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Formulation and Evaluation of Acyclovir - Loaded Emulgel for Topical Treatment of Viral Infections

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ABSTRACT

Acyclovir has low bioavailability mainly due to low solubility. This study aimed to formulate optimized acyclovir (ACV) emulgel for the slow, variable and incomplete oral drug absorption in a patient suffering from viral infection. The objective of study was to prepare the drug Acyclovir as emulgel. When we are preparing emulsions individually shows stability problems during manufacturing and storage that affect on drug release patterns. To increase the stability we are incorporated as emulgel. Emulgel is the most emerging and successful formulation to deliver hydrophobic drugs. It imbibes the properties of both gel and emulsion which results in enhancing the solubility of the hydrophobic drug to make the drug more bioavailable and enhances patient compliance as a topical drug delivery dosage form. The gel in formulations was prepared by dispersing Carbopol 934 separately in purified water with constant stirring at a moderate speed and then the pH was adjusted to 6.5 to 6.8 using Sodium hydroxide. The oil phase in the emulsion consists of liquid paraffin and span-20. The aqueous phase in the emulsion was prepared using Tween-20, propylene glycol and distilled water. The prepared emulgel were evaluated for their physical characteristic, Determination of pH, Washability, Extrudability study, Spreadability, Viscosity and *In-vitro* drug release studies. The appearance of prepared emulgel was white. The pH of the emulgel was found in the range of6.74 to 9.85. The *in vitro* drug release studies revealed that formulation F1-F6 showed the drug release at the end of 8 hrs. The drug release of the F3 formulation follows zero-order kinetics. The best formulation F3 showed better antiviral activity when compared with all formulations.

INTRODUCTION

Acyclovir (ACV) is a guanosine antiviral drug and is one of the antiviral drugs most commonly used for the treatment of herpes simplex virus infection, as well as varicella zoster (chickenpox) and herpes zoster (shingles). The topical application of ACV is limited by low transdermal penetration and poor solubility in water. Many strategies have been used to improve the therapeutic efficacy of ACV, including chemical modification, liposomes and nanoparticles. [1,2]ACV is slightly soluble in water, with solubility ranging from 1.2 to 1.6 mg/mL at room temperature[3] has relatively low oral bioavailability (10%–30%), has a short plasma half-life and is absorbed from the gastrointestinal tract via passive diffusion and by transporters but its absorption is slow, variable and incomplete. [4]

Dermal conveyance is an elective route however requires a suitable dosage form that guarantees profound skin penetration, permitting helpful impact at a particular site. Numerous broadly utilized topical preparations like ointments, and creams, have various disadvantages.[5,6] Semisolid preparations like ointments are normally sticky, making uneasiness to the patient when used topically. Additionally, they likewise have less spreading coefficient and need to apply with rubbing. They additionally display the issue of stability. Because of every one of these variables, inside the real gathering of semisolid dosage forms, the utilization of transparent gels has expanded both in beauty care products and pharmaceutical products.[7] A gel is a colloid that is normally 99% by weight fluid, which is immobilized by surface tension between it and a macromolecular system of strands worked from a little measure of a gelating substance. Despite numerous favorable circumstances of gels a noteworthy constraint is the incapability of transporting hydrophobic medications. To defeat this restriction an emulsion-based approach is being utilized so a hydrophobic moiety can be effectively fused and conveyed through gels.[8] Whenever gels and emulsions are consolidated together the dosage forms are specified as emulgels.[9]Because of the emulgel for have better application property in comparison to creams and ointments, gel formulations are superior topical formulations over any other topical formulations.[10]

Emulgels are considered to be an emerging field, but still, it isa less marketed product. This has made emulgels a fascinating and challenging dosage form to focus on. There are many advantages due to emulgel is considered being used as topical delivery.[11]

In this research, topical gel formulations of acyclovir were prepared using Carbopol-941 as water-soluble polymers. Gel formulations developed contain liquid paraffin and propylene

glycol as permeability enhancers.[12]The prepared emulgels were evaluated for physical appearance, FTIR studies, pH, viscosity, spreadability, extrudability and *in-vitro* drug release, studies. Our study aimed to develop a safe, effective and optimize emulgel formulation in the form of acyclovir emulgel for enhanced skin delivery of a model drug of antiviral, which was effective candidate for the treatment of viral infection.

MATERIALS AND METHODS

MATERIALS

Acyclovir was obtained as a gift sample from Macleods pharmaceuticals, Mumbai. Spans 20, tween 20 were purchased from SD Fine Chemicals Mumbai, India. Carbopol 941 was purchased from CDH Laboratories New Delhi, India. Liquid paraffin, propylene glycol, methyl parabens and propyl parabens extra pure were purchased from Hi-Media laboratories Mumbai, India. Double distilled water was prepared freshly and used whenever required. All other chemicals used in this study including those stated were of analytical reagent (A.R.) grade.

Methodology

Pre formulation study includes API characterization and a Standard graph.

API characterization

Organoleptic properties

Organoleptic properties the drug such as description, color, odour, taste of the drug were studied.

Fourier-Transform Infrared Spectroscopy (FTIR)

KBr pellet method

In the present study, the potassium bromide disc method was employed. The powdered sample was intimately mixed with dry powdered potassium bromide. Infrared spectrum is an important record that gives sufficient information about the structure of a compound. This technique provides a spectrum containing a large number of absorption band from which a wealth of information can be derived about the structure of an organic compound. The region from 0.8 μ to 2.5 μ is called Near Infra-red and that from 15 μ to 200 μ is called Far infra-red

region. Identification of Acyclovir was done by FTIR Spectroscopy concerning marker compound. Acyclovir was obtained as a white crystalline powder. It was identified from the result of IR spectrum as per specification. The IR spectrum of the sample drug shows the peak values which are characteristics of the drug and the graph were shown in Fig. 01.

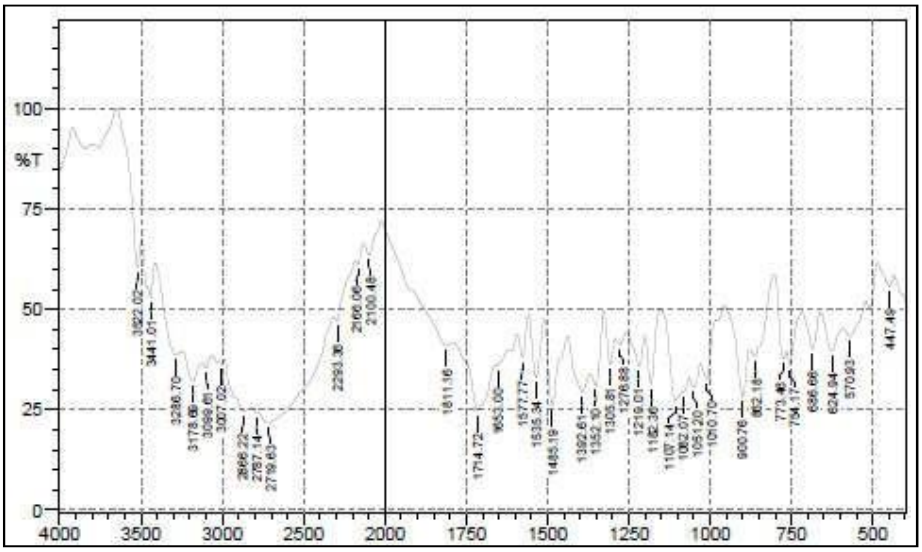

Figure 01: FT-IR Spectrum of the pure drug (Acyclovir)

METHODS

Formulation of emulsion either o/w or w/o

Oil phase

The oil phase was prepared by dissolving Span 20 in liquid paraffin in the different ratios given in Table 01.

Aqueous phase

the aqueous phase was prepared by dissolving Tween 20 in purified water.[13]1 gram of Acyclovir was dissolved in 5 ml of ethanol, while 0.15 g of methylparaben and 0.05 g of propylparaben were dissolved in 5 gm of propylene glycol and both were mixed with an aqueous phase. Both the oily and aqueous phases were separately heated to 70-80°C. Then, the oil phase was added to the aqueous phase with continuous stirring at 500 rpm until cooled to room temperature.

Preparation of carbopol gel

Fifty (50) grams of the carbopol gel was prepared by dispersing 1 gram of carbopol powder in 50 ml purified water with aid of a moderate speed stirrer (50 rpm), and then the pH was adjusted to 6.5-6.8 using 0.5 N of sodium hydroxide.[14]

Formulation of Acyclovir emulgel

Six formulations of Acyclovir were prepared by dispersing the obtained emulsions with the gel in a 1:1 ratio with gentle stirring until getting a homogenous emulgel.[11]The composition of different formulations was given in Table 01.

Table 01: Different formulations of Acyclovir emulgel (%w/w)

Formulation	Acyclovir (mg)	Carbomer 941	Liquid paraffin	Span 20	Tween 20	Propylene Glycol	Water (ml)
F1	500	0.5	10	2	1	5	Up to 100
F2	500	0.5	5	2	1	5	Up to 100
F3	500	1.0	10	4	1	5	Up to 100
F4	500	1.0	5	4	1	5	Up to 100
F5	500	1.5	10	2	1	5	Up to 100
F6	500	1.5	5	2	1	5	Up to 100

Determination of λ max of Acyclovir

The λmax of Acyclovir was determined by running the spectrum of drug solution in a double beam ultraviolet spectrophotometer. Accurately weighed 10 mg of drug was dissolved in 10 ml of ethyl alcohol in 10 ml of volumetric flask. The resulted solution 1000µg/ml and from this solution 1 ml pipette out and transfer into 10 ml volumetric flask and volume made up with 7.4 pH phosphate buffer solution prepare a suitable dilution to make it to a concentration range of 5-25 µg/ml. The spectrum of this solution was run in 200-400 nm range in the U.V. spectrophotometer (Labindia-3000+). The spectrum peak point graph of absorbance of Acyclovir versus wavelength.

Evaluation of emulgel

Physical Characteristic

The Physical Characteristic was checked for emulgel formulations (colour, clogging, homogeneity and texture) and observations were noted. [15]

Determination of pH

The pH of the emulgel was determined by digital pH meter. [16] One gram of gel was dissolved in 25 ml of distilled water and the electrode was then dipped into gel formulation for 30 min until the constant reading was obtained. And constant reading was noted. The measurements of pH of each formulation were replicated two times.

Washability

Formulations were applied on the skin and then ease and extent of washing with water were checked manually and observations were noted.

Extrudability study

The emulgel formulations were filled into collapsible metal tubes or aluminium collapsible tubes.[17]The tubes were pressed to extrude the material and the extrudability of the formulation was checked.

Spreadability

Two glass slides of standard dimensions (6×2) were selected. The emulgel formulation whose spreadability had to be determined was placed over one of the slides. The second slide was placed over the slide in such a way that the formulation was sandwiched between them across a length of 6 cms along the slide. 100 grams of weight was placed up on the upper slide so that the emulgel formulation between the two slides was traced uniformly to form a thin layer. The weight was removed and the excess of the emulgel formulation adhering to the slides was scrapped off. The lower slide was fixed on the board of the apparatus and one end of the upper slide was tied to a string to which a 20 gm load could be applied with the help of a simple pulley. The time taken for the upper slide to travel the distance of 6 cm and separate away from the lower slide under the direction of the weight was noted. The experiment was repeated and the average of 6 such determinations was calculated for each emulgel formulation.[18,19]

$$\text{Spreadability} = \frac{m.l}{t}$$

Where, S=Spreadability (gcm/sec)

m = weight tied to the upper slide (20 grams)

l= length of glass slide (6 cm).

t = time taken is seconds.

Viscosity

The measurement of the viscosity of the prepared gel was done using Brookfield digital Viscometer.[20] The viscosity was measured using spindle no. 6 at 10 rpm and 250 C. A sufficient quantity of gel was filled in an appropriate wide-mouth container. The gel was filled in the wide mouth container in such way that it should sufficiently allow to dip the spindle of the Viscometer. Samples of the gels were allowed to settle over 30 min at the constant temperature (25 ±/10 C) before the measurements.

Drug content

1 gm. of the prepared gel was mixed with 100 ml. of ethanol. Aliquots of different concentrations were prepared by suitable dilutions after filtering the stock solution and the absorbance was measured at 256 nm. The Percentage Drug content was calculated by linear regression analysis of the calibration curve shown in Table 02.

In-vitro drug release studies

Preparation of cellophane membrane for the diffusion studies

The cellophane membrane approximately 25 cm x 2cm was taken and washed in the running water. It was then soaked in distilled water for 24 hours before used for diffusion studies to remove glycerin present on it and was mounted on the diffusion cell for further studies.

Diffusion studies

The *in-vitro* diffusion of drug from the different gel preparations was studied using the classical standard cylindrical tube fabricated in the laboratory; a simple modification of the

cell is a glass tube of 15 mm internal diameter and 100 mm height. The diffusion cell membrane was applied with 1 gram of the formulation and was tied securely to one end of the tube, the other end kept open to ambient conditions which acted as donor compartment. The cell was inverted and immersed slightly in 250 ml of beaker containing neutralizing 7.4 pH phosphate buffer, freshly prepared as a receptor base and the system was maintained for 2 hrs at 37± 0. C. The media was stirred using magnetic stirrer. Aliquots, each of 5 ml volume were withdrawn periodically at the predetermined time interval of up to 4 hrs and replaced by an equal volume of the receptor medium. The aliquots were suitably diluted with the receptor medium and analyzed by UV-Vis spectrophotometer at 246 nm using neutralizing 7.4 pH phosphate buffer as blank.[21, 22]

Drug release kinetics study

The results of in-vitro release profile obtained for all the formulations were plotted in kinetic models as follows,

1. Cumulative of drug released versus time (zero-order kinetic model).

2. Log cumulative percent drug remaining to be absorbed versus time (First order model)

3. Cumulative amount of drug release versus square root of time (Higuchi model)

4. Log cumulative drug released versus log time (Korsmeyer-Peppas model)[23]

Release rate studies

Plot amount of drug permeated per square centimeter versus square root of time and calculate slope. Slope is release rate. Units - mg/cm2/hr1/2.

Permeation study

For the permeation studies locally fabricated modified Keshary - Chien diffusion cells with an area of 4.9 cm^2 and 20 ml receptor volume were used. The thawed rat skin was mounted onto diffusion cell such that the dermis side was in constant contact with receptor solution. 500 mg of gel was applied to the stratum corneum facing the donor compartment and the hydrodynamics in the receptor compartment were maintained by stirring on magnetic stirrer at 600 rpm. 1 ml sample was withdrawn at predetermined time intervals for 24 hours and drug content was analyzed by UV-VIS double beam spectrophotometer at 248 nm.

Calculation of permeability parameters

Parameters were calculated in this part of the study to compare the drug transfer and permeation properties among the tested formulae. Descriptions of these parameters include steady-state flux, permeability coefficient and enhancement ratio and lag time.

Steady state flux (@g/cm^2 /h)

Flux is defined as the rate of diffusion or transport of a substance through a permeable membrane. After reaching the steady state of drug permeation, flux was calculated.

Permeability coefficient (cm/hr)

The permeability coefficient (Kp) was calculated with the following equation:

$$Kp = JSS/ CV$$

Where 'CV' is the total donor concentration of the formulation 'JSS' is steady state flux

Enhancement ratio

Used to evaluate the effect of permeation enhancer on diffusion and permeation of selected drug molecules and is calculated by-

ER = Flux of drug with enhancer/ Flux of drug alone

RESULTS AND DISCUSSION

The IR spectrum of the sample drug shows the peak values which are characteristics of the drug and the graph were shown in Fig. 01. The λmax of Acyclovir was found to be 256 nm by running the spectrum of drug solution in double beam ultraviolet spectrophotometer in linearity range 5- 25µg/ml (Fig.02). The content of drug per 500 mg of emulgel ranged from 96.6 % to 98.8 % as given in Table 02, which indicates that efficient drug loading and uniform distribution of drug in the formulations. F3 (98.85 %) formulated using gelling agent and penetration enhancer propylene glycol in the concentration of 1% and 5% respectively has shown more drug content compared with other formulations. Emulgel formulations were white viscous creamy preparation with a smooth homogeneous texture and glossy appearance. All physical parameter results have been discussed in Table 03. The results of washability, extrudability and spreadability of all formulation were given in Table 04. From the result it was found that formulation F1-F6 has good washability ability, formulation F3,

F5 has good Extrudability and Spreadability of all formulation was found to in range of 11.45 to 13.65. The viscosity of the emulgel was obtained by using Brookfield digital viscometer. The viscosity of the formulations increases as the concentration of polymer increases and pH of prepared emulgel were measured by using pH meter (Orion Research, Inc., USA). The pH of the emulgel formulation was in the range of 6.74 to9.85 which considered acceptable to avoid the risk of skin irritation upon application to skin shown in Table 05. Optimized formulation F3 shows significantly improved in drug release rate as compare to marketed preparation. It was concluded that developed formulations deliver the drug for the treatment of viral infection (Table 06 and Fig 03). The kinetics of drug release from the optimized formulation (F3) was studied by mathematical modeling the drug release to zero order first order kinetics shown in Table 07.

Permeability parameters of optimized emulgels upon comparing the ratio of permeability of drug as shown in Table 08, The F3 formulation with Carbopol (1%) and liquid paraffin (10%) was optimized as it has shown high permeation and high skin deposition.

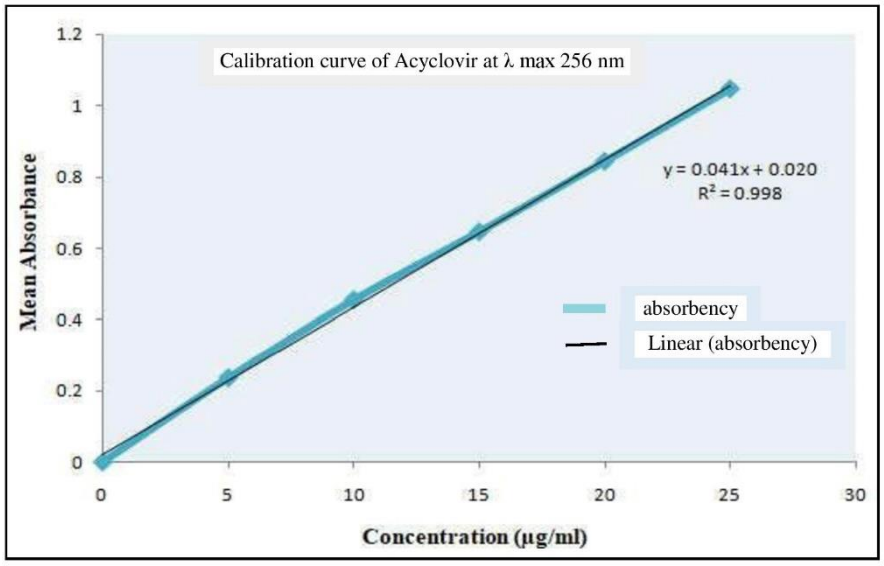

Figure 02: Calibration curve of Acyclovir at λ max 256 nm

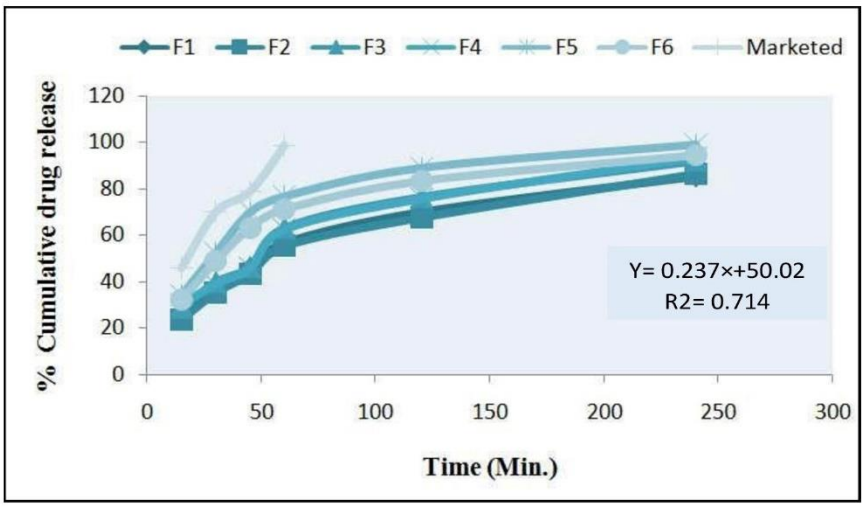

Figure 03: Cumulative% drug release of formulation F1-F6

Table 02: Results of % drug content of emulgel

Formulation	%Drug content
F1	96.65±0.25
F2	97.78±0.14
F3	98.85±0.32
F4	96.65±0.26
F5	99.74±0.15
F6	98.45±0.22

*All values expressed as Mean±SD, n=3

Table 03: Physical parameter of formulations

Formulation	Washability	Observation	Clogging	Homogeneity
F1	+++	White cream	Absent	Good
F2	+++	White cream	Absent	Good
F3	+++	White cream	Absent	Good
F4	+++	White cream	Absent	Good
F5	+++	White cream	Absent	Good
F6	+++	White cream	Present	Average

Note: Values are expressed as Mean ± SD, n = 3. Washability: +++ Excellent

Table 04: Result of washability extrudability and spreadability study

Formulation	Extrudability	Spreadability(gcm/sec)
F1	++	12.32±0.25
F2	++	11.45±0.36
F3	+++	13.36±0.42
F4	+++	12.14±0.21
F5	+++	13.65±0.15
F6	+	12.25±0.26

Note: Values are expressed as Mean ± SD, n = 3. Excellent:+++,Good:++,Average:+,Poor:-

Table 05: Results of viscosity and pH

Formulation	Viscosity(cps)	pH
F1	3456	6.98
F2	3485	6.92
F3	3675	9.85
F4	3695	6.74
F5	4258	6.82
F6	4262	6.75

Table 06: % Cumulative drug release of formulation F1-F6

S.No.	Time(min)	%Cumulative drug release						
		F1	F2	F3	F4	F5	F6	Marketed Formulation
0	0	0	0	0	0	0	0	0
1	15	24.45	23.65	28.85	29.98	34.45	32.25	45.65
2	30	36.65	35.45	39.98	38.85	52.56	48.85	69.98
3	45	45.58	43.32	46.65	45.65	69.98	63.32	78.85
4	60	56.65	55.45	63.32	62.23	76.65	71.14	98.74
5	120	69.98	67.78	76.65	75.52	88.85	83.32	-
6	240	85.45	86.65	92.23	93.35	98.85	94.45	-

Table 07: *In-vitro* drug release data for optimized formulation F3

S. No.	Time (min)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release ± SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	15	3.873	0.588	34.45	1.537	65.55	1.817
2	30	5.477	0.739	52.56	1.721	47.44	1.676
3	45	6.708	0.827	69.98	1.845	30.02	1.477
4	60	7.746	0.889	76.65	1.885	23.35	1.368
5	120	10.954	1.04	88.85	1.949	11.15	1.047
6	240	15.492	1.19	98.85	1.995	1.15	0.061

Note: Values are expressed as Mean ± SD, n = 3

Table 08: Permeability parameters of optimized emulgel

Permeability Parameters	F3	F5	F6
Q8 (g/cm^2)	308.45 ± 0.05	239.45 ± 0.02	213.45 ± 0.05
Flux (g/cm^2/hr)	37.29 ± 0.04	26.08 ± 0.01	28.08 ± 0.02
Permeability coefficient (cm/hr×10-3)	3.56 ± 0.04	2.40 ± 0.05	2.82 ± 0.05
Skin content (mg/g)	1.20 ± 0.01	2.38 ± 0.35	2.82 ± 0.54

Note: Values are expressed as Mean ± SD, n = 3

CONCLUSION

From the above results, we can conclude that the Acyclovir emulgel formulations prepared with carbopol- 941, light liquid paraffin, tween-20, span-20, and propylene glycol showed acceptable physical properties, % drug release, which remained unchanged upon storage for 3 months. However, the carbopol-941based emulgel in its low concentration with the formulation code F3 proved to be the formula of choice, since it showed the highest drug release for viral infection. *In-Vitro* studies indicated that the F3 formulated with Carbopol-

941 in the concentration of 1% and liquid paraffin as penetration enhancers has shown better release of acyclovir for 8 h with the flux of 37.29 ± 0.045g/cm2 /hr and Q8 of 308.45 5g/cm2. So, Acyclovir emulgel can be used as an antiviral medication for topical drug delivery.

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DECLARATION OF INTEREST

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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