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Research Article

Formulation and Evaluation of Immediate-Release Oral Tablets Containing Magnesium Aluminum Silicate-Loaded Simvastatin

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Abstract

Background: Simvastatin (SIM) is a lipid-lowering agent to prevent disorders caused by clogged blood vessels. Because of its low solubility, it has low bioavailability. The adsorption technique is effective in improving drug solubility and dissolution rate. ***Objective***: To use magnesium aluminum silicate (MAS) as an adsorbent in combination with Soluplus® as a hydrophilic polymer to formulate SIM as immediate-release tablets (IRTs). ***Methods***: We used the solvent evaporation method to make MAS-loaded SIM in the presence of Soluplus®, making sure that the ratio of SIM to MAS to SOLU was 1:6:3. We then used this mixture to make IRTs. Using the direct compression method, we made all of the SIM-IRT formulas. We used diluents like Avicel®PH102, Avicel®PH101, and starch, as well as super disintegrants like Crospovidone (CP), Croscarmellose sodium (CCS), and sodium starch glycolate (SSG). We evaluated these formulas for their weight variation, hardness, friability, disintegration time, drug content, and dissolution profile. ***Results***: We prepared the tablet formula (T5) using MAS-loaded SIM, Avicel®PH102 as a diluent, and CCS 3% as a super disintegrant. This formula showed the shortest disintegration time (0.61 min) and best drug release in phosphate buffer pH 7.0, releasing more than 80% of the drug within 30 minutes. ***Conclusion***: Using suitable excipients, adsorption was an efficient method to enhance the solubility of SIM for preparation as IRTs.

Keywords: Adsorption technique, Immediate-release tablets, Magnesium Aluminum silicate, Simvastatin, Soluplus®.

صياغة وتقييم الحبوب ذات الاطلاق الفوري المحتوية على سليكات الالمنيوم المغنيسيوم المحملة بالسمفستاتين

الخلاصة

الخلفية: السمفستاتين هو دواء مضاد لارتفاع الدهون بالدم ، يستخدم لمنع المشاكل الطبية الناجمة عن انسداد الاوعية الدموية . انه ينتمي الى المجموعة الثانية و فقا لنظام التصنيف الصيدلاني الحيوي مع توافر حيوي منخفض بسبب قلة ذوبانيته. تعتبر تقنية الامتزاز من التقنيات الفعالة في تحسين الذوبان ومعدل الانحلال لمثل هذه الادوية. **الهدف:** تعزيز قابلية ذوبان السمفستاتين باستخدام تقنية الامتزاز باستعمال سليكات الالمنيوم المغنيسيوم، كمادة ممتزة مع السولبلس كبوليمر محب للماء ليتم صياغته بشكل حبوب ذات اطلاق فوري. **الطرق:** تم استخدام طريقة تبخيرالمذيب لتحضير سليكات الالمنيوم المغنيسيوم المحملة بالسمفستاتين بوجود السولبلس بنسبة 3:6:1 (سمفستاتين: سليكات الالمنيوم المغنيسيوم: سولبلس) لاستخدامها في تحضير حبوب الاطلاق الفوري. تم تحضير جميع صيغ الحبوب بطريقة الكبس المباشرباستخدام أنواع مختلفة من المواد المخففة (افيسيل PH102، افسيل PH101، و النشا) و مفتتات ممتازة مختلفة (كروسبوفيدون، ملح الصوديوم للكروسكارميلوز و ملح الصوديوم لجلايكولات النشا) تقييمها من حيث تباين الوزن، الصلابة و الهشاشة، وقت التفكك، محتوى الدواء، صورة تحرر الدواء خارج الجسم. **النتائج:** أظهرت صيغة الحبوب T5 اللتي تم تحضيرها باستخدام السمفستاتين الممتز على سليكات الالمنيوم المغنيسيوم المحملة بالسمفستاتين و افيسيل PH102 كمادة مخففة و 3% من ملح الصوديوم للكروسكارميلوز كمادة مفككة ممتازة، اقصر وقت تفكك (0.61 دقيقة) و افضل تحرر للدواء في محلول الفوسفات ذو اس هيدروجيني 7 حيث تم اطلاق اكثر من 80% من الدواء خلال 30 دقيقة. **الاستنتاج** : كانت تقنية الامتزاز فعالة في تعزيز قابلية ذوبان السيمفستاتين ليتم تحضيرها كحبوب ذات تطلاق فوري باستخدام سواغات مناسبة.

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INTRODUCTION

Oral dosage forms remain the favored forms for systemic impact, as they account for over 90% of all pharmaceutical drugs on the market [1]. Solid dosage forms, including tablets and capsules, are the most advantageous among them because of their ease of administration, accurate dosage, pain avoidance, and, most importantly, high patient compliance. A tablet is a solid compressed entity that contains active medicinal substances with suitable pharmaceutical excipients, and it can be characterized as immediate or modified releases based on their release pattern [2]. Immediate-release tablets are designed to disintegrate and dissolve quickly in order to release their active components rapidly without a specific rate-controlling quality, such as a coating or unique diluents or carriers that lead to prolonging or delaying the release. Among the benefits of an immediate-release tablet are increased patient compliance, high drug loading ability, and cost-effectiveness [3].

Simvastatin (SIM) belongs to the group of medicines called HMG-CoA reductase inhibitors, or statins. Simvastatin (SIM) is one of the seven licensed statins (lovastatin, simvastatin, pravastatin, fluvastatin, rosuvastatin, atorvastatin, and pitavastatin) for controlling high cholesterol levels [4]. This drug may help to prevent medical problems caused by clogged blood vessels (heart or blood vessel problems, heart attacks, or strokes) [5]. Researchers also found that SIM, either alone or in combination with omega-3, has an anti-obesity effect [6]. SIM is a lipophilic drug with a log P value of 4 and an aqueous solubility of 70 µg/ml. The biopharmaceutical classification system classifies it as a class II drug due to its low solubility and high permeability. As a result, it has a low and variable bioavailability that is associated with dissolution rate-limited absorption after oral administration [7]. Techniques for solubilization can address the issue of low solubility. One of those techniques is the adsorption of porous materials, which is amorphization that changes the crystal form to an amorphous state. Adsorption is the interphase accumulation of concentrations of drugs at a surface or interface [8].

Materials with mesoporous structures, like mesoporous silica, are very good at changing the shape of drugs because they can keep drug molecules inside their nanometer-sized pores. Formulators are interested in using mesoporous silica for this method because they have a high surface area, inert and biocompatible, which makes them a good excipient for drug delivery [9]. In this research, we used Magnesium Aluminum Silicate (MAS), an example of mesoporous silicate, to prepare immediate-release tablets of MAS-loaded SIM using a direct compression method with different diluents and super disintegrants.

METHODS

Materials

We purchased Simvastatin (SIM) and magnesium aluminum silicate (MAS) from Hangzhou Hyperchem. Soluplus$^{(R)}$ (SOLU) was purchased from CDH, India. Crospovidone (CP), croscarmellose sodium (CCS), and sodium starch glycolate (SSG) were supplied by Pioneer Pharmaceutical Company, Iraq, as a gift sample. Microcrystalline cellulose (Avicel®) PH101, microcrystalline cellulose (Avicel®) PH102, and starch were supplied by Modern Company for the Iraqi the Iraqi drug industry. Polyvinylpyrrolidone (PVP K30), talc, and magnesium stearate were supplied from Himedica, India.

Preparation and evaluation of MAS-loaded simvastatin

Researchers utilized the principle of using an adsorbent in the presence of a surfactant to enhance the solubility of poorly soluble drugs [10]. Therefor we conduct a trial using the solvent evaporation method, utilizing a weight ratio of 1:6:3 (SIM: MAS: SOLU). For this preparation, we dissolved SIM and SOLU in ethanol, then gradually add MAS to the solution while gently stirring with a magnetic stirrer for 1 hour. We then poured the mixture into a Petri dish and placed it in an oven at 40 °C for 24 hours to fully evaporate the solvent. We then pulverized the resulting solid mass in a mortar to obtain a dry, free-flowing powder [11]. We passed the powder through a #60 mesh sieve. We transferred the resulting mass to desiccators containing CaCl2 and stored it for further use. We evaluated the resultant product for its percentage yield by comparing its weight to the total weight of the starting materials, for its drug content using ethanol as an extracting solvent, and for its saturated solubility in water using the flask shake method at 25°C. We also determined its dissolution in phosphate buffer (pH 7.0) and compared it with the pure drug and the prepared tablets.

Immediate-release tablet preparation by direct compression

We prepared tablets containing the MAS-loaded SIM formula, equivalent to 10 mg SIM, using the direct compression method with various diluents and super disintegrants (Table 1). Using a mortar and pestle, we mixed the MAS-loaded SIM formula with super disintegrants, diluent, and binder for approximately 30 minutes to achieve immediate release of SIM. The lubricant and glidant were then added and mixed for 2 minutes. A tablet machine (Hangzhou Shengde Machinery Co., China) compressed the resulting powder blend [12].

Pre-compression evaluation of SIM-IRT powder blends

The pre-compression parameters of the powder blend were determined and compared with those of pure SIM and MAS loaded SIM, to investigate the factors affecting these parameters.

Table 1: Composition of different SIM IRT blends

Ingredient (mg)	Formula code					
	T1	T2	T3	T4	T5	T6
MAS loaded SIM equivalent to 10 mg SIM	120.5	120.5	120.5	120.5	120.5	120.5
Cross povidone (CP)	7.5	7.5	7.5			
Croscarmellose Sodium (CCS)				7.5	7.5	
Sodium Starch Glycolate (SSG)						7.5
PVP	7.5	7.5	7.5	7.5	7.5	7.5
Avicel PH101	107			107		107
Avicel PH102		107			107	
Starch			107			
Talc	5	5	5	5	5	5
Mg stearate	2.5	2.5	2.5	2.5	2.5	2.5
Total weight of tablet	250	250	250	250	250	250

Angle of repose

The funnel method can determine the angle of repose, an estimation for the flowability of powder. To estimate the angle of repose, pour the sample throughout the funnel, ensuring its lower tip is at a height of 2.0 cm above the hard surface. We poured the samples until the upper tip of the powder pile surface made contact with the lower tip of the funnel. The angle of repose (θ), and the experiment was done in triplicate [13].

$$\tan(\theta) = h/r \dots\dots \text{eq } 1$$

θ is the angle of repose obtained by calculating the tan $^{-1}$, where h is the height of the resulting powder cone, and r is the radius of the resulting powder cone.

Bulk density

It is the ratio of the powder's total mass to its bulk volume. We measured it by pouring a specific weight of powder into a measuring cylinder and noting the initial weight. This initial volume is referred to as the bulk volume. We calculate the bulk density using the following formula: It is expressed as g/mL [14].

$$\text{Bulk density} = \frac{\text{Powder mass}}{\text{Bulk volume}} \dots\dots \text{eq } 2$$

Tapped density

It is the ratio of the powder mass to the tapped volume. We measure it by pouring a specific weight of powder into a graduated cylinder, manually tapping the cylinder until we observe no further change in powder volume, and then recording the final volume using the following equation [14].

$$\text{Tapped Density} = \frac{\text{Powder mass}}{\text{Tapped volume}} \dots \quad \text{eq } 3$$

Compressibility index (Carr's index)

Compressibility index indicated the flow properties of the powder. It can be defined as the ability of the powder to decrease in volume under pressure. It is expressed in percentage and was estimated by the next equation [13].

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk dnsity}}{\text{Tapped dnsity}} \times 100 \dots \text{ eq } 4$$

Hauser's ratio

It is related to Carr's index and is considered as an indirect method to predict the flow property of powder. It can be estimated by the following equation [13]:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \dots \text{eq } 5$$

Post compression evaluation

The tablet should be free of cracks, problems, pinholes, and other issues. The tablet's color and cleanliness should be consistent over its entire surface. The surface of the tablets should be smooth [15]. We randomly selected twenty tablets and weighed each one individually. Calculate the average weight, and compare the individual tablet weight to the average. Not more than two of the individual weights deviate from the average weight by more than the percentage shown, and none deviate by more than twice the percentage [14]. Tablets require a certain amount of strength or hardness to withstand the mechanical shocks of handling in manufacture, packaging, and shipping. Tablet hardness has been defined as the force required to break a tablet in a diametric compression test. We measured the tablet hardness of all the formulations using an electronic hardness tester (YD-1, Beijing, China). We determined the hardness of three tablets from a formulation, taking the average value into consideration [16]. We apply a friability test to determine the friction effects and shocks, which often lead to tablet chipping, caps, or breaks. The friability result is expressed in percentages. Ten tablets from each formula were weighed (W initial), and then the tablets were placed in a plastic chamber of a friabilator (TAR 120, Erweka, Germany), which was revoluted for 4 minutes at 25 rpm. The weight of the tablet after friabilization (W final) was measured by balance, and the percentage of friability was calculated as in the below equation [14,17].

$$\text{Friability\%} = \frac{\text{W initial} - \text{W final}}{\text{W initial}} \times 100 \dots \text{eq } 6$$

We determined the disintegration time (DT) of the prepared IRTs using 0.1N HCl as a disintegration medium. We estimated the DT using a disintegration apparatus (Copley Scientific, UK) that included a basket rack assembly containing six open-ended

tubes. One tablet was placed in each tube, and the basket with the bottom surface made of a stainless-steel screen (mesh no. 10) was immersed in the 900 ml of 0.1N HCl kept at 37±0.5 ºC. We estimated the total disintegration time of the tablet in each tube using a stopwatch [18]. To estimate the drug content, we crushed and powered three tablets into a mortar. We weighed and dissolved the powder equivalent to 10 mg of SIM in 50 ml of ethanol, sonicated it for 15 minutes, and then filtered it through a 0.45 µm filter syringe. We diluted one ml of the filtrate with 10 ml of ethanol, and then used ethanol as a blank to analyze the resultant solution for SIM content using a UV spectrophotometer at 237 nm [19].

In vitro dissolution of SIM IRTs

We conducted in vitro dissolution studies for pure SIM, MAS-loaded SIM and SIM IRTs in accordance with the USP monograph. 10 mg of SIM samples were added to 900 mL of 0.01 M phosphate buffer pH 7.0 and 0.5% sodium dodycel sulfate at 37±0.5°C. The medium was then stirred at 50 rpm using apparatus II (RC-6, China) [14]. Aliquots of 5 mL were withdrawn at specified time intervals and filtered through filter syringe no. 0.45 µm. To maintain the volume of dissolution medium, we replaced it with an equal volume of fresh medium. We analyzed the filtered samples spectrophotometrically at 238 nm. This test was done in triplicate. The dissolution profile was statistically analyzed using a similarity factor ($f2$) as calculated by using DDSolver software. The two dissolution profiles are considered similar when *f2 values are* greater than 50 (50–100); otherwise, the profiles are not similar [20].

Release profile of selected formula and marketed product

The chosen formula was compared to the marketed tablet (Simvatin® Pharma International 10 mg) in terms of their release profile. This was done in 0.01 M phosphate buffer pH 7.0 with 0.5% sodium dodecyl sulfate at 37±0.5°C and 50 rpm stirring to see how similar the best prepared formula was the marketed tablets.

Statistical analysis

We expressed the experiment data as a mean for triplicate samples with a standard deviation (SD) and assessed them using one-way analysis of variance (ANOVA). Using GraphPad Prism, a test level of $p<0.05$ was considered statistically significant.

RESULTS

We obtained a high percentage yield (91.3%) and drug content (83.3%) from the prepared MAS-loaded SIM formula. Additionally, the adsorption formulation made SIM much more soluble ($p<0.05$); it was 1.32±0.20 mg/ml compared to 0.0074±0.00 mg/ml for the pure drug. As shown in Figure 1, comparing the *in-vitro* dissolution profiles of the pure SIM and the prepared formula indicated that the prepared MAS-loaded SIM exhibited improved dissolution rates ($f2$= 38.9) in comparison to the pure SIM.

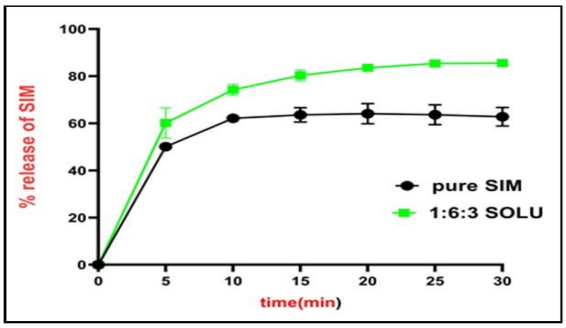

Figure 1: Comparison between the *in-vitro* dissolution profile of the pure SIM and the prepared MAS loaded SIM formulation in 0.01 M phosphate buffer pH 7.0 with 0.5% SDS at 37 °C.

The flow characteristics of the powder blends showed that the SIM powder had passable flowability and very poor compressibility, which improved when loaded on MAS. The prepared tablet blends further improved the flow properties compared to the MAS-loaded SIM formula, as Table 2 illustrates.

Table 2: Powder blends flow properties

Formula Code	Hausner's ratio (n=3)	Carr's Index (n=3)	Compressibility	Angle of repose (n=3)	Type of flow
Pure SIM	1.56±0.01	36.03±0.55	Very Poor	43.2±0.61	Passable
MAS-loaded SIM	1.37±0.01	27.2±0.76	Poor	33.4±1.6	Good
T1	1.27±0.01	21.4±0.63	Passable	20.2±0.9	Excellent
T2	1.32±0.115	24.7±0.665	passable	22.1±0.26	Excellent
T3	1.27±0.0	21.4±0.034	passable	36.6±0.771	Fair
T4	1.11±0.01	11.6±0.05	Good	12.1±0.8	Excellent
T5	1.14±0.01	13.6± 0.11	Good	11.3± 0.76	Excellent
T6	1.29±0.6	21.7±0.02	passable	13.3±0.64	Excellent

Values were expressed as mean±SD.

As indicated in Table 3, with the exception of T3, all the prepared tablets had a uniform appearance and demonstrated acceptable hardness, drug content, friability, weight, and DT according to BP criteria [17].

All the prepared tablets had a uniform appearance and showed acceptable hardness, drug content, friability, weight, and DT according to BP criteria [17]. Hence, the data in Table 2 and Table 3 revealed the impact of excipients on the results of pre- and post-evaluation tests.

Table 3: General appearance, weight variation, drug content, hardness, friability, disintegration test

Formula Code	Appearance	Drug content (mg/tablet) (n=3)	Hardness (kg) (n=3)	Friability (n=10)	Weight (mg) (n=20)	Disintegration Time (min) (n=3)
T1	Capping	100±0.1	8.36±1.48	0.37	244.6±1.17	1.90±1.11
T2		99±0.4	8.63±1.02	0.09	245.2±1.1	3.76±1.56
T3						
T4		98±0.5	7.1±1.7	0.25	246.2±1.4	0.9±0.44
T5		98.2±0.4	5.7±0.28	0.09	247.4±1.6	0.61±0.44
T6		93.5±0.5	5.5±0.72	0.46	245±1.31	1.0±0.0

Values were expressed as frequency, percentage, and mean±SD.

Different DT were obtained, where the order of DT according to super disintegrants was CCS< SSG< CP. It was also higher amount of SIM released from T5 than T6 made with SSG (*f*2=75) or T2 with CP (*f*2=55.7) when CCS was present (Figure 2).

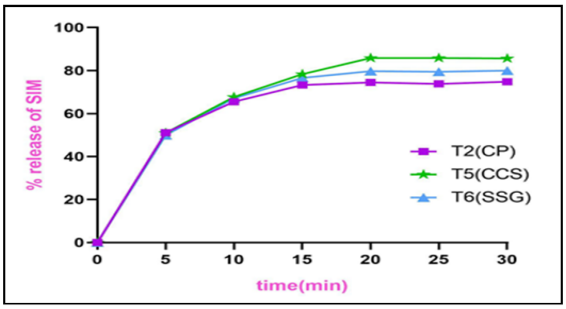

Figure 2: Effect of different types of super-disintegrants on the release of SIM from SIM IRT in phosphate buffer pH 7.0 with 0.5% SDS at 37 °C.

Moreover, Figure 3 shows that CCS-based formulae (T4 and T5), prepared with different types of Avicels®, obtained similar dissolution profiles (*f*2=79.8).

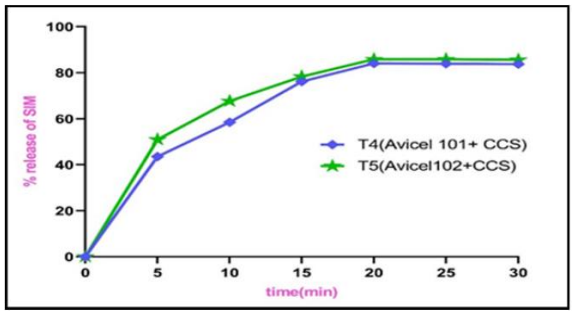

Figure 3: Effect of different types of diluents on the release of SIM from SIM IRT in phosphate buffer pH 7.0 with 0.5% SDS at 37 °C.

However, the T5 with the shortest DT among the prepared formulas and with that of marketed tablets (2±0.3 minutes) and lower friability than the T4 was selected as the preferred formula for further study. As shown in Figure 4, similar dissolution profiles were obtained (*f*2=58.6) by T5 and the available marketed tablet (Simvatin® Pharma International), and both comply with the USP requirements where 75% was released within 30 minutes.

DISCUSSION

The percentage yield and drug content values obtained by the MAS-loaded SIM indicated that the preparation method was suitable and efficient, although some loss may occur during scratching of the dried product from the Petri dish.

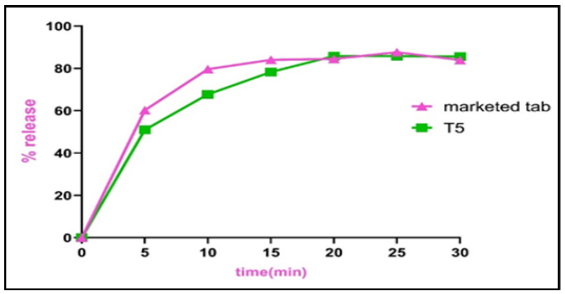

Figure 4: Comparison between release of SIM from T5 and marketed product in phosphate buffer pH 7.0 with 0.5% SDS at 37°C.

However, the apparent decrease in drug content may be due to some of the loaded drug molecules being tightly bound to the silica surface or attached to pores, which were inaccessible for ethanol to extract them, while the enhanced solubility could be explained by the adsorption of SIM on porous adsorbent (MAS), which led to the high surface area due to the large pore volume that provided a large exposed surface area for drug loading, which greatly enhanced drug saturated solubility [21,22]. Furthermore, the addition of Soluplus® as a wetting agent enhances the wettability of the hydrophobic drug, leading to a significant increase in its solubility [10]. Moreover, the high surface area of MAS and the hydrogen bond interaction between the drug and MAS contribute to the improved solubility of SIM, resulting in a non-crystalline state of the drug and consequently enhanced drug dissolution rates [23,24]. Also, the effect of the additives was seen in tests done before and after evaluation. Table 2 shows that T4 (Avicel®PH101) and T5 (Avicel®PH102) have the best flow property compared to the other formulas. This is because both types of Avicel® have the same density, so the same compressibility was obtained despite their mean particle size, which varies from 50 to 100 microns, respectively [25]. It's possible that the capping problem seen by T3 was caused by starch not being able to compress well as a diluent, so this formula was thrown out for further study [26]. CCS-containing tablets (T4 and T5) achieved the shortest disintegration time due to a dual mechanism of action: water wicking and rapid swelling. The swelling ability of CCS is more dominant, so it can change the tablet's formation, resulting in a fast drug dissolution rate. This result is in agreement with previous studies [27,28]. However, since both types of Avicel® have similar dissolution profiles, this suggests that the type

of disintegrants has a more pronounced effect on the drug's dissolution than the type of diluent.

Conclusion

The adsorption method worked to improve the solubility and dissolution rate of SIM when MAS was used as an adsorbent and Soluplus® was used as a hydrophilic polymer. Furthermore, by controlling the types of additives, we were able to obtain acceptable immediate-release tablets containing MAS-loaded SIM. Using Avicel® PH102 as a diluent and CCS 3% as super disintegrants, we produced tablets with the shortest disintegration time and the best SIM release profile, which were similar to the marketed tablets. As a result, this formula may be considered for SIM tablet production.

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Conflict of interests

No conflict of interests was declared by the authors.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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