DEVELOPMENT AND EVALUATION OF TIZANIDINE HYDROCHLORIDE LOADED SOLID LIPID NANO PARTICLES

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ABSTRACT

Objectives: The primary objective of the present study is to develop and evaluate tizanidine hydrochloride (TZ) solid lipid nanoparticles (SLNs) using solid lipids/triglycerides.

Methods: TZ SLNs were prepared by hot homogenization followed by ultrasonication technique. The prepared SLNs were characterized for drug content, entrapment and loading efficiency, particle size, zeta potential, polydispersity index (PDI), and in vitro release kinetics.

Results: TZ SLNs were prepared. The particle size ranged from 49.7 to 523.7 nm. PDI of all formulations was good within the range of 0.189–0.487. The zeta potential of blank SLNs was −15.2 mV whereas drug-loaded SLNs showed zeta potential from −8.85 mV to −42.0 mV. Entrapment efficiency observed was in the range of 34.5–75.0%. The cumulative percentage release of TZ from different TZ nanoparticles varied from 35.28% to 83.98% depending on the drug-lipid ratio and the type of lipid and surfactant used. The release kinetic studies of optimized formulation showed that the release was first order and the release mechanism was non-Fickian type.

Conclusion: The prepared SLNs were able to sustain the drug release for 24 h, thus reducing dosing frequency and occurrence of side effects, thereby increasing the effectiveness of the drug.

INTRODUCTION

Most of the people prefer oral route of administration as the major route of administration of pharmaceuticals having the advantage of being pain-free, convenient to handle, and noninvasive [1]. However, the oral dosage form has several disadvantages. To overcome the disadvantages of the oral route of administration, many new powerful drug substances have been found due to new technologies employed in drug discovery. Solid lipid nanoparticles (SLNs) are the novel drug delivery system in which the active drug is incorporated into lipid carriers with the help of the stabilizers. They are solid colloids having the size in nanometers that range from 10 to 1000 nm at least in one dimension (generally 50–500 nm) [2]. SLNs combine the advantages of and simultaneously avoid the limitations of polymeric nanoparticles, fat emulsions, and liposomes [3].

Spasticity or increased tone is the tightness that patients report with passive movement of the limb. In more scientific language, spasticity is a motor disorder characterized by a velocity-dependent increase in the tonic stretch reflex [4]. Tizanidine is an agonist at α2-adrenergic receptor sites and presumably reduces spasticity by increasing presynaptic inhibition of motor neurons [5]. It acts mainly at the spinal cord level and is used for the symptomatic relief of spasticity associated with spinal cord injury or diseases or multiple sclerosis [6]. In the present study, we aim to develop tizanidine hydrochloride (TZ) loaded SLNs, which sustains the drug release thereby increasing the efficiency of the treatment.

MATERIALS AND METHODS

Materials
TZ was procured from the Swapnroop drug and pharmaceuticals, Ahmadabad. Tristearin (TS) was purchased from Sasol, Germany. Compritol 888 (CM) was obtained from Gattefosse, France. Glyceryl monostearate (GMS) was purchased from Research Lab Fine Chem Industries, Mumbai. Methanol, tween 80 (TW) and chloroform were purchased from SD Fine Chem Limited, Bengaluru. Soy lecithin (SL) and poloxamer 188 (PL) were obtained from Himedia Laboratories Pvt. Ltd, Bengaluru. All the reagents used were of analytical grade.

Methods

Determination of λmax of TZ in phosphate buffer of pH 7.4
Accurately weighed the quantity of 10 mg of TZ was taken in 100 ml volumetric flask and was dissolved using phosphate buffer of pH 7.4 and the volume was made up to 100 ml with phosphate buffer of pH 7.4 to produce 100 µg/ml solutions. From the above stock solution, 10 µg/ml solutions were prepared and scanned between 200 nm and 400 nm by keeping phosphate buffer of pH 7.4 as blank [7]. The absorption maxima of 320 nm for TZ was obtained and used for further studies.

Preparation of calibration curve in phosphate buffer of pH-7.4
Accurately weighed quantity of 10 mg of TZ was taken in 100 ml volumetric flask and was dissolved in phosphate buffer of pH-7.4. Finally, the volume is made up to 100 ml with phosphate buffer of pH-7.4 to produce 100 µg/ml solutions (stock solution-I). 0.2, 0.4, 0.6, 0.8, 1.0, and 1.2 ml of stock solution-I were taken and transferred to 10 ml volumetric flasks, and volume was made up to 10 ml using phosphate buffer of pH-7.4 to get 2, 4, 6, 8, 10, and 12 µg/ml solutions, respectively. The absorbance of these solutions was determined in ultraviolet (UV)-spectrophotometer at 320 nm, and the calibration curve was plotted [8].

Preparation of SLNs with TZ using lipids (CM, TS, and GMS)
SLNs were prepared using lipids (CM, TS, and GMS) and surfactants (TW and PL). Lipid was first melted by heating in a boiling tube and then SL

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surfactant (PL/TW) was dissolved in water in a test tube and heated to a temperature equal to that of the lipid phase. This aqueous phase was transferred to the lipid phase in small quantities by continuous homogenization. This mixture was homogenized at 20,000 rpm for 5 min and then immediately placed in probe ultrasonicator at 75% amplitude for 30 min. Blank nanoparticles were prepared in a similar manner omitting the TZ in the preparation [9]. The composition of all formulations is listed in Table 1.

**Table 1:** Composition of TZ loaded SLNs containing different lipids and surfactants

| Formulation code | Formulation no. | TZ mg | CM mg | TS mg | GMS mg | PL mg | SL mg | DW ml |
|------------------|----------------|-------|-------|-------|--------|-------|-------|-------|
| TZ-SLN-CM-TW 0.75 | F 1           | 10    | 50    | -     | -      | 25    | -     | 25    | 10    |
| TZ-SLN-CM-PL 0.75 | F 2           | 10    | 50    | -     | -      | 25    | -     | 25    | 10    |
| TZ-SLN-CM-TW 0.75 | F 3           | 10    | 100   | -     | -      | 50    | -     | 50    | 10    |
| TZ-SLN-CM-TW 0.75 | F 4           | 10    | 200   | -     | -      | 100   | -     | 100   | 10    |
| TZ-SLN-CM-TW 0.75 | F 5           | 10    | 150   | -     | -      | 75    | -     | 75    | 10    |
| TZ-SLN-CM-PL 0.75 | F 6           | 10    | 150   | -     | -      | 75    | -     | 75    | 10    |
| TZ-SLN-TS-TW 0.75 | F 7           | 10    | -     | 150   | -      | 75    | -     | 75    | 10    |
| TZ-SLN-TS-PL 0.75 | F 8           | 10    | -     | 150   | -      | 75    | -     | 75    | 10    |
| TZ-SLN-GMS-TW 0.75 | F 9           | 10    | -     | 150   | -      | 75    | -     | 75    | 10    |
| TZ-SLN-GMS-PL 0.75 | F 10          | 10    | -     | 150   | -      | 75    | -     | 75    | 10    |
| TZ-SLN-NS-PL 0.75 | F 11          | -     | -     | 150   | -      | 75    | -     | 75    | 10    |

*F 1 is a blank formulation. TZ: Tizanidine hydrochloride, CM: Compritol, TS: Tristearin, GMS: Glycerol monostearate, TW: Tween, PL: Poloxamer, SL: Soy lecithin

**Evaluation of TZ SLNs**

**Fourier-transform infrared spectroscopy (FTIR)**

Drug-polymer interactions were studied by FTIR spectroscopy. Pure drug, excipients, and physical mixture of drug and excipients were subjected to FTIR studies. The spectra were recorded by scanning in the wavelength of 400–4000 cm⁻¹ in an FTIR spectrophotometer [10].

**Differential scanning calorimetry (DSC)**

The melting point of the pure drug and the compatibility of the drug with the lipids were studied by the DSC [11]. It was performed using Shimadzu DSC-60 by keeping the samples in aluminum crucibles.

**In vitro drug release study**

In vitro drug release studies were carried out in Franz diffusion cell. 2 ml of nanoparticles dispersion was placed in donor compartment, while the receiver compartment consists of 22 ml of diffusion medium, phosphate buffer pH of 7.4 maintained at 37±1°C in Franz diffusion cell. The rpm of the magnetic bead was maintained at 50 rpm. 2 ml of the sample was withdrawn at predetermined intervals, and the samples were analyzed for the drug content by UV-spectrophotometer at 320 nm. An equal volume of the diffusion medium was replaced in the receiver compartment after each withdrawal to maintain sink condition. Three trials were carried out for all formulations. From the data obtained, the percentage cumulative drug release was calculated and plotted against the function of time to study the pattern of drug release [11].

**Drug content**

About 0.2 ml of drug-loaded SLNs was added into 5 ml of methanol in the centrifuge tube. The solution was vortexed for 10 min and then centrifuged at 5000 rpm for 30 min. The supernatant was collected. The drug content in the supernatant was analyzed by UV-spectrophotometer for TZ at 319 nm [11].

Drug content was calculated using the following formula.

\[
\text{% Drug content} = \frac{\text{Practical amount of drug obtained}}{\text{Theoretical amount of drug}} \times 100
\]

**Percentage drug entrapment efficiency**

About 2 ml of SLNs loaded with TZ was placed in the outer chamber of the Centriscart device, and the sample recovery chamber was placed nearby. About 2 ml of nanoparticles dispersion was placed in donor compartment, and the sample recovery chamber was placed in Franz diffusion cell. The rpm of the magnetic bead was maintained at 50 rpm. 2 ml of the sample was withdrawn at predetermined intervals, and the samples were analyzed for the drug content by UV-spectrophotometer at 320 nm. An equal volume of the diffusion medium was replaced in the receiver compartment after each withdrawal to maintain sink condition. Three trials were carried out for all formulations. From the data obtained, the percentage cumulative drug release was calculated and plotted against the function of time to study the pattern of drug release [11].

**Table 2:** Interpretation of Fourier-transform infrared spectroscopy studies

| Compound Name | Type of vibration | Characteristic absorption (cm⁻¹) | Observed peak (cm⁻¹) |
|---------------|------------------|---------------------------------|---------------------|
| TZ            | Secondary amine N-H stretch | 3100–3500 | 3246.31 |
|               | Aromatic C-H stretch | 3000–3100 | 3074.63 |
|               | C=C aromatic ring stretch | 1600 and 1475 | 1606.76 and 1473.66 |
|               | Secondary amine C-N stretch | 1100–1300 | 1188.19 |
|               | Aromatic C=O stretch | 1035–1100 | 1068.6 |
|               | Ring bending | Strong peak near 700 | 709.83 |
| TZ and tristearin | Secondary amine N-H stretch | 3100–3500 | 3246.31 |
|               | Aromatic C-H stretch | 3000–3100 | 3074.63 |
|               | C=C aromatic ring stretch | 1600 and 1475 | 1606.76 and 1469.81 |
|               | Secondary amine C-N stretch | 1100–1300 | 1192.05 |
|               | Aromatic C=O stretch | 1035–1100 | 1068.6 |
|               | Ring bending | Strong peak near 700 | 711.76 |
| TZ and glyceryl monostearate | Secondary amine N-H stretch | 3100–3500 | 3246.31 |
|               | Aromatic C-H stretch | 3000–3100 | 3074.63 |
|               | C=C aromatic ring stretch | 1600 and 1475 | 1606.76 and 1471.74 |
|               | Secondary amine C-N stretch | 1100–1300 | 1182.4 |
|               | Aromatic C=O stretch | 1035–1100 | 1068.6 |
|               | Ring bending | Strong peak near 700 | 709.83 |

TZ: Tizanidine hydrochloride
Fig. 1: Fourier-transform infrared spectroscopy spectra of (a) tizanidine hydrochloride, (b) physical mixture of drug and Compritol, (c) physical mixture of drug and tristearin, (d) physical mixture of drug and glyceryl monostearate

on the top of the sample. The unit was centrifuged at 5000 rpm for 20 min. The SLNs along with the encapsulated drug remained in the outer chamber, and the aqueous phase was moved into the sample recovery chamber through filter membrane (molecular weight cutoff 20,000 Daltons). The resulting aqueous phase was analyzed by UV-spectrophotometer for TZ at 320 nm. The entrapment efficiency was calculated using the following relationship [12].

\[
\text{% Entrapment efficiency} = \frac{\text{Total amt of drug} - \text{amt of drug in aq. phase}}{\text{Total amt of drug}} \times 100
\]

**Particle size analysis**

The particle size was determined by dynamic light scattering (DLS), using a Malvern System, with vertically polarized light supplied by an argon-ion laser (Cyronics) operated at 40 mW. Experiments were performed at a temperature of 25.0±0.1°C at a measuring angle of 90° to the incident beam [13].

**Zeta potential**

Zeta potential was measured using Malvern Zetasizer. Nanoparticles were diluted with distilled water and placed in a clear disposable zeta cell at 25°C. The sample was subjected to three zeta runs to determine both size and potential [14].
Polydispersity index (PDI)
In light scattering, the term polydispersity and % polydispersity are derived from the PDI; a parameter calculated from a cumulants analysis of the DLS-measured intensity autocorrelation function. Particle size, zeta potential, and PDI are determined by the same instrument, i.e., Malvern Zetasizer [14].

Kinetic modeling of drug dissolution profiles [15]
The results of in vitro release profile obtained for all the formulations were plotted in models of data treatment and are as follows:
1. Zero-order kinetic model – cumulative % drug released versus time
2. First-order kinetic model – log cumulative percentage drug remaining versus time
3. Higuchi's model – cumulative percentage drug released versus square root of time

RESULTS AND DISCUSSION

Preformulation studies
Drug-polymer interaction study by FTIR spectrophotometer
The FTIR was performed for the drug (TZ), lipids (CM, TS, and GMS), and physical mixture of drug and lipids (TZ and CM, TZ and TS, and TZ and GMS). Fig. 1 shows the FTIR spectra of pure drug and the mixture of drug and lipids. Interpretation of the spectrum is shown in Table 2. The spectrum shows that there was no interaction between the drug and the lipid.

Table 3: Percentage of cumulative drug release of F_1–F_4 formulations (n=3)

| Time h | F_1 | F_2 | F_3 | F_4 |
|--------|-----|-----|-----|-----|
| 0.5    | 13.45±1.2 | 17.2±2.81 | 17.29±2.37 | 10.9±2.49 |
| 1.0    | 17.07±0.5 | 25.39±1.18 | 28.95±1.79 | 13.49±1.98 |
| 1.5    | 37.65±1.3 | 47.89±1.73 | 38.6±1.81 | 13.53±3.07 |
| 2.0    | 52.21±2.4 | 62.14±2.71 | 43.5±3.81 | 14.63±2.18 |
| 3.0    | 68.87±1.8 | 68.19±3.91 | 53.1±2.73 | 18.71±1.46 |
| 4.0    | 71.01±2.1 | - | 61.0±3.45 | 21.19±2.85 |
| 5.0    | - | - | 69.25±2.49 | 25.74±3.45 |
| 6.0    | - | - | 72.1±1.87 | 28.13±1.09 |
| 12.0   | - | - | - | 32.87±2.75 |
| 24.0   | - | - | - | 35.28±1.25 |

*F_1, F_2, F_3 formulations showed a decrease in % CDR after 4, 3, and 6 h of diffusion, respectively.

4. Korsmeyer equation/Peppas model – log cumulative percentage drug released versus log time.
Table 5: Entrapment efficiency and drug content of all formulations

| F. No. | Formulation code       | Amount of tizanidine hydrochloride | Entrapment efficiency (%) | The drug content in percentage |
|--------|------------------------|-----------------------------------|---------------------------|--------------------------------|
|        |                        | In aqueous phase (mg)              | In lipid phase (mg)       |                                |
| F₅     | TZ-SLN-CM-TW₂₅         | 6.55                              | 3.45                      | 34.50                          | 84.50                          |
| F₆     | TZ-SLN-CM-PL₂₅         | 6.18                              | 3.82                      | 38.20                          | 88.32                          |
| F₇     | TZ-SLN-CM-TW₆₀         | 6.42                              | 3.58                      | 35.80                          | 79.20                          |
| F₈     | TZ-SLN-CM-TW₇₅         | 4.35                              | 5.65                      | 56.50                          | 94.35                          |
| F₉     | TZ-SLN-CM-TW₇₅         | 2.88                              | 7.12                      | 71.20                          | 80.40                          |
| F₁₀    | TZ-SLN-CM-PL₅₀         | 3.42                              | 6.58                      | 65.80                          | 91.76                          |
| F₁₁    | TZ-SLN-TS-TW₂₅         | 3.18                              | 6.82                      | 68.20                          | 96.12                          |
| F₁₂    | TZ-SLN-TS-PL₂₅         | 2.77                              | 7.23                      | 72.50                          | 98.71                          |
| F₁₃    | TZ-SLN-GMS-TW₂₅        | 2.72                              | 7.28                      | 72.80                          | 97.49                          |
| F₁₄    | TZ-SLN-GMS-PL₂₅        | 2.50                              | 7.50                      | 75.00                          | 96.85                          |

TZ: Tizanidine hydrochloride, SLN: Solid lipid nanoparticle, GMS: Glyceryl monostearate, TW: Tween, PL: Poloxamer

DSC studies
The thermal measurement of pure TZ and physical mixture of TZ and CM, TZ and TS were carried out using DSC. The pure drug TZ showed a peak at 294.3°C. In a physical mixture of TZ and CM, TZ showed a peak at 289.47°C. In a physical mixture of TZ and TS, TZ showed a peak at 295.31°C. It shows that the drug is stable with different lipids at different conditions. (Fig. 2 shows the DSC curve of pure drug and the mixture of drug and TS).

Preparation of standard graph of TZ in phosphate buffer of pH-7.4
Calibration curve of TZ was determined using a phosphate buffer of pH 7.4 at 320 nm. The regression was found to be 0.9996 (Fig. 3 shows the standard graph).

Release studies
The drug release from the nanoparticles was studied by Franz diffusion method. The cumulative percentage release of TZ from different TZ nanoparticles varied from 35.28% to 83.98% depending on the drug, surfactant, and the type of lipid used. Tables 3 and 4 show the percentage of cumulative drug release of all the formulations.

The experiment showed that the drug release from F₁ to F₄ formulations was not sustained for 24 h and formulations containing 150 mg of lipid sustained the drug release for 24 h and showed maximum drug release.

Entrapment efficiency and drug content
The entrapment efficiency of TZ loaded SLNs was determined by measuring the concentration of un-entrapped drug in an aqueous medium by centrifugation method using Centrisart device. The formulations containing 150 mg of lipid showed good entrapment efficiency. Results of entrapment efficiency and drug content are mentioned in Table 5.

Table 4: Percentage of cumulative drug release of F₅–F₁₀ formulations for 24 h (n=3)

| Time in h | Percentage of cumulative drug release (%) |
|-----------|------------------------------------------|
| 0.5       | 9.63±1.56                                |
| 1.0       | 14.21±1.11                               |
| 1.5       | 18.25±0.85                               |
| 2.0       | 20.94±0.89                               |
| 3.0       | 27.30±1.30                               |
| 4.0       | 34.13±1.47                               |
| 5.0       | 41.55±1.19                               |
| 6.0       | 45.45±0.45                               |
| 12.0      | 61.21±1.51                               |
| 24.0      | 69.46±3.03                               |

*F₁₀ formulation showed the highest % CDR and F₅ formulation showed the lowest % CDR
Table 6: The particle size, polydispersity index, and zeta potential of the formulations

| Formulation No. | Formulation code | Particle size (nm) | PDI   | Zeta potential (mV) |
|-----------------|------------------|--------------------|-------|---------------------|
| F₁              | TZ-SLN-CM-TW₁₅   | 433.90             | 0.189 | -22.60              |
| F₂              | TZ-SLN-CM-PL₁₅   | 523.70             | 0.487 | -37.40              |
| F₃              | TZ-SLN-TS-TW₁₅   | 49.70              | 0.204 | -8.85               |
| F₄              | TZ-SLN-TS-PL₁₅   | 119.70             | 0.256 | -23.90              |
| F₅              | TZ-SLN-GMS-TW₁₅  | 97.67              | 0.278 | -30.70              |
| F₆              | TZ-SLN-GMS-PL₁₅  | 133.00             | 0.279 | -42.00              |
| F₇              | TZ-SLN-TS-PL₁₅   | 108.00             | 0.408 | -15.20              |

TZ: Tizanidine hydrochloride, SLN: Solid lipid nanoparticle, GMS: Glyceryl monostearate, TW: Tween, PL: Poloxamer

Table 7: The regression values of the tizanidine hydrochloride loaded SLNs

| Formulation No. | Formulation code | Regression factor | Peppas model |
|-----------------|------------------|-------------------|--------------|
|                 |                  | Zero-order | First-order | Higuchi model | R² | n value |
| F₁              | TZ-SLN-CM-TW₁₅   | 0.8095     | 0.9026     | 0.9463       | 0.9748 | 0.5493 |
| F₂              | TZ-SLN-CM-PL₁₅   | 0.7802     | 0.8917     | 0.9309       | 0.9692 | 0.4926 |
| F₃              | TZ-SLN-TS-TW₁₅   | 0.7341     | 0.8529     | 0.9036       | 0.9412 | 0.5699 |
| F₄              | TZ-SLN-TS-PL₁₅   | 0.862      | 0.9603     | 0.9724       | 0.9766 | 0.6277 |
| F₅              | TZ-SLN-GMS-TW₁₅  | 0.5712     | 0.6713     | 0.7823       | 0.8896 | 0.4279 |
| F₆              | TZ-SLN-GMS-PL₁₅  | 0.6701     | 0.7928     | 0.8473       | 0.939  | 0.4261 |

*R² is the regression factor. TZ: Tizanidine hydrochloride, SLNs: Solid lipid nanoparticles, GMS: Glyceryl monostearate, TW: Tween, PL: Poloxamer

Fig. 6: (a) Zero-order kinetics model of optimized formulation F₄, (b) first-order kinetics model of optimized formulation F₅, (c) Higuchi model of optimized formulation F₄, (d) Peppas model of optimized formulation F₅
Among 10 formulations, the % cumulative drug release of F_{1}, F_{2}, F_{3} and F_{4} formulations in 24 h was not remarkable, and the entrapment efficiency was found to be very low. Hence, these formulations are eliminated from further studies such as particle size analysis, zeta potential, PDI, and release kinetics.

**Characterization of nanoparticles**

**Particle size and zeta potential**

Particle size analysis of the TZ SLNs was performed by the Malvern System.

Zeta potential measures the charge on the particles. It allows prediction about the storage stability of colloidial dispersion because of repulsion between the particles. Malvern Zetasizer is the most widely used instrument for the measurement of zeta potential. Table 6 shows the particle size, PDI and zeta potential of F_{5–F_{10}} formulations including blank formulation. Figs. 4 and 5 show the particle size distribution and zeta potential of F_{6} formulation (optimized), respectively.

**Release kinetics**

Data obtained from in vitro release studies were fitted to various kinetic equations such as zero-order, first-order, Higuchi model, and Korsmeyer-Peppas model. A model processing of the in vitro release for F_{5–F_{10}} formulations is tabulated below. The regression values of the formulations are listed in Table 7. The kinetic models of F_{6} formulation are shown in Fig 6.

**CONCLUSION**

In this study, an attempt was made to formulate TZ SLNs using CM, TS, and GMS as carrier matrices, TW and PL as surfactants, SL as a stabilizer. FTIR and DSC studies were carried out to find out the possible interaction between the selected drug and lipids (CM, TS, and GMS). It revealed that there was no interaction between the selected drug and lipids.

TZ SLNs were prepared by hot homogenization technique. The method was able to produce nanoparticles of acceptable range and stability. All the formulations from F_{5} to F_{10} showed high entrapment efficiencies. SLNs were developed by taking three different types of lipids and with two different types of surfactants. Among all batches, in case of TZ_SLN_TS_CL, lipid and surfactant were optimized after considering their particle size, zeta potential, and in vitro drug release profile.

Size, PDI, and zeta potential of F_{5–F_{10}} formulations developed were in the acceptable and suitable range. The average entrapment efficiency of F_{5–F_{10}} formulations was found to be >70%. The release kinetics revealed that the drug release follows first-order kinetics. The release from TZ nanoparticles from the Korsmeyer-Peppas equation indicates that the release mechanism was non-Fickian. Based on the observations, it can be concluded that the formulated lipid nanoparticulate delivery system of TZ using widely accepted and physiologically safe lipids were capable of exhibiting sustained release properties for 24 h. They may be thus used to reduce the frequency of dosing, thereby minimizing the occurrence of side effects, improve bioavailability and increase the effectiveness of the drug.

**AUTHORS' CONTRIBUTIONS**

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

**CONFLICTS OF INTEREST**

There are no conflicts of interest.

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