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Article · December 2024

DOI: 10.22037/ijps.v19i4.43816

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Original Article

Preparation and Evaluation of Polymeric Nanofibers Containing Griseofulvin – Microemulsion by Electrospinning Process

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Abstract

In this study, the purpose of preparing CS/PVA nanofibers loaded GRF microemulsion is to increase the solubility of Low soluble drug griseofulvin by using microemulsion nanocarrier, and nanofiber was used as a technique for a new product. This drug is one of the antifungal drugs, and its uses are for skin diseases. Therefore, a topical route can be a good option. Chitosan /polyvinyl alcohol (CS/PVA) nanofiber containing griseofulvin (GRF) loaded microemulsion was obtained. The microemulsion comprised oleic acid and Transcutol P as the oil phase, Span20 and Labrasol as the surfactant, and Plurol oleique as the cosurfactant. Formulations were prepared with a ME(GRF): polymer ratio (30: 70) and (40: 60) and a polymeric solution containing chitosan (2%) and polyvinyl alcohol (10%) at two weight ratio (20: 80) and (10: 90), respectively. The physicochemical characteristics of the GRF-CS/PVA nanofibers were evaluated. The differential scanning calorimetry (DSC) study showed the amorphous state of the GRF-loaded microemulsions and PVA polymer embedded into the nanofibers. The entrapment efficiency percentage of GRF in the mats was approximately 66.67% - 88.89%. Drug release behavior showed controlled and slow release of drugs that are affected by the type of microemulsion formulation and the ratio of polymers used in nanofibers.

Keywords: Grisofulvin; Microemulsion; Electrospinning; Biodegradable polymers; Nanofiber.

1. Introduction

Griseofulvin is an antifungal agent produced from *Penicillium griseofulvum* in 1939 by Oxford *et al.* [1]. It is effective on Microsporum, Trichophyton, and Epidermophyton floccosum [2]. Griseofulvin is a selective drug for treating tinea capitis and tinea corporis [3, 4]. This drug has very poor water solubility and a variable bioavailability (25 to 70%), with numerous systemic side effects due to the long treatment period (two to several months) [5-8]. Due to the limitations associated with its oral tablet administration, the topical application seems more beneficial.

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Cite ths article as: Shariat Razavi F, Salimi A, *Preparation and evaluation of polymeric nanofibers containing griseofulvin –microemulsion by electrospinning process*, Iran. J. Pharm. Sci., 2023, 19 (4): 339-349.

DOI: https://doi.org/10.22037/ijps.v19i4.43816

In recent years, microemulsions (MEs) have been more often used for topical and transdermal applications [9]. Microemulsion systems are transparent, thermodynamically stable, and isotropic liquid mixtures of oil, water, surfactant, and co-surfactant. They have a 10-100 nm nano-size range and very low surface tension [10, 11]. Microemulsions can be a selective carrier for poorly water-soluble drugs such as griseofulvin [9, 12, 13].

Polymer nanofibers have gained attention due to their widespread use in various applications. Reducing polymer fiber diameter to the nanometer scale enhances surface-to-volume ratio [14], Changes in wetting behavior [15, 16], controlled release of drugs [17], high anisotropic electrical conductivity [18], and enhanced light scattering and photoluminescence [19]. Polymer nanofibers possess exceptional properties that make them the ideal candidates for numerous important applications. Experimental studies have shown that their size affects the mechanical and thermodynamic properties of nano-objects. This is evident in the elastic moduli of hollow fibers[20] and electrospun nanofibers[21, 22]. Various techniques, such as drawing, template synthesis, phase separation, self-assembly, and electrospinning, have recently been employed to fabricate polymer nanofibers.

Electrospinning (ES) is the technique that can produce continuous nanofibers from polymers, composites, and semiconductors. ES is a simple and versatile method for producing fibers with a diameter ranging from a few nanometers to several micrometers by applying vigorous electrical forces (1 to 30 kv) on the polymer solution or melt [23]. Electrospinning has recently been used to produce nanofiber from emulsions [24, 25]. The electrospinning of emulsions can produce composite nanofibers with nano-size drug particles surrounded by emulsifiers and distributed in a biocompatible nanofiber or biodegradable polymer. Microemulsion electrospinning can encapsulate applied materials in fibers as core-shell structures [26]. It has been reported that water-soluble drugs and proteins can be encapsulated in biodegradable polymer fibers by water-in-oil (W/O) emulsions for controlled release. Lipophilic compounds can also be added to electrospun fibers from oil-in-water (O/W) emulsions [27]. The properties of the composite nanofiber can be controlled by the type of polymer, emulsifier, drug used, solvent, and electrospinning process conditions [28].

In this study, the nanofibers with loaded GRF microemulsion were prepared. First, the phase titration method prepares the MEs (W/O) and incorporates them into electrospun nanofibers (CS/PVA). The process is based on the electrospinning of water in an oil microemulsion with two polymers, chitosan and polyvinyl alcohol (PVA). PVA was chosen because of its safety and biocompatibility [29], and its high molecular weight fulfills the requirement of electrospinnable materials [30, 31]. Additionally, PVA is often mixed with natural biopolymers such as chitosan, hyaluronic acid, and sodium alginate to overcome the electrospinning limitations or

add preferable properties to the resultant nanofibers [32-34]. Ultimately, the nanofibers were evaluated for entrapment efficiency, *in vitro* drug release, and the formation of a fibrous scaffold.

2. Materials and Methods

2.1. Materials

Griseofulvin (GRF) was obtained from Toliddaru Pharmaceutical Company (Iran). Oleic acid and span20 were purchased from Merck Chemical Company Germany), Caprylocaproyl macrogol glycerides (Labrasol), Diethylene glycol monoethyl ether (Transcutol P) and Plurol oleique were provided from GATTEFOSSE Company (France). Polyvinyl alcohol (average Mw 130000, 99+% hydrolyzed), chitosan (with a deacetylation degree of 97% and viscosity grade of <25 cps) was purchased from Primex (Siglufjordur, Iceland).

2.2. Phase diagram construction

Phase diagrams were supplied to define the range of concentration of the substances for the existing range of ME, and the two-phase diagrams were constructed with the 3:1 and 5:1 mass ratios of surfactant (Span20 and labrasol) to cosurfactant (Plurol oleique) (Smix) respectively. For preparing each phase diagram, the surfactant/cosurfactant blend was added into the oil phase (Oleic acid: Transcutol-P) (10:1) at the mass ratios of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1. The prepared mixtures were vigorously mixed using a magnetic stirrer and then diluted dropwise with double distilled water at 25°C. The production of a clear liquid appearance was considered as the basis for creating microemulsion (**Table 1)**.

Table 1: Formulas of the microemulsions prepared at different ratios of the Smix with different percentages of oil and water phases.

No. formulation	Smix Ratio (S/C)	Smix % w/w	Oil phase % w/w	Water phase % w/w
ME1	5:1	67	30	3
ME2	5:1	90	5	5
ME3	3:1	67	30	3
ME4	3:1	65	30	5

2.3. Preparation of GRF-loaded microemulsion systems

Four ME formulations with low and high levels of oil (5% and 30%), water (3% and 5%), and S/Co ratio (3:1 and 5:1) were determined for preparing MEs. Various MEs were prepared from the phase diagram with weight ratio surfactant: cosurfactant (3:1) and (5:1) of Span 20: Labrasol: Plurol oleique. (Table 1). GRF (0.2%) was added to the oil and Smix (surfactant and co-surfactant), stirred using a constant speed magnetic stirrer, and then diluted dropwise with double distilled water until a clear liquid was formed.

2.4. Characterization of microemulsion formulations

2.4.1. Measurement of droplet size and Zeta Potential

The droplet size of the ME samples was determined immediately with and without the drug at room temperature using SCATTER SCOPE 1 QUIDIX (South Korea). Directly and with no sample dilution .Also, the zeta potential

of the ME samples was determined at room temperature using Zetasizer Nano-series(Nano ZS, Malvern Instruments, England) after 10-fold dilution [35].

2.4.2. Measurement of viscosity

A Brookfield rheometer (USA) was used for measuring the viscosities of MEs at 25˚C. The viscosity of the ME samples was determined using spindle No.34 under shear rates of 100 rpm.

2.5. Preparation of spinning solution and Electrospinning process

PVA solution (10% w/v) was supplied by dissolving PVA in distilled water at 40 ◦C for 24h by magnetic stirrer. Chitosan solution (CS 2%w/v) was prepared by dissolving in acetic acid at a 2:1 weight ratio. Polyvinylalcohol and chitosan solution were mixed to prepare PVA/CS solutions with volume ratios of 80:20 and 90:10. Then, GRF-loaded microemulsions (containing 0.2% drug) were mixed with polymeric blended solutions (containing 60-70% of polymer) as shown in **Table 2**.

Table 2: Composition of solutions used in the electrospun process.

No. fiber mat	ME(GRF): polymer	CS: PVA
F1	30:70	10:90
F2	30:70	20:80
F3	40:60	20:80
F4	40:60	10:90

Finally, the obtained solutions were used for the electrospun process. A 5 mL syringe was filled with the solution and placed in the holder. The feeding rate was controlled by a syringe pump (Cole-Pham®, USA) and was fixed at 2.0 ml/h. A high voltage supply fixed at 10–18 kV was applied under 60 rpm rotation speed, and a piece of aluminum foil was used to collect the ultrafine fibers with a horizontal distance of 15 cm from the needle tip. The solutions were electrospinning at room temperature, and electrospun nanofibers were collected and stored in a desiccator for further investigation.

2.6. Differential scanning calorimetry

Differential scanning calorimetry was used to determine the thermal behavior of the nanofiber mats and the physical status of GRF in the nanofibers using a Mettler Toledo DSC apparatus equipped with a heating system (until -45°C). Approximately 10 mg of each nanofiber sample was weighted into aluminum pans and quickly sealed to prevent water evaporation from samples. Simultaneously, an empty hermetically sealed pan was used as a reference. ME nanofiber samples were exposed to 20 to 350°C (scan rate: 10°C/min) [36].

2.7. Measurement of GRF content

The total amounts of GRF in the CS/PVA nanofiber-loaded GRF microemulsion were measured using a UV-visible spectrophotometer at 294 nm. The Entrapment efficiency (%) and loading capacity (%) were calculated according to Eqs. (1) and (2), respectively:

% Entrapment efficiency = Ma / Mt ×100 (1)

Where Ma is the quantity of GRF in the nanofiber mats, and Mt is the theoretical quantity of GRF incorporated into the nanofiber mats.

% Loading capacity = Ma / Mm × 100 (2)
where Ma is the quantity of GRF incorporated in the nanofiber mats, and Mm is the mass of nanofiber mats.

2.8. In vitro release behavior of GRF nanofibers

he release percentage of GRF loaded into nanofibers was determined in the phosphate buffer saline (pH 7.4). Briefly, nanofiber samples were placed directly in 25 mL of the phosphate buffer saline (pH 7.4) with ethanol at 37 ◦C under stirring using a magnetic stirrer with constant speed. A Hydroethanolic GRF solution of 0.2% was used as a control. A 2 mL sample was withdrawn at definite intervals, and an equal volume (2 ml) of the fresh-release medium was added to maintain sink conditions. The withdrawn samples were then analyzed at 294 nm by a UV spectrophotometer (Biowave II, WPA, England). The percentages of drugs released at different time intervals were plotted, and their behavior was determined by fitting them to different kinetic models such as zero, first, and Higuchi.

3. Results and Discussion

3.1. Characterization of microemulsion

The Pseudoternary Phase Diagrams of the water-in-oil structures and existing range of Microemulsions are shown in **Figure 1**. The weight ratios of oil, surfactant, cosurfactant, and water in the microemulsions were selected according to the constructed phase diagrams. The mean particle size, Zeta Potential, and viscosity of all microemulsion formulations are shown in **Table 3**. Examination of particle size samples showed a significant increase in samples with the drug compared to those without the drug. The lowest value of particle size is for the ME4 formulation, and the highest is related to the ME3 formulation. At the same time, small particle size increases stability against flocculation and deposition.

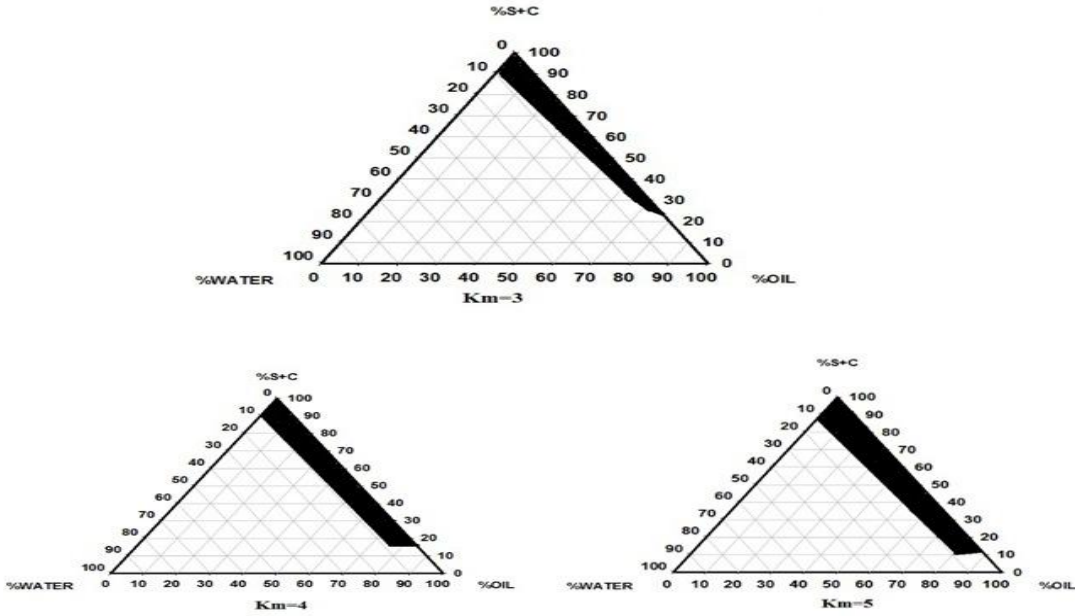

Figure 1. The Pseudoternary Phase Diagrams of the Oil-surfactant/Cosurfactant Mixture-water System at the 3:1 and 5:1 Weight Ratio or Labrasol/span 20/ Plurol oleique at 25 C°, Dark Area Show Microemulsions Zone [38].

Table 3: Particle size, Zeta Potential, and viscosity data of microemulsion samples. (Mean±SD, n=3).

No. formulation	Droplet size mean (nm) with drug	Droplet size mean (nm) without drug	Zeta Potential (mv)	Viscosity (cps) with drug	Viscosity (cps) without drug
ME1	45.14±5.1	30.2±6.7	-9.14±0.1	254.5±1.54	251.4±1.21
ME2	57.3±8.6	38.2±4.3	-5.97±0.4	350.3±0.95	343.4±1.1
ME3	67.7±3.9	56.9±7.2	-14.2±0.6	281.8±1.32	277.5±0.98
ME4	30.9±6.4	19.7±8.5	-20.82±0.3	280.1±1.62	276.2±1.42

However, ME2 and ME3 formulations had the largest particle sizes and viscosities, with higher surfactant/cosurfactant and oil phase content than other formulations. The ME samples revealed a Zeta Potential range (-5.97 to -20.82mv). Also, the ME4 formulation showed the highest value of Zeta potential (-20.82 mv) compared to other formulations.

Regarding the viscosity of the MEs, there was a significant increase in samples with the drug compared to those without the drug; the ME2 formulation showed the highest viscosity (350.3 ±0.95 cps) compared to other formulations. ME2 formulation, possessing a low oil content of 5% w/w. The average particle size and viscosity have increased with a lower percentage of oil phase in some MEs. Although oil increases viscosity, the viscosity decreases due to the microemulsion property due to the formation of the microemulsion structure [37].

3.2. Characterization of the nanofibers with Differential scanning calorimetry

Differential scanning calorimetry (DSC) was conducted to determine the physical state of griseofulvin in the nanofibers **Figure 2**. The DSC curve of the pure drug displayed a characteristic sharp endothermic peak of melting at a temperature of 222 °C.

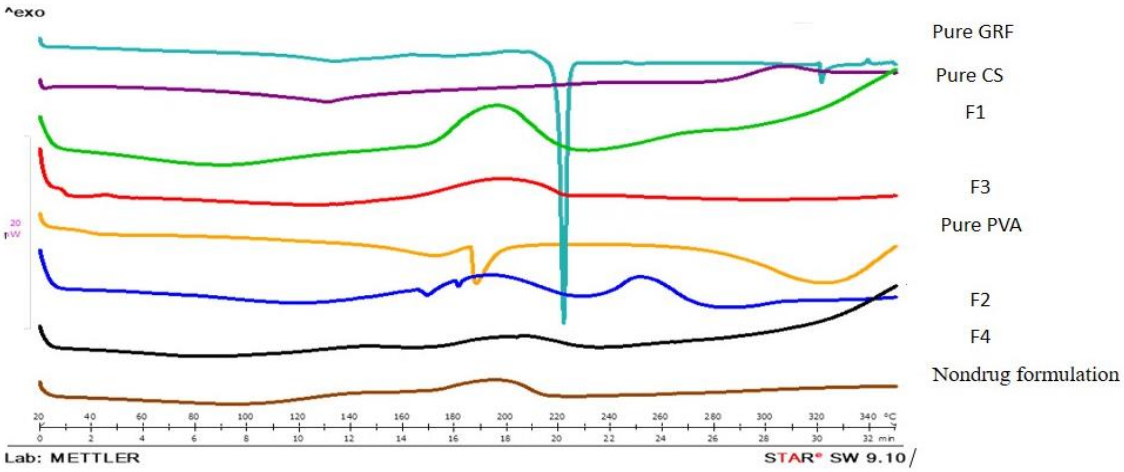

Figure 2. DSC thermograms of pure GRF, pure CS, formulations (F1, F3) of GRF-loaded nanofibers, pure PVA, formulations (F2, F4), and nondrug formulation up to down at the heating rate of 10 °C/min.

In the curve of the pure CS, the broad endothermic peak beginning from around 25 °C and finishing around 190°C is due to the presence of water molecules inside the CS structure. Pure PVA thermogram had two endothermic peaks, a glass transition temperature at 38 °C and a relatively large and sharp melting peak at 191°C. After the modulation of different formulations of GRF microemulsions into the nanofiber, the absence of obvious crystalline domains was observed, indicating that GRF was embedded into the CS/PVA nanofiber and PVA polymer are in an amorphous state due to the fast solidification process during electrospinning. The electrospinning process was found to have decreased the polymer's crystallinity, and this effect was acknowledged [39]. It is likely due to the reduction in the related order of PVA polymer chains resulting from hydrogen bonding between the –OH groups of PVA and – OH and –NH2 groups of chitosan, and it is found in the amorphous state [40, 41]. This finding is important for improving the dissolution rate and bioavailability.

3.3. Determination of GRF content and loading capacity

In order to calculate the loaded drug and the amount of released drug, this test was performed. The total GRF content in the CS/PVA nanofibers loaded GRF microemulsion was calculated. The entrapment efficiency (%) and loading capacity (%) of GRF in the nanofibers are presented in **Table 4**. The F3 formulation showed the highest entrapment efficiency and loading capacity. It may be due to the higher initial proportion of drug-loaded (ME(GRF): polymer) in the formulation and the type of microemulsion.

Table 4: Entrapment efficiency (%) and loading capacity (%) of the different samples of GRF nanofibers. (Mean±SD, n=3).

No. formulation	Entrapment efficiency (%)	Loading capacity (%)
F1	66.67±4.1	5.173±0.87
F2	66.67±3.8	3.7±0.59
F3	88.89±4.7	13.23±2.4
F4	88.89±6.3	5.27±0.62

3.4. In vitro release behavior of GRF nanofibers

Figure 3 shows the release profiles; the release rate of the GRF from nanofibers was slow and gradually increased, with less than 5% of the embedded drug released from the samples (F1-F2-F4) within the first four h, but in the F3 formulation, more than 5%. The burst effect was significantly decreased in the CS/ PVA nanofibers compared to that of the GRF solution (S). In the F2 and F3 nanofibers, more release was observed, probably because they have a higher ratio of CS polymer in their structure compared to other nanofibers. This finding was proven by researchers [40], and we also observed it in the DSC curve. Increasing the ratio of CS polymers has led to further reduction of the structural order and crystallinity of PVA polymers, and decreased crystallinity results in higher drug loading in the nanofiber structure, which may be associated with greater drug release.

On the other hand, due to the microemulsion load in nanofibers, microemulsions have different release behaviors due to the diversity

of internal structure, which is due to the interactions between the drug and the surfactant and the drug distribution between the two aqueous oil phases and their effect on release [38, 42]. Hence, the microemulsion formulation loaded into nanofiber F3 has a low S/C ratio and a high percentage of oil; thus, the rate of slow release may also be related to the GRF molecules that finely dispersed in nanofibers, and with increasing the period of incubation, these molecules were slowly moved from inside the fibers to the surface and finally to the release medium.

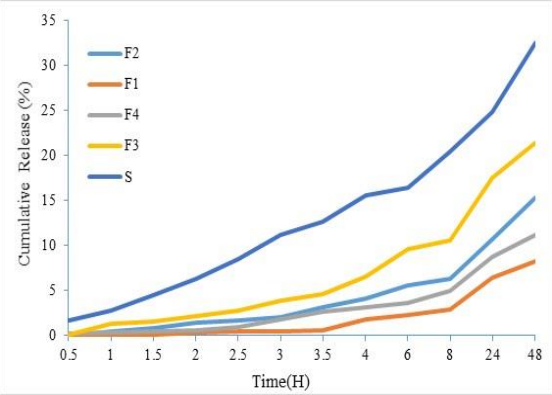

Figure 3. Release profiles of GRF from GRF-loaded microemulsion containing nanofibers prepared (F1 to F4) and Hydroethanolic GRF solution (S).

3.5. Determination of release kinetic

Release kinetic parameters for several nanofibers containing GRF microemulsion and drug solution were determined using different mathematical models, and the results are presented in **Table 5**. The release from nanofiber samples and drug solution conformed to the Higuchi model based on the highest Correlation coefficients (RSQ). This model is used for Water-soluble drugs and low water-soluble drugs embedded in a solid/semisolid polymer matrix. The Higuchi equation (3) suggests that drug release by diffusion is associated with the release time. In Korsmeyer – peppas equation (4), n is estimated from linear regression of log (Amount of drug released at a time 't'/ Total amount of drug in dosage form) Vs log t. If the amount of expontional is less than 0.45, it follows the Fickian diffusion mechanism, and if the amount of power is more than 0.45, it follows the non-fickian diffusion mechanism. Non-Fickian diffusion refers to the combination of both diffusion and erosion-controlled rate release.

$Q=K_H t^{1/2}$ (3)

Q = cumulative amount of drug release at time "t"

K_H = Higuchi constant

t = time in hours

$F = K_m t^n$ (4)

F = Fraction of drug released at time't'

N = Diffusion or release exponent

K_m = Kinetic constant

t = Time in hours.

Table 5: Correlation coefficients and kinetics of drug release from different formulations and drug solutions of GRF.

No. form.	Zero order	First order	Higuchi	Hixon – Crowell	Papas	
	RSQ				RSQ	N
F1	0.91	0.91	0.97	0.91	0.82	1.71
F2	0.90	0.91	0.98	0.90	0.82	1.13
F3	0.83	0.86	0.95	0.85	0.81	1.03
F4	0.87	0.88	0.96	0.88	0.90	0.95
S	0.74	0.79	0.89	0.77	0.87	0.65

4. Conclusion

In this study, the purpose of preparing CS/PVA nanofibers loaded GRF microemulsion is to increase the solubility of Low soluble drug

griseofulvin by using microemulsion nanocarrier, and nanofiber was used as a technique for a new product. GRF microemulsions loaded with CS/PVA nanofibers were successfully produced, and their performance was determined as a carrier for the controlled release of griseofulvin. Decreased crystallinity of drug and polymer was observed by DSC analysis. The hydroxyl groups of PVA can form hydrogen bonds with CS, which could decrease crystallites and increase the amorphous state, which could increase solubility and release of griseofulvin. We evaluated kinetic models for griseofulvin release from CS/PVA nanofibers; the Higuchi model best fits data based on the highest correlation coefficients(RSQ). Finally, *in vivo* studies are needed to evaluate this product further.

Acknowledgments

None.

Conflict of interest

The authors declare to have no conflict of interest.

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