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Research Article

Formulating and evaluating a gel that contains Eletriptan-loaded transferosomes

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Abstract

Transdermal-vesicular drug delivery systems offer various advantages over conventional drug delivery systems, such as bypassing first-pass metabolism, site-specific delivery, reduced dosing frequency, and more. The objective of the present research involves the formulation and in-vitro evaluation of Eletriptan transferosomal gel to reduce dosing frequency. Transferosomes act as vehicles for on-site drug delivery, and they are vesicular systems with a flexible membrane. By formulating this type, we can achieve a higher concentration at the site of action, thereby reducing dosing frequency.

Fourier-transform infrared spectra revealed that there was no interaction between the drug and excipients. Transferosomal formulations were prepared by the thin-film hydration technique and were incorporated into 1.5% Carbopol gel. From the results, Formulation code-ET6, containing Lecithin: Tween-80, has higher entrapment efficiency and maximum drug release, and is hence considered the optimized formulation. Stability studies performed for optimized transferosomal gel formulations indicate that the prepared transferosomal gel has more stability at a lower temperature.

The conclusion is that, based on the above data, it is confirmed that the prepared Eletriptan transferosomal gels can be considered as one of the promising approaches to reducing dosing frequency and maintaining drug concentration at the desired site for a longer time.

Keywords: Transdermal drug delivery, Eletriptan, Transferosomes, Thin Film Hydration Method, Carbopol gel.

INTRODUCTION

Transdermal drug delivery acts as a safe and effective way to deliver drugs to the site of action, thereby achieving localized action at lower concentrations for a longer duration by bypassing first-pass metabolism in the liver ¹. To attain an effective concentration at the site of action, overcoming the stratum corneum serves as the primary rate-limiting step. This can be achieved through either physicochemical change in the drug's properties or modifications in the vehicle for drug delivery ².

In the present study, a modification in the vehicle for drug delivery is chosen as the approach to achieving a higher drug concentration at the target site. Vesicular carriers such as liposomes, niosomes, transferosomes, ethosomes, etc., can be utilized as vehicles to transport drugs through the semi-permeable membrane, making permeation more flexible and therefore presenting a promising approach. According to research, among vesicular carriers, transferosomes, which are deformable vehicles, are gaining importance ³.

Getting into the history of transferosomes, the term 'transferosomes' is derived from the Latin word 'transfere,' meaning to carry across, and the Greek word 'soma,' meaning body. The term was first used by Gregor cevč in 1991 ⁴. These are elastic and flexible vesicles made up of

phosphatidylcholine (PC) and surfactants like sodium cholate, spans, and tweens, which act as edge activators (EAs). The property of the EAs is to make vesicles easily permeate through the membrane ⁵.

The drug of choice for the present study is Eletriptan. It is used for the treatment of migraine headaches and is a second-generation triptan drug developed by Pfizer Inc ⁶. The drug is well-absorbed after oral administration with a mean absolute bioavailability of approximately 50% and a half-life of 4-7 hours. The bioavailability of the drug is less due to extensive first-pass metabolism, so the amount of drug available during a migraine attack is less, and frequent oral dosing is necessary to achieve a therapeutic effect ⁷. Oral dosing of Eletriptan has side effects like nausea, feelings of tingling/numbness, weakness, tiredness, drowsiness, or dizziness. It is reported that Eletriptan causes a dose-dependent increase in serotonin levels leading to a very serious condition known as serotonin syndrome/serotonin toxicity ⁸.

Due to the above-cited drawbacks evident after oral administration of Eletriptan, in the present study, an attempt is made to deliver the drug through the transdermal route in the form of a nano vesicular carrier like transferosomes to overcome first-pass metabolism and achieve enhanced therapeutic action by increasing bioavailability with minimal side effects.

MATERIALS AND METHODS:

Materials

Drug-Eletriptan was procured from Chandra Labs Hyderabad, India. Phospholipid-Soya Lecithin from Bright Laboratories, Edge activator like Span 80, Tween 80 from Merck specialties pvt. Limited (Mumbai), Volatile Solvents-Methanol, Chloroform from S.D. Fine Chemicals, Mumbai. Gelling agent-Carbopol-934 was from Research lab fine chem. Industries (Mumbai). All reagents and chemicals used in experiment were of analytical grade.

Table 1: Formulation Table of Eletriptan Transferosomal Gel

Formulation Code	Drug (mg)	Lecithin (mg)	Span80 (mg)	Tween80 (mg)
ET1	20	95	5	--
ET2	20	90	10	--
ET3	20	85	15	--
ET4	20	95	--	5
ET5	20	90	--	10
ET6	20	85	--	15

Typically, the procedure for the thin film hydration method involves dissolving the prescribed amount of lipid, surfactant, and drug in a solvent. The content is then refluxed on a rotary flash evaporator under vacuum at 60 rpm for 1 hour at room temperature. Upon evaporation of the organic solvent, a thin film is deposited on the walls of the flask, which is subsequently hydrated using phosphate buffer saline (pH 6.8) on a rotary flash evaporator at 60 rpm for 15 minutes^{9,10}.

In the present work, lipid (lecithin), surfactant (span80/tween80), and the drug (Eletriptan) are dissolved in 5ml of organic solvent (Chloroform and Methanol mixture at a ratio of 3:1). The organic solvent is then removed on a rotary flash evaporator under vacuum. The deposited lipid film is hydrated with phosphate buffer (pH 6.8) by rotating at 60 rpm for 1 hour at room temperature. The resulting vesicles are set aside for 2 hours at room temperature to allow for the swelling of vesicles. The multilamellar lipid vesicles (MLV) are then sonicated using an ultrasonicator for 30 minutes^{9,10}.

Preparation of transferosomal gel:

Carbopol 934 (1.5 g) was weighed and dispersed in water with mild stirring, allowed to swell for 24 hours to obtain a 1.5% gel.

Untrapped drug was separated from the entrapped drug by centrifugation, and the obtained sediment was incorporated into the gel vehicle by slow mechanical mixing at 25 rpm for 10 minutes. The procedure for separating entrapped and untrapped drug involved taking the optimized formulation in a volumetric flask, diluting it up to 10 ml with pH 6.8 phosphate buffer, and centrifuging at 10,000 rpm for 2 hours at 4 °C. The obtained supernatant was decanted, and the sediment was then incorporated into the gel vehicle."

Evaluation of transferosomes:

Surface Morphology: Formulations were observed under microscope to confirm formation of vesicles.

Entrapment efficiency:

Spectral analysis

The spectral analysis of drug (Eletriptan), lipid (soya lecithin) and surfactants which were employed in the preparation of Eletriptan transferosomal gel were studied by Fourier Transform Infra- Red (FTIR) Spectroscopy to know the incompatibility.

Formulation of transferosomes containing Eletriptan

Using thin film hydration method six transferosomal gels of Eletriptan were prepared by varying the ratio of Phospholipid and surfactants as per the formulation Table-1.

Entrapment efficiency was determined by taking 5 mg equivalent of the optimized formulation in a volumetric flask and diluting it up to 10 ml with pH 6.8 phosphate buffer (PB). This mixture was transferred to Eppendorf tubes and ultracentrifuged at 10,000 rpm for 2 hours at 4 °C. The supernatant was carefully collected and filtered. The filtered sample was then diluted and analyzed by UV at 222 nm to determine the drug present in the supernatant. The entrapment efficiency of the drug is calculated using the following formula,

$$DEE = (WT - WF) / WT \times 100 \%$$

Where, DEE is the drug entrapment efficiency, WT is the total amount of drug in transferosomal gel, WF is the free amount of drug that was found in the supernatant^{9,11,12}.

Depending on entrapment efficiency, formulation was optimized.

Physicochemical evaluation of Eletriptan transferosomal gel

Appearance and homogeneity: The optimized formulation was visually evaluated for physical appearance and homogeneity.¹³

pH: The formulated product was checked for its pH using digital pH meter (JENWAY 350, UK) by diluting the optimized formulation in distilled water^{9,13}.

Determination of viscosity: Viscosity of optimized gel was determined using a Brookfield viscometer (model LVDV-II+PRO). The spindle number 64 was rotated at 15 rpm and experimentation was repeated thrice to get average viscosity value^{12,13}.

Spreadability: The spreadability of the optimized formulation was determined using the parallel plate method. In this method, the formulation is placed between glass plates with dimensions of 20 x 20 cm, and a weight of 250g is applied on the top for 1 minute. The diameter of the spread sample was then measured^{12,14}.

Estimation of drug content: One gram of optimized formulation was dissolved using methanol in volumetric flask

of 10ml and subsequent dilutions were made using 6.8 pH PB. Diluted sample was filtered and analyzed spectrophotometrically at 222nm¹⁵.

Extrudability: About 20g of gel was taken in collapsible tube of aluminium. The tube was pressed firmly to extrude the contents and was clamped so that there is no roll back of gel. The amount of gel extruded was weighed and grades were allotted (+++ Good; ++ Fair; + Poor)^{12,13}.

In-Vitro Drug Release Studies: Diffusion studies of transferosomal gel formulations were performed using a Franz diffusion cell. The volume of the receptor compartment was 50 ml, filled with pH 6.8 phosphate buffer (PB). A cellophane membrane, used for diffusion studies, was placed between the donor and receptor compartments. Gel formulations were uniformly applied to the membrane, and the donor and receptor compartments were clamped together. The buffer in the receptor compartment was continuously stirred at 50 rpm with a magnetic bead and maintained at a temperature of 37 °C. At predetermined time intervals, 5 ml samples from the receptor compartment were withdrawn using a syringe and replaced with an equal volume of buffer.

The withdrawn samples were filtered and analyzed after appropriate dilution at the λ max of 222 nm using a UV spectrophotometer^{9,16}.

Stability Studies: Stability studies were conducted by placing the optimized formulations in 10 g collapsible aluminum tubes and subjecting them to stability testing for one month at freezer temperature, as lipids are not stable at room temperature. A known amount of transferosomal gel was withdrawn at different time intervals (0, 1st, 2nd, 4th week) and analyzed for entrapment efficiency and drug content¹⁷.

RESULTS AND DISCUSSION

Spectral analysis:

Fourier-transform infrared spectrophotometer (FTIR) studies were conducted to verify any interaction between the pure drug (Figure 1) and the excipients (Figures 2, 3) used. The spectrum of the drug + excipients (Figure 4) shows no interaction, indicating the possibility for further studies.

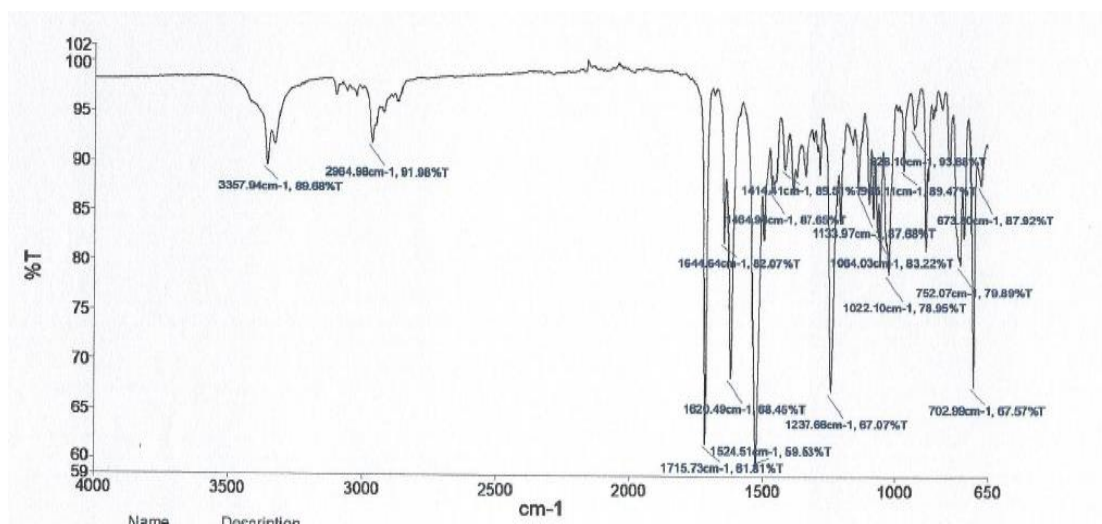


Figure 1: FTIR spectra of Eletriptan pure drug

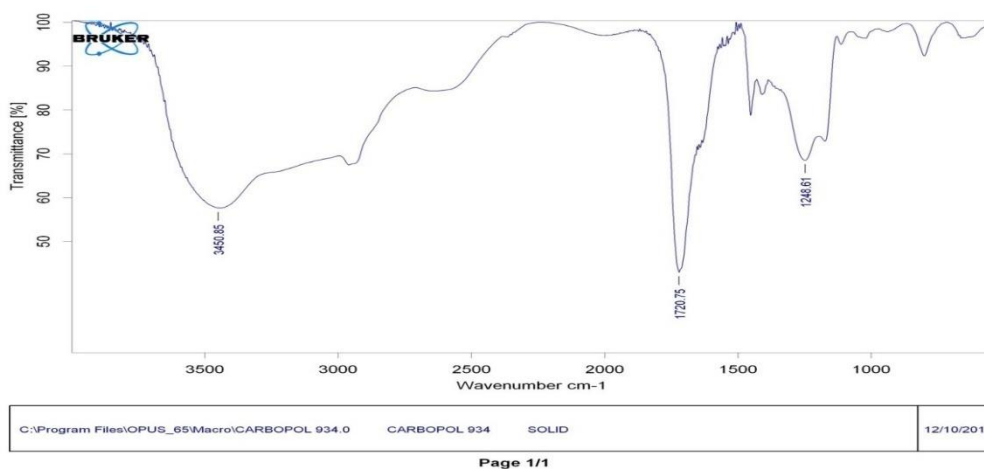


Figure 2: FTIR spectra of Carbapol 934

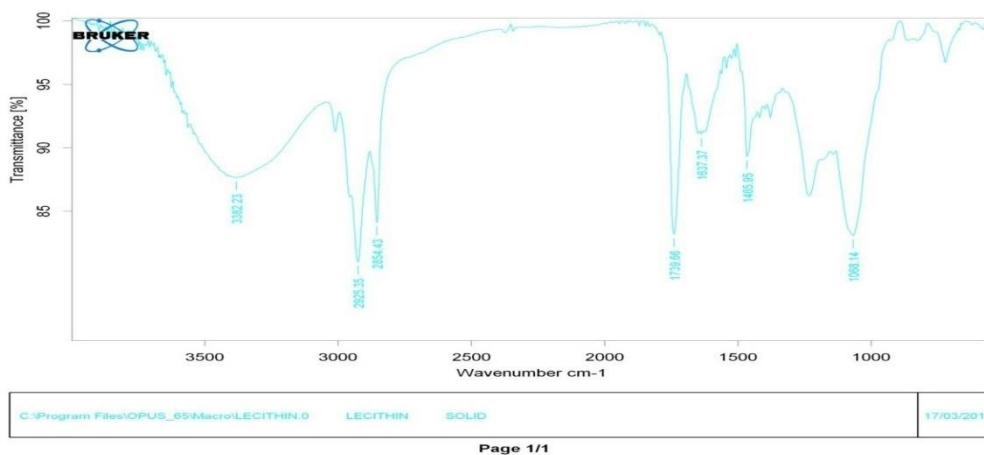


Figure 3: FTIR spectra of Soya Lecithin

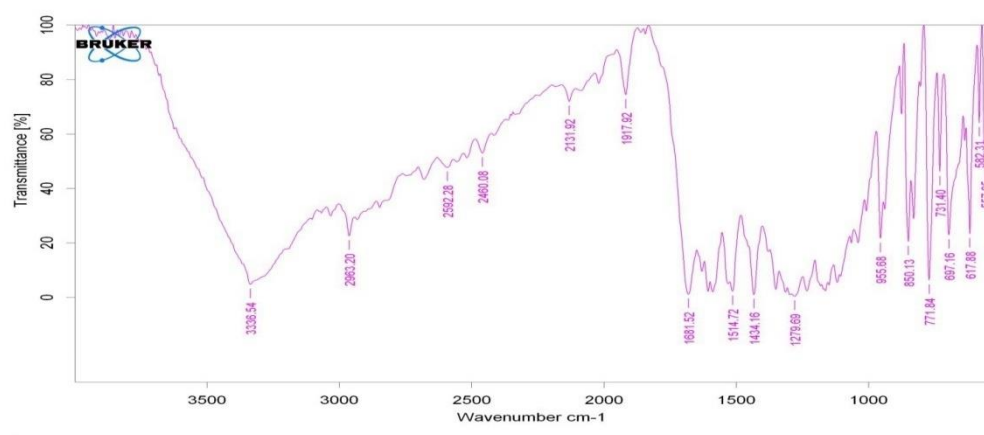


Figure 4: FTIR Spectra of optimized transfersome formulation

Surface Morphology:

Optical microscopy was performed to confirm the formation of vesicles, and it indeed confirmed vesicle formation, appearing in round shapes.

Entrapment efficiency (EE):

The % entrapment efficiency of deformable vesicles formulations were found to be in the range of 83.40 to 89.32 (Table 2). Entrapment efficiency of the ET6 formulation was high (maximum 89.32) which contains lecithin at 85%.

Table 2: Physicochemical Evaluation of Formulations

Formulation	% Entrapment Efficiency	% Drug content	pH	Homogeneity	Extrudability	Spreadability (g.cm/sec)	Viscosity (cps)
ET1	86.5	90.14	6.0	++	+++	3.3	3300
ET2	84.92	92.0	6.1	+++	+++	2.6	3560
ET3	87.11	90.81	6.2	+++	+++	3.1	4140
ET4	83.40	94.6	6.3	++	+++	3.5	3660
ET5	84.25	95.0	6.5	+++	+++	3.4	3710
ET6	89.32	95.07	6.4	+++	+++	3.3	3620

Note +++ Excellent, ++ Good, + Satisfactory, cps=centipoises

Physicochemical Evaluation of Gel Formulations

Visual appearance and homogeneity:

All the prepared gels of transfersomal formulations were spreadable, transparent, smooth, and homogenous with semisolid consistency.

pH

The pH of all prepared gels, as shown in Table 2, was found to be in the range of 6.0 to 6.5, which is considered ideal for transdermal formulations.

Viscosity

The viscosities for all the formulations, as indicated in Table 2, were found to be in the range of 3300-4100 cps.

Spreadability

Spreadability of all the formulations, as indicated in Table 2, were found to be in the range of 2.6 to 3.5.

Drug content

The % drug content of the transfersome formulations was determined, and the results obtained showed 90.14% to 95.07% drug content in the formulations (Table 2), indicating efficient drug loading.

Extrudability

Extrudability of optimized formulations was excellent, as depicted in Table 2.

In-Vitro Diffusion Studies

Optimization was achieved by selecting the in-vitro release of the drug as a critical parameter. The preparation of this system involved keeping the other variables constant. The results of the diffusion studies are presented in Table 3. In-vitro diffusion studies in phosphate buffer at pH 6.8 were conducted using a Franz diffusion cell following a specific procedure, and the results are illustrated in Figure 5.

Table 3: In-Vitro Drug Release of Transfersome Gel (ET1 to ET6 in %)

Time(hr.)	ET1	ET2	ET3	ET4	ET5	ET6
0	0	0	0	0	0	0
1	20.51	21.5	23.1	22.71	24.81	24.39
2	24.28	28.04	27.81	28.54	29.88	26.51
3	29.41	31.41	30.44	33.14	34.36	30.06
4	34.51	38.82	37.91	39.51	40.80	37.87
5	40.28	43.61	42.84	44.80	44.72	39.87
6	48.17	45.81	44.90	48.71	47.81	43.10
8	56.78	48.31	53.28	53.20	50.20	49.29
12	60.43	59.80	66.94	58.18	66.43	68.18
24	82	79.0	85.30	73.83	74.14	87.50

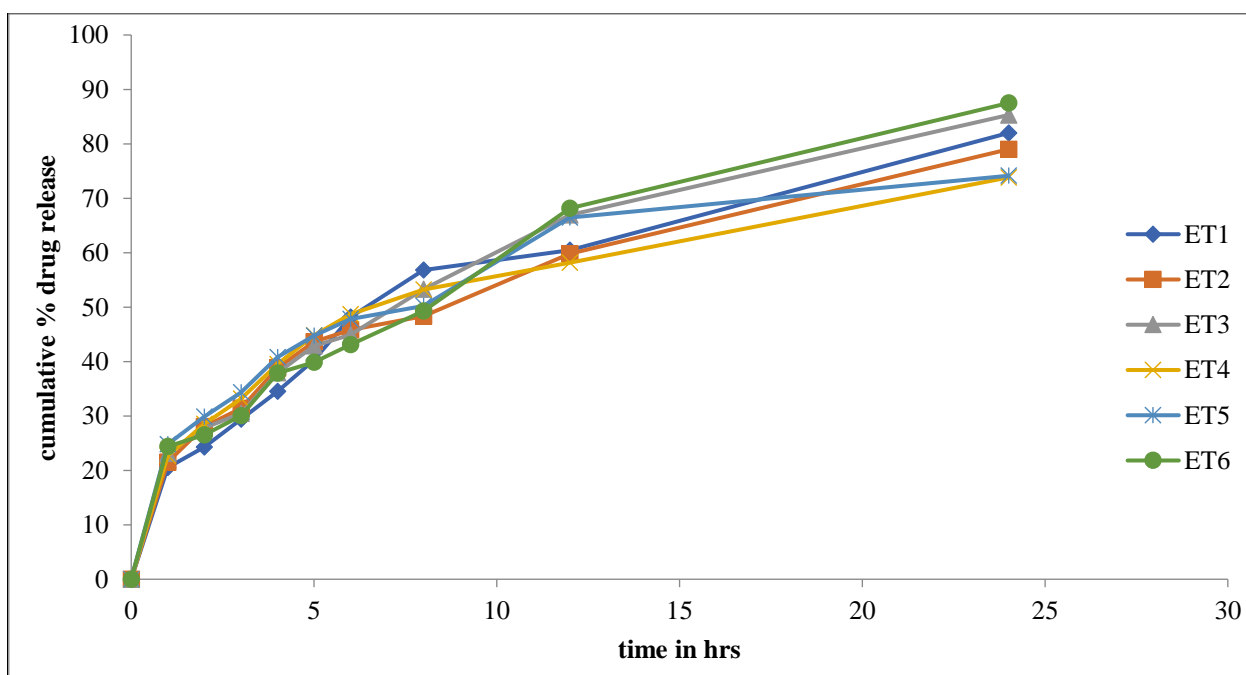


Figure 5: In-Vitro drug release study for transfersomal gel formulation ET1-ET6

Stability Studies

Stability studies were done on ET6 formulation at freezer temperature and there was no significant change observed in various parameters, Table 4.

Table 4: % Entrapment efficiency and % Drug content after stability studies (ET6)

Number of Days	% Entrapment Efficiency at temperatures			% Drug Content at temperatures		
	4±2°C	25±2°C	37±2°C	4±2°C	25±2°C	37±2°C
15	90.2	89.8	90.2	95.6	95.2	94.3
30	90.1	89.9	90.1	95.7	95.1	94.5
45	90.0	89.9	90.4	95.2	95.2	94.8
90	89.9	89.7	90.1	95.3	95.3	94.9

SUMMARY

The work aimed to prepare Eletriptan transferosome gel to achieve a sustained-release effect at the site of administration, thereby enhancing the concentration of the drug at the site of action and reducing the dosing frequency.

Pre-formulation studies, such as UV analysis of Eletriptan and FTIR, were conducted in compliance with BP standards. The FTIR spectra revealed no interaction between the drug and excipients.

Transferosome formulations were prepared using the thin film hydration technique and incorporated into a 1.5% Carbopol gel. Formulation ET6, containing Lecithin: Span-80, exhibited higher entrapment efficiency and maximum drug release.

Stability studies conducted on the optimized transferosomal gel formulations indicate that the prepared transferosomes have greater stability at freezing temperatures than at room temperature.

Based on the above data, it was confirmed that the prepared Eletriptan transferosomal gel (ET6) can be considered a promising approach to reducing dosing frequency and maintaining drug concentration at the desired site for a longer time.

CONCLUSION

From the results of the present study, it can be concluded that transferosome gel enhances transdermal delivery, prolongs release, and improves the site specificity of the drug Eletriptan. Transferosomes present a new opportunity for the well-controlled transdermal delivery of drugs that face challenges with administration via other routes.

In terms of future scope, the efficacy of the formulation needs to be validated through preclinical and clinical studies. Once proven effective, it can be utilized for the treatment of migraines, ensuring a therapeutic concentration at the site of action and reducing dosing frequency.

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Conflicts of interest

Authors declare there were no conflicts of interests.

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