmaceutical systems in drug delivery. In this research, gelatin and chitosan have been used as a polymer coating, which leads to the stability of barium hexaferrite nanoparticles in the pharmaceutical structure and prevents the accumulation of substances. Also, glycerin was used to improve the flexibility of drug structure containing diclofenac sodium. When nanoparticles are dispersed in a polymer substrate or coated with polymers, the improvement in performance of drug release systems can be achieved. For this purpose, in the laboratory, solutions with the same pH as blood in the human body were prepared and the effect of different parameters on the amount and manner of diclofenac release were investigated. Also, analyzes such as FTIR, XRD, SEM and VSM were used to characterize the nanostructures.

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INTRODUCTION

Conventional methods of drug release in the body, mainly through digestive (pills, capsules, syrup) and non-digestive such as injections, eye drops, topical creams, are done at specific time intervals of drug consumption. In most of these methods, the path of the drug travels in the body, during exposure to the acidic environment of the stomach, passing through the tough junctions of the intestinal wall cells and entering the intrahepatic cycle, which is finally absorbed into the bloodstream [1-6]. At present, most of the drugs reach their place of effect through traditional methods and systemic absorption and with the waste of the drug during the passage through the digestive system, circulatory system

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and intermediate tissues. Therefore the used drug dose is unrealistic and more than the amount needed for treatment. The foundations of this attitude are based on the fact that if a sufficient concentration of the drug enters the blood circulation, some of it will eventually reach its place of action to treat the disease, but still, a large amount of the drug in healthy tissues of the body will cause side effects [6-10]. The process of targeted drug delivery maintains the level of appropriate drug concentrations for a long period of time and reduces many limitations of conventional treatment such as the number of doses consumed, the initial concentration of the drug, as well as the side effects caused by the simple release of the drug in an uncertain systemic distribution [11-14]. Each targeted delivery system includes a drug, a carrier and a targeting ligand, in which the distribution, metabolism and cellular absorption of the drug are determined according to the physicochemical properties and biological behavior of the carrier and ligand. Therefore, the design of suitable carrier and ligand increases the efficiency of the drug in the diseased tissue and reduces the toxicity of the drug in other healthy tissues. In all drug delivery systems, the purpose of connecting drugs to carrier molecules is to reduce side effects, increase the efficiency of drugs, and control their release time and concentration in the desired location, such as blood or any body tissue. Some drug delivery systems increase the time of presence and slow release of the drug in the bloodstream. In this case, the momentary concentration of the active form of the drug in the blood is low, and it causes the rate of excretion of the drug through the kidneys to decrease, and as a result, the number of administered drug per unit of time is reduced.

The purpose of this paper is to synthesize nanostructures containing nanostructures to control the release of the diclofenac sodium, which is used to reduce pain and inflammation. Slowing down the release of diclofenac sodium due to reducing its side effects by using zinc oxide, barium hexaferrite and core-shell nanostructures and synthesis of optimal biocompatible nanocomposite as well as achieving a stable formulation are among the important goals of this paper. For this purpose phosphate buffer (pH = 7.4) was used as release medium, similar to body condition.

MATERIALS AND METHODS

Materials and Methods

$Fe(NO_3)_3.9H_2O$, $Ba(NO_3)_2$, NaOH and acetic acid were obtained from Merk, Germany. Chitosan was obtained from Sigma-Aldrich Company. Glycerin was made by Nima Gostar Chemical Industry Complex (NCIC). Phosphate buffer tablet (PBS) was purchased from Medicago AB Uppsala, Sweden.

A multi-wave ultrasonic generator (Bandeline MS 73), equipped with a converter/transducer and titanium oscillator, operating at 20 kHz with a maximum power output of 150 W was used for the ultrasonic irradiation. Room temperature magnetic properties were investigated via a vibrating sample magnetometer device, made by Meghnatis Kavir Kashan company (Iran) in an applied magnetic field sweeping between ±10000 Oe. Scanning electron microscopy images were obtained using a LEO instrument (model 1455VP). XRD patterns were recorded by a Philips, X-ray diffractometer using Ni-filtered CuKα radiation. FT-IR spectra were recorded on Galaxy series FTIR5000 spectrophotometer.

Preparation of barium hexaferrite nanoparticle by precipitation method

0.002 mol of barium nitrate and 0.024 mol of iron nitrate were dissolve in 200 ml of distilled water under ultrasonic waves (ultrasonic device) until it becomes completely homogeneous and the solution becomes uniform, then sodium hydroxide solution (1 M) was added slowly for 30 minutes until a brown sediment is formed. After that the solution was centrifuged 3 times at 4000 rpm and was washed with distilled water after each centrifugation step. Then the formed sediment was dried in environment temperature, after that the product was calcined at 850 ^{0}C for 2 hours.

Coating of barium hexaferrite with chitosan/ gelatin

To prepare the coating of nanoparticles, first specific weight of barium hexaferrite nanoparticles was dispersed in 50 ml of acetic acid (1wt%), then a specific amount of gelatin and chitosan as a coating agent was added. To improve the flexibility of pharmaceutical structures, 0.001 gr of glycerin was added to the solution.

Loading of sodium diclofenac

After coating the desired nanoparticles with

gelatin and chitosan, sodium diclofenac drug was loaded. For this purpose, 0.015 gr of sodium diclofenac was weighed and dissolved in 10 ml of distilled water and then was added to the solution containing nanoparticles coated with gelatin and chitosan. The solution was homogenized for three hours on a stirrer at temperature of 70 ^{0}C and then was dried in a sheet form on a petri dish at temperature of 50 ^{0}C. The composition of the prepared samples is given in the Table 1.

Calibration curve

In quantitative analysis, it is necessary to draw a calibration graph, which is a graph of absorbance values of standard samples according to their concentration. The calibration graph resulting from the concentration plot is not linear in all concentrations, but several factors cause the calibration graph to become linear only in a certain range and follow Beer's law. For this purpose, solutions of sodium diclofenac with different concentrations were prepared and their absorbance's were measured at the wavelength of 306 nm (λ_{max}).

Evaluation of drug samples

Determining the amount of drug release:

A certain amount of nanocomposite medicinal content was inserted in 50 ml of phosphate buffer (pH=7.4) at 37 ° C, and then the absorbance of the solution was measured by a spectrophotometer at 306 nm in a certain period of time. Using the standard absorption curve and the obtained equations, the concentration of drug in solution was calculated.

Water penetration rate

A nanocomposite sample with a specific cross section of 2 x 2 cm was inserted in 50 ml of phosphate buffer and its weight was measured

Table 1: The composition of prepared samples.

Sample	Hx_1	Hx_2	Hx_3	Hx_4
Diclofenac (gr)	0.015	0.015	0.015	0.015
Gelatin (gr)	0.4	0.4	0.4	0.4
Chitosan (gr)	0.1	0.1	0.1	0.1
Glycerin (gr)	0.001	0.001	0.001	0.001
$BaFe_{12}O_{19}$ (gr)	0.05	0.06	0.07	0.1

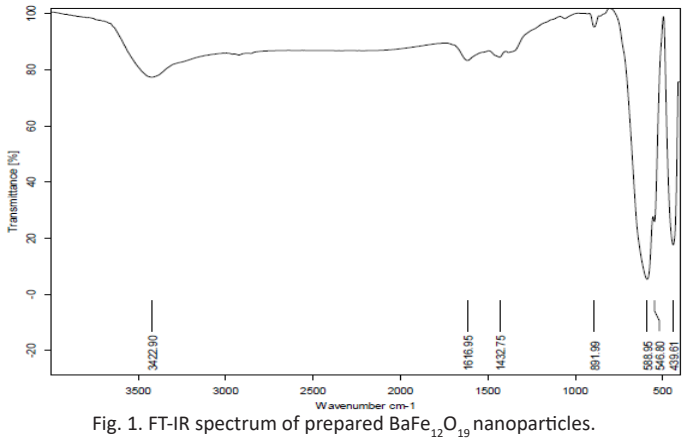

Fig. 1. FT-IR spectrum of prepared $BaFe_{12}O_{19}$ nanoparticles.

every 3 hours during 24 hours. The water penetration rate was evaluated by the equation (1):

$$V = \frac{1}{2\,\rho\,A} \times \frac{dw}{dt} \quad (1)$$

V represents the water penetration rate; dw/dt represents the slope of swelling versus time; ρ is the density of water and A is the cross-sectional area of the nanocomposites sample.

Swelling index

A specific amount of nanocomposites was immersed in 50 ml of phosphate buffer and after 24 hours, it was centrifuged at 1500 rpm and its weight was compared with the original weight according to the equation (2):

$$\text{Swelling index } (\%) = \frac{Wt - Wd}{wt} \times 100 \quad (2)$$

W_t is the weight of the hydrated nanocomposite at time t and W_d is the dry weight.

RESULTS AND DİSCUSSİON

Investigation of the FT-IR spectra of $BaFe_{12}O_{19}$

The FT-IR spectrum of $BaFe_{12}O_{19}$ in the range of 450-4000 cm^{-1} is shown in Fig. 1. The observed

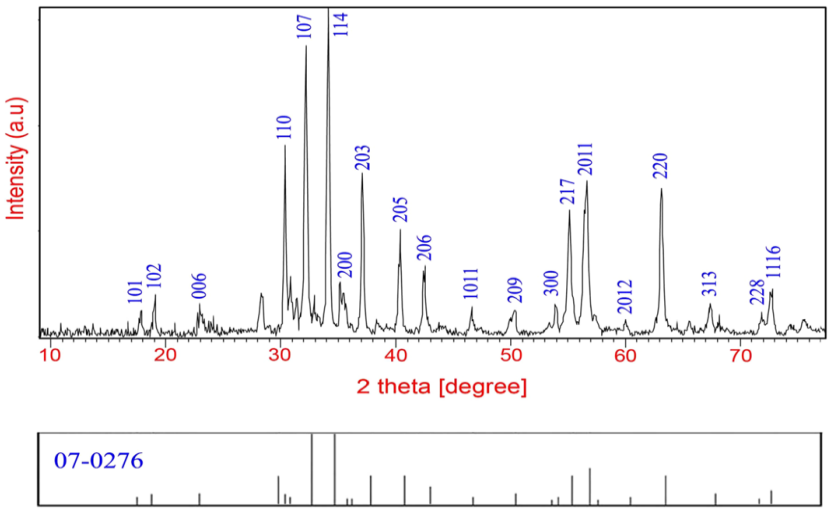

Fig. 2. The XRD pattern of BaFe12O19 nanoparticles.

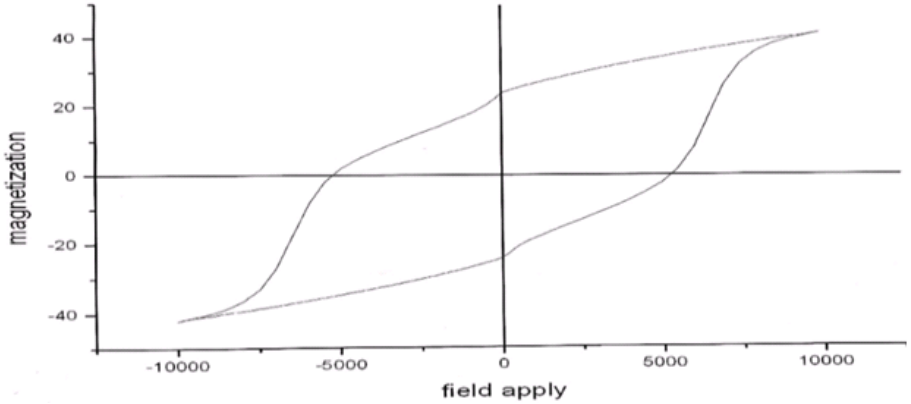

Fig. 3. The hysteresis diagram of the synthesized barium hexaferrite.

peaks at 588.95 cm^{-1} and 439.61 cm^{-1} are related to Ba-O and Fe-O bonds which can prove the synthesis of barium hexaferrite.

XRD pattern of $BaFe_{12}O_{19}$ nanoparticles

The XRD pattern of $BaFe_{12}O_{19}$ nanoparticles is shown in Fig. 2. Comparing the obtained XRD pattern with the reference (JCPDS No. 07-0276) confirms the formation of $BaFe_{12}O_{19}$ nanostructures. The Scherer's equation was employed to evaluate Crystallite size. The obtained crystallite size is about 34.5 nm.

Investigating the magnetic properties of $BaFe_{12}O_{19}$

Fig. 3 shows the hysteresis diagram of the synthesized barium hexaferrite. As it is clear from the magnetic properties of this sample, synthesis in aqueous environment and calcination show two

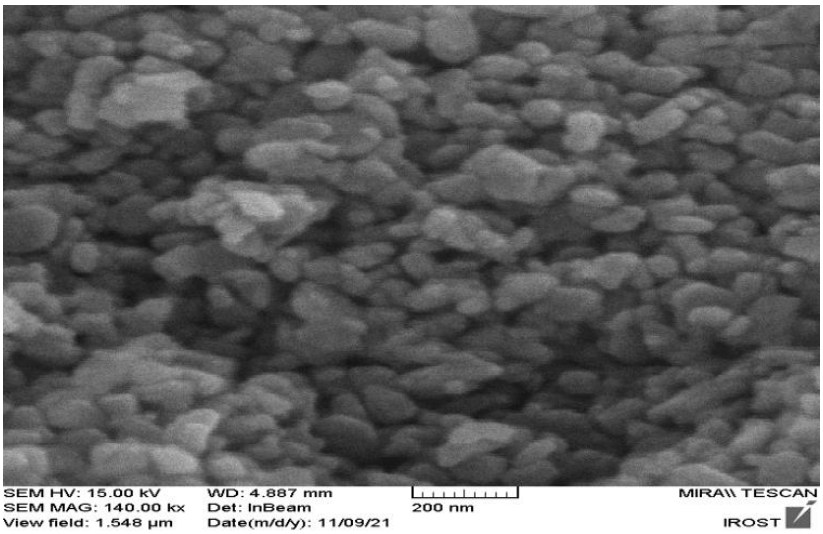

Fig. 4. SEM image of prepared barium hexaferrite nanoparticles.

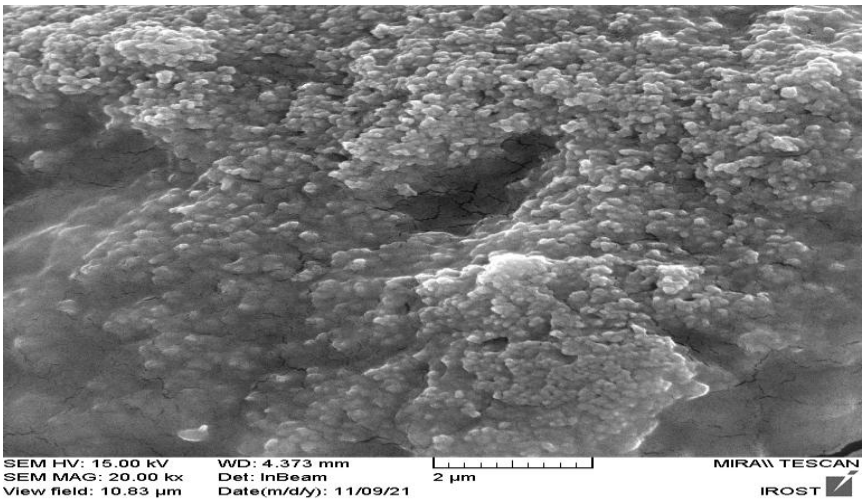

Fig. 5. SEM image of prepared chitosan /gelatin /$BaFe_{12}O_{19}$ nanocomposite.

important quantities of saturation magnetism and magnetic coercive force, which value of saturation magnetism is 43 emu/g and value of coercive force is 5825 orstet.

SEM images of prepared barium hexaferrite nanoparticles and polymeric nanocomposites

As it is clear from Fig. 4, the average size of barium hexaferrite nanoparticles is below 100

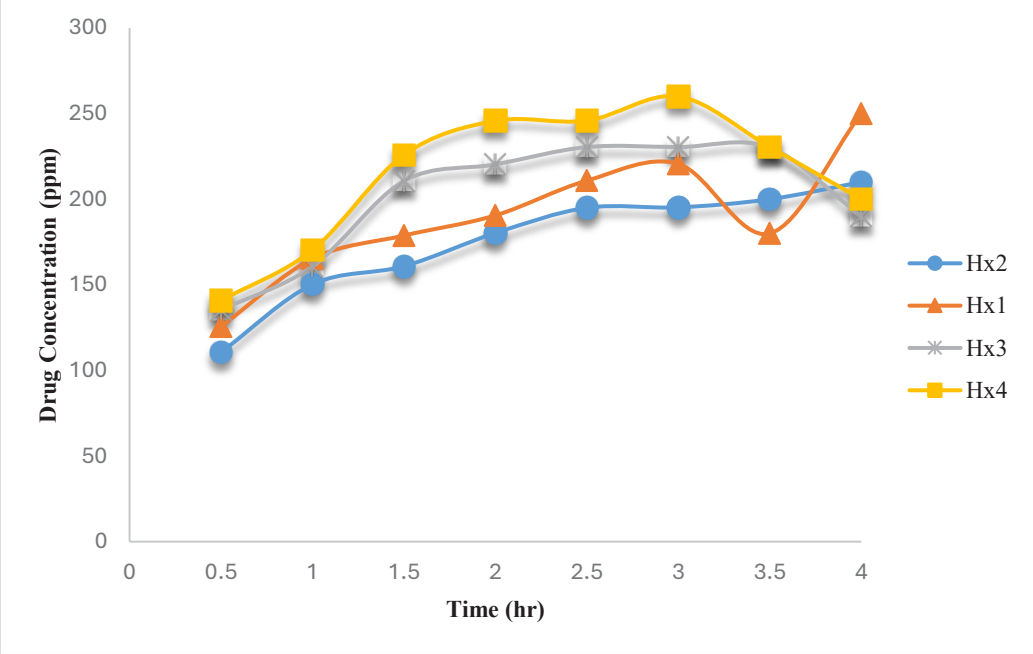

Fig. 6. Drug release profile of prepared nanocomposites samples.

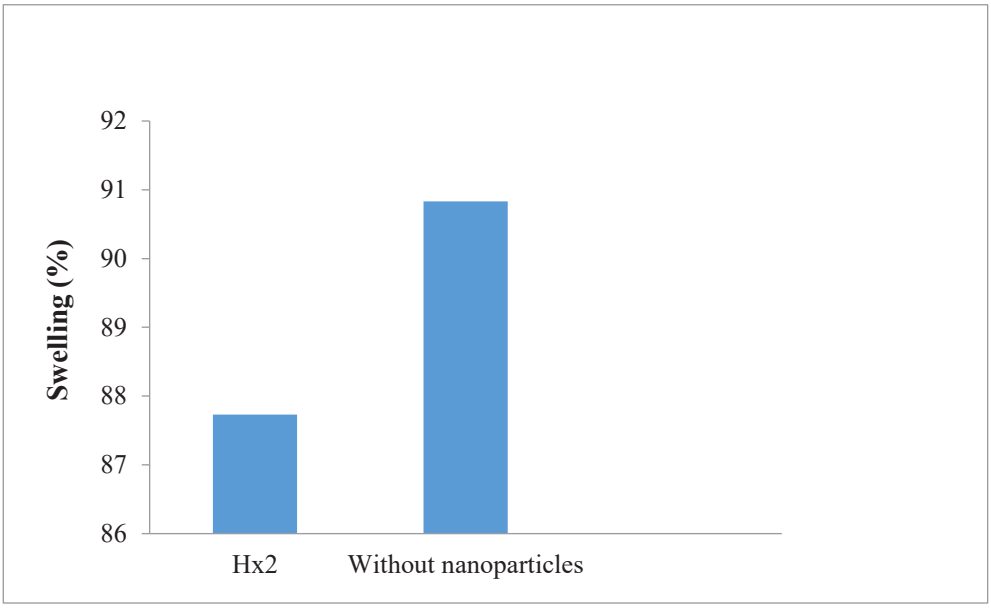

Fig. 7. The swelling of prepared samples.

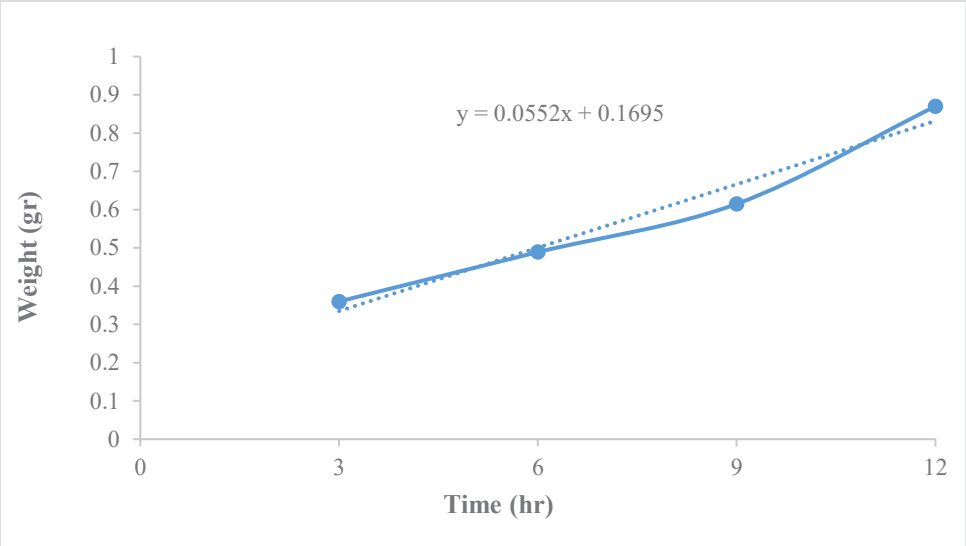

Fig. 8. The weight of hydrated samples according to time.

nm, and the sphericity and proper distribution of nanoparticles can be clearly.

Also, the loading of barium hexaferrite nanoparticles with an average size below 100 nanometers in a uniform and dispersed manner in the polymer matrix (chitosan/ gelatin) can be seen in Fig. 5.

Measurement of drug release

Barium hexaferrite nanoparticles have magnetic properties, which helps in the controlled drug delivery and drug release. The optimal amount of barium hexaferrite nanoparticles is Hx2 (Fig. 6). The results show that in the Hx4 and Hx3 samples, no release was done after 3 hours, and the nanocomposite structure lost its cohesion after this period.

Swelling Investigation

In order to test the swelling index, the weight of samples in phosphate buffer after 24 hours was measured. According to the data (Fig. 7), in the comparison between the polymer without nanoparticles and in the presence of nanoparticles, barium hexaferrite nanocomposite have lower swelling index. Thus, fewer amounts of water could penetrate inside the structure, which led to the release of fewer amounts of water-soluble diclofenac [15].

Water penetration rate

A certain amount of the prepared drug structures in dimensions of 2 × 2 cm was weighed and placed in phosphate buffer. According to the equation 1, water penetration rates were obtained. The results are shown in Fig. 8. According to the diagram, the weight of the nanocomposites was taken every 3 hours, and the obtained swelling results were used to calculate the Water penetration rate. The water penetration rate for the optimal nanocomposite sample (Hx2) was calculated as 0.68 m/s.

CONCLUSION

The design and synthesis of an optimized nanocarrier for use in drug delivery is of particular importance. In this research barium hexaferrite nanoparticles was prepared by co-precipitation method and its properties was analyzed using SEM, XRD pattern, FT-IR and VSM. Also, a simple, repeatable and practical method was used to measure the release of diclofenac in the presence of $BaFe_{12}O_{19}$ nanoparticles, and as a result, the drug was released slowly in a certain period of time. Chitosan and gelatin are abundant biopolymers that are used as suitable drug carriers for drug release due to their characteristics such as biocompatibility, biodegradability and as a suitable coating for drug preservation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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