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Research Article

Evaluation of three tropical starches as polymers for the formulation of diclofenac sodium microspheres

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Abstract

Starches are derived from three botanical sources, such as unripe mature banana fruits (*Musa sapientum L.*), cocoyam (*Colocasia esculenta* L. Schott), and bitter yam (*Dioscorea dumetorum* Pax) tubers, have been evaluated as polymers in the design of microspheres incorporating diclofenac sodium as a model drug. Using the ionic gelation process, the starches were pregelatinized and used as polymers in conjunction with sodium alginate to produce diclofenac sodium microspheres with 2% calcium chloride as a crosslinking agent. The morphology, swelling properties, Entrapment Efficiency (EE), and drug release properties of the microspheres were evaluated. Fitting the in-vitro dissolution data into multiple kinetic models yielded the drug release pathways. Spherical discrete microspheres with rough surfaces were obtained with diameters ranging from 580 to 670 μm and EEs ranging from 68.0 to 80.7% w/w. For more than 5 hours, diclofenac sodium was released in a controlled manner. The type and concentration of starch in the polymer blend affected drug release from the microspheres, with banana starch at a 4:1 ratio demonstrating the slowest dissolution rate. Drug release from microspheres is best described by the Korsmeyer-Peppas model, which implies that drug release is governed by both diffusion and erosion mechanisms. The finding shows that tropical starches could be used to develop diclofenac sodium microspheres with controlled release.

Keywords: starch, microspheres, drug release, sodium alginate, diclofenac sodium

Introduction

Microspheres are discrete spherical particles with diameters ranging from 1 to 1000 μm that are used in multi particulate system formulation. They distribute better in gastric fluid, resulting in more uniform and reproducible drug absorption and potentially enhancing bioavailability [1]. As a result, more substantial therapeutic effects with less localized mucosal injury are achieved. Microspheres have been utilized to help regulate drug distribution and target drugs to certain human organs. Natural and synthetic polymers are used to make microspheres, which act as medication transporters. As a result of the toxicity of synthetic polymers, natural polymers have been developed as carriers [2]. On the other hand, natural polymers, such as starches, offer the advantages of being less toxic, cost-effective, biodegradable, and widely available, making it more suitable drug delivery polymers. They can also be chemically and physically altered to change their physicochemical properties, resulting in various functional characteristics that could make them useful as polymers in several drug delivery systems. New polymer discovery and design are crucial for expanding the range of drug carriers and satisfying the unique needs of drug formulators [3,4].

Efforts are also ongoing to develop starches derived from additional botanical sources that could be used as excipients in various pharmaceutical formulations [5]. There are three tropical starches: banana starch from *Musa sapientum* L unripe fruits, cocoyam starch from *Colocasia esculenta* (L.) Schott tubers,

and bitter yam starch from *Dioscorea dumetorum* Pax "tubers, that have been shown to have potential as excipients in tablet formulation [5-7]. These tropical starches have been demonstrated to be effective as binding and disintegrating agents in tablet formulations [6]. However, they have not been tested as polymers in the formulation of microspheres, which are multi particulate systems that have been shown to provide controlled drug delivery. Banana, cocoyam, and bitter yam starches were pregelatinized and used as polymer composites to make diclofenac sodium microspheres in this study. When administered orally for a long time, diclofenac sodium is an effective anti-inflammatory medication that might cause side effects such as stomach ulcers or gastrointestinal wall perforation, which leads to ineffective therapy and poor patient compliance [8]. The development of controlled-release diclofenac sodium microspheres could result in a more efficient delivery mechanism with fewer gastrointestinal side effects.

Materials and Methods

Sodium alginate (Carl Roth GmbH, Karlsruhe, Germany), diclofenac sodium (Fagron GmbH, Barsbttel, Germany), calcium chloride (Grussing GmbH and the Bahn Achtung, Germany), *Dioscorea dumetorum* Pax (Bitter yam), *Colocasia esculenta* (Cocoyam), and unripe fruit of *Musa sapientum* (Banana) were procured from local farmers (Ibadan, Nigeria). The procedure for extracting the starches has been earlier reported. [5,9].

Preparation of the gelatinized starches

Odeku et al. [10] described a method for preparing the gelatinized form of the starches. Aqueous starch slurry (20% w/v) was cooked for 15 minutes in a crucible over a water bath at 80^{o}C with constant stirring. The polymer blend used in the microsphere formulations was made by mixing the starch gel with sodium alginate.

Viscosity analysis

The viscosity of a 4% w/v aqueous suspension of pregelatinized starches, sodium alginate, and starch: alginate composites was measured with a Roto Visco 1 viscometer (Haake, Germany) at 25^{o}C and a shear rate of 50 rpm. Table 1 shows the starch-to-sodium-alginate ratios used to prepare the polymer composites.

Preformulation Studies

Preformulation studies were carried out to assess the ability of pregelatinized starches to form microspheres using the ionic gelation method alone or in combination with sodium alginate [11]. Several formulations were developed by varying the concentrations of pregelatinized starches alone and in combination with sodium alginate, the concentrations of chelating agents (zinc chloride and calcium chloride) (2, 5, and 10% w/v), the mixing speed (200, 300, and 400 rpm), and the curing time (15, 30 and 60 min).

Preparation of Microspheres

The ionic gelation method [11] was used to produce the microsphere. To make a 2% w/v polymer gel concentration, 10–50 % w/w pregelatinized starch was mixed with sodium alginate. The dispersion was extruded into calcium chloride solution (2% w/v) with a syringe fitted with a 0.90mm needle at a dropping rate of 2ml/min and stirred at a speed of 200 rpm with a magnetic stirrer achieve a total polymer/drug ratio of 2:1. (VEVOR SH-3, Vevor Corporation GmbH, Cologne, Germany). The microspheres were decanted, rinsed with distilled water, and dried in a hot air oven at 40°C for 24 hours after drying for around 15 minutes.

Characterization of Microspheres

Size and morphology

The microspheres were gold-sputtered, and their shape and surface properties were examined using scanning electron microscopy (Hitachi Model S-2460N, Japan) at a 25 KV accelerating voltage. A

computerized microscope coupled with a coloured video camera (Leitz Laborlux II, Wetzlar, Germany) was used to determine the particle sizes of 100 microspheres [4].

Swelling index

The swelling index of the microspheres was calculated using the method reported by Odeku et al. [4]. Dried microspheres with a known weight (W0) were soaked in 5 ml phosphate buffer, pH 6.8, in a measuring cylinder containing (10 ml). After 24 hours, the microspheres were removed from the solution, wiped to remove any extra liquid from the surface, and weighed (Wt). The swelling index (% w/w) was determined using the following formula:

$$\text{Swelling Index (\%)} = \frac{Wt - W0}{W0} X\ 100 \quad (1)$$

Entrapment Efficiency

Drug-loaded microspheres (50mg) were accurately weighed and crushed with a pestle in a glass mortar before being suspended in 10ml phosphate buffer (pH 7.4) [4]. After 24 hours of steady stirring, the solution was filtered, diluted with phosphate buffer, and spectrophotometrically analyzed for diclofenac sodium at 274 nm (U.V Perkin Elmer GmbH, Uberlingen, Germany). The percentage EE was estimated using the following formula:

$$\text{EE (\%)} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} X\ 100 \quad (2)$$

Drug release study

The *in-vitro* dissolution tests were performed on diclofenac sodium loaded microspheres (500mg) in 900ml of dissolution medium (phosphate buffer, pH 6.8) at 37 ±0.5^{o}C using the USP paddle method rotated at 50 rpm in 900ml of dissolution medium (phosphate buffer, pH 6.8) [4]. Samples (10ml) were taken and replaced with the same volume of fresh medium at one-hour intervals. The amount of diclofenac sodium released was determined spectrophotometrically (U.V. Perkin Elmer GmbH, Uberlingen, Germany) at a wavelength of 274 nm after the sample was diluted. The average of three determinations was used to arrive at the final outcome.

Release profile modelling and comparison

To investigate the drug release mechanism, in-vitro drug release data were fitted to zero-order [12], first-order [13], Higuchi [14], Hixon-Crowell [15], Korsmeyer – Peppas [16], and Hopfenberg [17] kinetic equations (s). The best-suited model(s) were found by comparing the correlation coefficient values.

Data analysis

Statistical analysis (ANOVA) was performed using the computer software GraphPad Prism(R) 4 to compare the differences between the formulations (Graphpad Software Inc. San Diego, CA, USA). At a 95% confidence level, $p \leq 0.05$ was considered significant.

Results and discussions

Viscosity analysis

The viscosity of the pregelatinized starches, sodium alginate, and polymer composites used in the microsphere formulation (Table 1) revealed that sodium alginate had a considerably higher viscosity ($p<0.000$) than all of the pregelatinized starches and polymer composites. The viscosity ranking for starch-alginate composites was cocoyam>banana>bitter yam, with the viscosity of the polymer composites decreasing as the starch concentration in the polymer composites increased. Cocoyam gel, the starch with the highest viscosity among the starches, provided the starch-alginate composites with the highest viscosity. The viscosity properties of pregelatinized starch appeared to change depending on sodium alginate content. High viscosity has been linked to sodium alginate, which is associated with

its molecular weight and glucuronic acid content: stronger gels are associated with higher molecular weights or glucuronic acid concentration [18].

Table 1. The composition and viscosity of polymers.

Polymer(s) 4%	Polymer ratio	Viscosity(mPas)
Alginate	0:1	6183.0±2.05
Banana	1:0	13.8±0.01
Banana: Alginate	1:1	832.1±1.27
Banana: Alginate	2:1	572.0±1.41
Banana: Alginate	3:1	415.0±0.94
Banana: Alginate	4:1	358.5±0.32
Cocoyam	1:0	40.1±0.33
Cocoyam: Alginate	1:1	1127.3±0.25
Cocoyam: Alginate	2:1	712.0±0.75
Cocoyam: Alginate	3:1	592.9±0.57
Cocoyam: Alginate	4:1	326.2±1.11
Bitter yam	1:0	9.8±0.02
Bitter yam: Alginate	1:1	859.3±0.21
Bitter yam: Alginate	2:1	656.8±0.69
Bitter yam: Alginate	3:1	416.3±0.25
Bitter yam: Alginate	4:1	265.4±0.32

Preformulation studies

Preformulation studies revealed that pregelatinized starch, zinc chloride, and high chelating agent concentrations were not acceptable for microsphere formulation. High stirring speed (300 and 400 rpm) and curing time (30 and 60 minutes) produced sticky, aggregated microspheres that deteriorated as the speed and curing time increased (data not shown). At a stirring speed of 200 rpm and a curing duration of 15 minutes, stable spherical microspheres were produced only with composites of pregelatinized starch and sodium alginate with calcium chloride as the chelating agent (2% w/v). The optimized microspheres' compositions are listed in Table 1. Under mild conditions, sodium alginate can form gels with divalent cations like zinc and calcium, and it is often employed as a gelling agent [19]. The "egg-box" model describes the ionotropic gelation of sodium alginate with cations like calcium, in which cations interact with guluronic acid monomers to produce cavities that potentially entrap drugs [19, 20]. Thus, sodium alginate alone, with higher molecular weights and apparent viscosities, formed stable microspheres with calcium chloride, while the pregelatinized starches did not have sufficient glucuronic acid and viscosity to form stable microspheres [4]. Because of the inclusion of sodium alginate in the composite, the alginate: starch composite could produce stable microspheres, even though calcium alginate has been linked to increased gel strength [4, 20].

Table 2. Properties of diclofenac sodium microspheres formulations containing the polymer composites (mean ± SD, n=3).

Starch	Starch:Alginate ratio	Swelling index (%)	Particle Size (mm)	Entrapment Efficiency (%)	t_{15} (hr)	t_{50} (hr)	t_{90} (hr)
Alginate	0:1	4.2±0.47	0.67±0.05	73.3±6.5	0.6±0.5	1.5±0.4	2.7±0.6
Banana	1:1	27.1±0.8	0.58±0.04	73.4±4.2	0.9±0.5	1.5±0.3	2.7±0.5
	2:1	28.1±0.6	0.60±0.03	75.0±5.3	0.8±0.6	1.4±0.2	2.4±0.6
	3:1	29.6±1.3	0.61±0.04	77.8±5.6	1.0±0.5	1.7±0.2	3.1±0.4
	4:1	32.1±0.9	0.63±0.04	78.3±5.5	1.0±0.5	1.9±0.2	5.0±0.4
Cocoyam	1:1	27.7±1.4	0.58±0.04	72.5±6.3	0.9±0.6	1.5±0.4	2.7±0.6
	2:1	29.4±3.0	0.64±0.05	70.3±4.5	1.0±0.3	1.5±0.4	2.8±0.7
	3:1	35.5±0.7	0.65±0.06	74.5±5.6	1.0±0.2	1.6±0.3	3.0±0.8
	4:1	42.4±2.3	0.66±0.10	74.8±6.4	1.1±0.7	1.6±0.1	3.3±0.5
Bitter yam	1:1	12.8±1.3	0.61±0.03	68.0±4.5	0.8±0.6	1.5±0.6	2.8±0.4
	2:1	11.6±2.4	0.61±0.04	69.0±7.1	0.8±0.3	1.4±0.4	2.6±0.2
	3:1	15.6±3.3	0.63±0.03	69.6±5.6	0.9±0.7	1.6±0.3	3.0±0.6
	4:1	17.3±0.9	0.67±0.08	80.7±6.4	1.0±0.4	1.8±0.2	3.7±0.5

Physicochemical properties of the microspheres

Figure 1 shows SEM images of diclofenac sodium microspheres with 4:1 starch: alginate composites. The SEM indicated that the higher concentration of starches in the polymer composites, the less spherical and more translucent the microspheres (data not shown). The microspheres were round, compact, and discrete, with a rough surface shape. As the starch content in the polymer composite increased, the surface of the microspheres became rougher and more porous.

Table 3. Correlation coefficients for the diclofenac sodium microspheres using the drug release mathematical models (n = 3)

Starch	Starch:Alginate Ratio	Zero order	First order	Korsemeyer		Higuchi	Hixson-Crowell	Hopfenberg
				r^2	n			
Alginate	0:1	0.8024	0.9480	0.9846	0.7918	0.8945	0.9325	0.8376
Banana	1:1	0.8231	0.8770	0.9839*	1.0119	0.8815	0.9684	0.8377
	2:1	0.7949	0.8983	0.9838*	0.7917	0.8803	0.9496	0.8180
	3:1	0.8544	0.9147	0.9853*	1.2181	0.8825	0.9053	0.9112
	4:1	0.8927	0.9866	0.9904*	0.9498	0.9025	0.9560	0.9604
Cocoyam	1:1	0.8147	0.8828	0.9841*	0.9981	0.8736	0.8528	0.8213
	2:1	0.8190	0.9473	0.9852*	0.9117	0.8793	0.9105	0.8891
	3:1	0.8425	0.9657	0.9852*	0.9826	0.8903	0.9408	0.8940
	4:1	0.8564	0.9718	0.9877*	0.9102	0.9068	0.9497	0.9480
Bitter yam	1:1	0.8302	0.9648	0.9845*	0.9596	0.8859	0.9246	0.8700
	2:1	0.8095	0.9664	0.9850*	0.8252	0.8904	0.8909	0.8503
	3:1	0.8367	0.9574	0.9847*	1.0313	0.8709	0.9208	0.8597
	4:1	0.8714	0.9674	0.9866*	1.2543	0.8782	0.9442	0.9391

* Drug release kinetics with the highest correlation coefficient

The microsphere size ranged from 0.58±0.04 to 0.67±0.08 mm, and the swelling index ranged from 4.2±0.47% to 42.4±2.3%, according to the physicochemical parameters reported in Table 2. The microsphere size and swelling index in polymer composites rose as the starch concentration increased, with cocoyam starch formulations having the highest values and bitter yam formulations having the lowest. The swelling index of the microspheres containing the polymer composites was significantly higher ($p<0.05$) than that of sodium alginate alone; however, the formulations comprising the starch: alginate composites showed no significant change. The microsphere size did not differ substantially ($p>0.05$) across all formulations. The EE of microspheres measures the processing technique's reproducibility and efficiency, although inadequate solubility can impair the EE [21,22]. The microsphere entrapment efficiency ranged from 68.0±4.5% to 80.7±6.4%, with banana starch formulations having the highest efficiencies and bitter yam starch formulations having the lowest. As the starch concentration in the polymer composite grew, the EE also increased. As a result, starch in the polymer composites appeared to hinder or obstruct drug diffusion in the polymer droplets. The type of the drug, polymer concentration, drug-polymer ratio, and starch: alginate ratio has all been found to influence drug entrapment efficiency in microspheres [23].

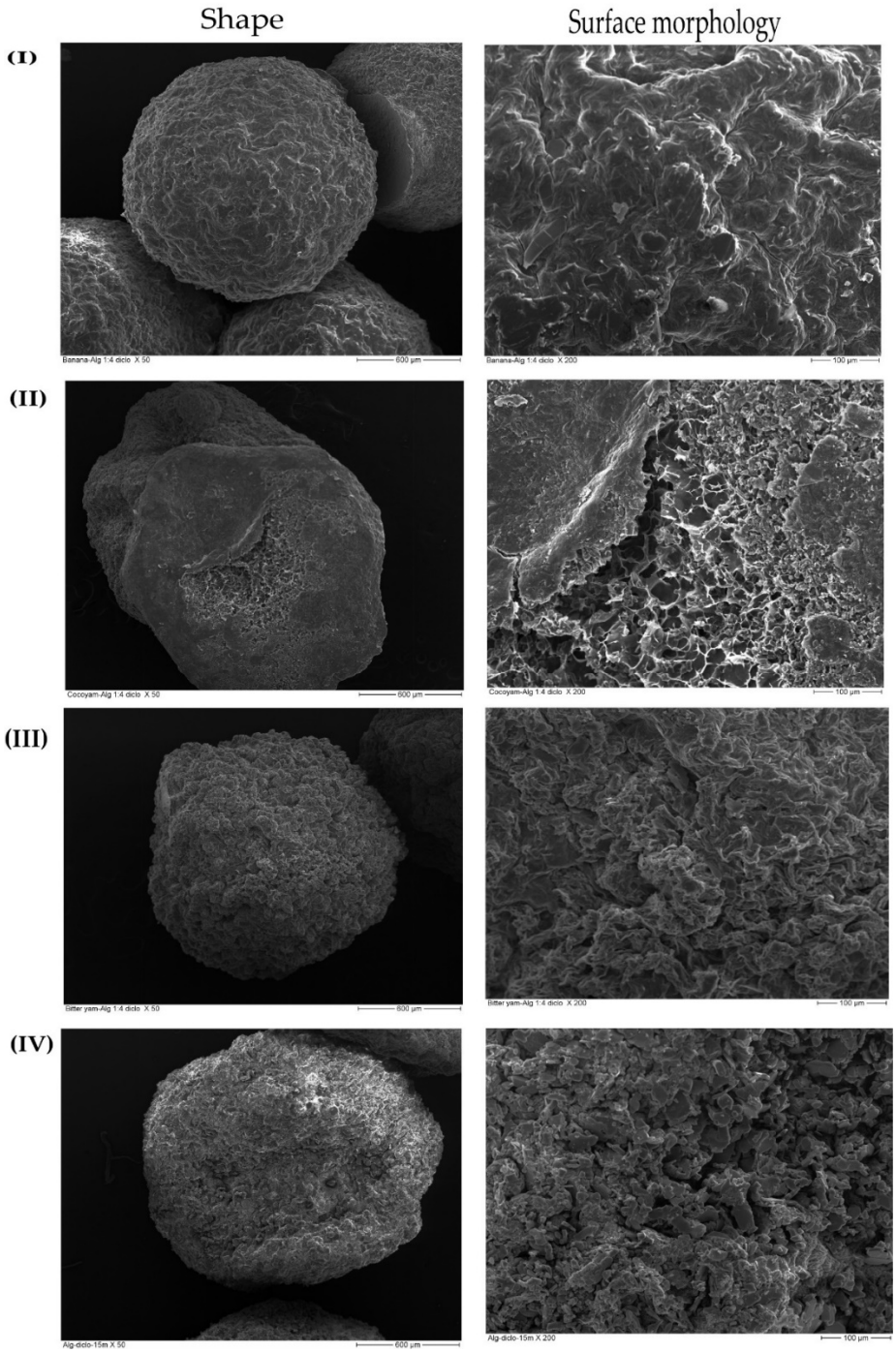

Figure 1. SEM images of diclofenac sodium-loaded microspheres containing 4:1 starch:alginate composites (i) banana: alginate; (ii) cocoyam: alginate; (iii) bitter yam: alginate and (iv) 2% sodium alginate.

Drug release study

Figure 2 and Table 2 demonstrate plots of diclofenac sodium release profiles from microsphere formulations and the values of t_{15}, t_{50}, and t_{90} (time for 15%, 50%, and 90% drug release, respectively). According to the dissolution profiles, the amount of diclofenac sodium released increased slowly and consistently over time. The drugs were entrapped within the "egg-box" microsphere rather than loosely bound to its surface, evidenced by the lack of burst release [20,24]. The results showed that the higher the amount of starch in the polymer composites, the slower drug release. Higher starch concentrations resulted in non-shrinkable, hard shell and skeletal structure matrices, which explained the drug's delayed release and longer dissolution time. The microsphere formulations with a 4:1 (starch: alginate)

ratio of banana starch had higher t_{50} values than the others, indicating better-sustained release properties.

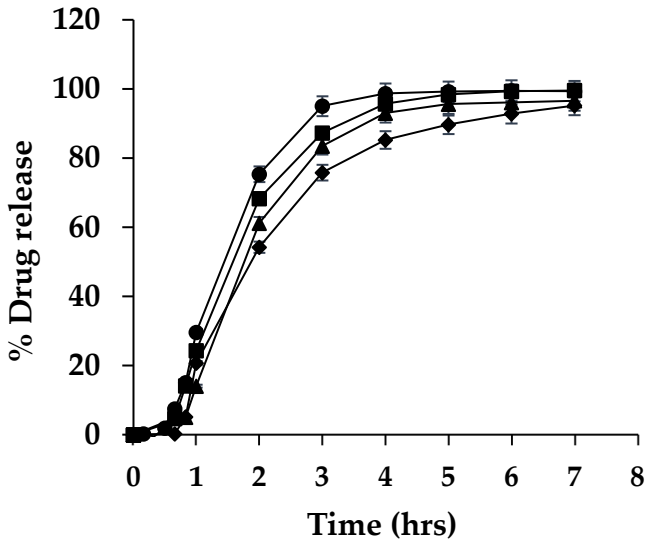

Figure 2. Dissolution profiles of diclofenac sodium microspheres containing 4:1 starch: alginate composites ♦ banana: alginate; ■, cocoyam: alginate; ▲ bitter yam: alginate; and • alginate only at 15mins curing time.

The dissolution times, t_{15}, t_{50} and t_{90} for formulation containing the starches were generally in the rank order of banana>cocoyam>bitteryam>alginate. The starch type and concentration in the polymer composites affected the dissolution times. Therefore, the starch content could be used to regulate drug release from the microsphere.

The correlation coefficients for diclofenac sodium microspheres derived using various mathematical models (Table 3) demonstrated that diclofenac sodium release followed the Korsmeyer-Peppas model with $r^2 \geq 0.98$ for all formulations. This suggests that diclofenac release from these formulations is governed by several processes, most notably the diffusion and erosion mechanisms [16]. The kinetics of drug release from delivery systems are significant due to their impact on the dosing frequency, bioavailability, patient compliance, and, in many cases, toxic or adverse effects. The kinetics of drug release from dosage forms are critical because they influence the bioavailability, dosing frequency, patient compliance, and, in many cases, the manifestation of toxic or unfavourable effects [25]. The 'n' values ranged from 0.7 to 1.2, demonstrating that all of the microspheres released the drug via the case-II transport mechanism, a combination of the microsphere's swelling and erosion.

Conclusion

Diclofenac sodium microspheres designed using starch-alginate composites were helpful for the controlled release of diclofenac sodium for over 5 hours. The starch type and concentration influenced the drug release properties of the microspheres in the polymer composites used in their preparation. Starches obtained from the three plant sources may be helpful in the formulation of microspheres for both immediate and controlled release and may be used as an alternative to synthetic polymers in drug delivery.

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Declaration of interest

The authors declare no conflict of interest.

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