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# Formulation and Evaluation of Metformin Hydrochloride Sublingual Film

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**Abstract**

Metformin hydrochloride (HCl) fast-dissolving sublingual films were formulated to enhance bioavailability and minimize side effects through rapid onset of action and optimized drug-release and dissolution characteristics. Initially, the same formulation design with different ratios of metformin HCl (Drug), polymer A and plasticizer B was used to formulate nine batches of sublingual films utilizing solvent casting methods. The film formulations were evaluated based on morphological properties (color, clarity, flexibility and smoothness, trinocular microscopic image of film), physical properties (weight variation, thickness uniformity, folding endurance, surface pH, percentage of moisture loss, disintegration time, content uniformity), incompatibility (differential scanning calorimetry (DSC), Fourier-transform infrared (FTIR)), and drug release pattern. Compatibility studies deduced that there was minimal interaction between metformin HCl (drug) and the excipients (polymer, plasticizer etc), whereas trinocular microscopic images revealed the information about the surface of the film and the distribution of medication and polymer within the fast-dissolving film. Physical characterization of metformin HCl sublingual film was performed via morphological evaluations, weight variation, thickness uniformity, folding endurance, surface pH, percentage of moisture loss, *in-vitro* disintegration, *in-vitro* dissolution, drug content uniformity. The best formulation of films among all nine batches of film formulations was P1 with satisfactory outcome with respect to *in-vitro* dissolution 89.05% within 5 minutes, least disintegration time (28 sec), lowest thickness (221.4 ± 0.87) and optimum folding endurance (195 times). This study presents that the proposed metformin HCl film formulation can dramatically reduce dosage suffices to attain the effective drug concentration at the targeted region.

**Key words:** Fast dissolving sublingual film, metformin hydrochloride (hcl), polymer a, solvent casting, bioavailability.

## Introduction

The oral route is one of the most convenient and preferred route of drug administration which consists of tablets, capsules, chewable tablets etc (Alqahtani *et al.,* 2021). However, due to the risk of choking, this kind of ingestion is not appropriate for elderly and paediatric patients with dysphasia, bedridden patients and noncompliant patients. Fast-dissolving drug delivery system (FDDDS) have been developed to reduce the risk of choking and improve patient compliance. Polymeric films, also known as fast-dissolving or oral thin films, were first introduced in 1970 (Rajagopalan *et al.,* 2024). Other names for these fast-dissolving films included melt-in-mouth dose forms, mouth-dissolving films, Oro-dispersible films, and quick disintegrating films. Transdermal patch technology served as the foundation for these formulations (Karki *et al.,* 2016)

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The solvent-casting approach, which dissolves the water-soluble components to create a clear, viscous solution, is the preferred method for creating the oral thin films. The bulk films are mixed with smaller amounts of the API and other agents that have been dissolved in the solution. The viscous aqueous solution is mixed with this mixture. When choosing an appropriate solvent, the physicochemical characteristics of the API are crucial and should be taken into account. These characteristics include the polymorphic nature of the chosen API, temperature sensitivity, compatibility with solvents and compatibility with other film-forming excipients (Lee, 2017).

Metformin hydrochloride (MET) is chemically designated as N, N-dimethyl-imidodicarbonimidic-diamide hydrochloride (1,1-dimethylbiguanide hydrochloride). It functions by diminishing intestinal glucose absorption, lowering hepatic glucose synthesis and enhancing insulin sensitivity (Migdadi *et al.*,2018). This study is designed to develop a sublingual film of metformin HCl to minimize gastrointestinal side effects and complications associated with the oral delivery route.

## Materials and Methods

*Materials:* Metformin hydrochloride was obtained from Active Fine Chemicals Ltd., Dhaka, Bangladesh. Polymer A, plasticizer B, citric acid (anhydrous) and cross-povidone were purchased from Merck, Germany. Distilled water was manufactured in the pharmaceutical technology lab of the State University of Bangladesh.

*Preparation of Metformin Hydrochloride sublingual film:* Table 1 shows the constituents of metformin hydrochloride sublingual film formulations.

*Calculation of drug quantity:* For 100 mm × 100 mm glass plate, total surface area of glass plate = (100 × 100) $mm^2$ = 10000 $mm^{2;}$ Size of individual film = (20 × 20) $mm^2$ = 400 $mm^2$;

So, theoretically total number of films per glass plate= 10000÷400 = 25 pcs. Dose of drug per film =40 mg; Total quantity of drug should be taken in one batch = (40 × 25) mg = 1000 mg.

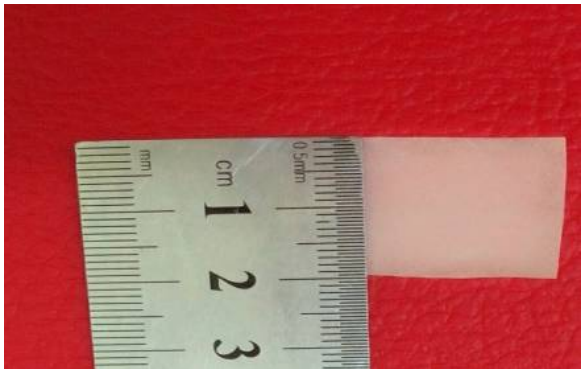


Figure 1. Metformin hydrochloride sublingual thin film

**Table 1. Formulation of metformin hydrochloride sublingual film.**

| Ingredients/films | Formulation Code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | P1 | P2 | P3 | P4 | P5 | P6 | P7 | P8 | P9 |
| Metformin hydrochloride (API) (mg) | 40.13 | 40.13 | 40.13 | 40.13 | 40.13 | 40.13 | 40.13 | 40.13 | 40.13 |
| Polymer A (mg) | 20 | 40 | 60 | 80 | 100 | 120 | 140 | 160 | 180 |
| Plasticize B (mg) | 20 | 20 | 20 | 30 | 30 | 30 | 40 | 40 | 40 |
| Citric Acid (mg) | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Crosspovidone (mg) | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Distilled water (ml) | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |

*Method of preparation of sublingual film:* For the preparation of a sublingual film of metformin hydrochloride, a solvent casting method was used (Alam *et al.*, 2014). The following process shows the method of preparation, in which API (Metformin hydrochloride) was incorporated into a polymeric film consisting of polymer A, plasticizer B, disintegrating agent and saliva stimulating agent. Polymer A and solvents were dissolved at low heat in a beaker. In another beaker drug solution was prepared by continuous stirring with plasticizer B and citric acid. Cross-povidone solution was prepared in

another vessel and added after addition and mixing of polymer solution and API solution. Then the resulting solution was casted into a 100 mm × 100 mm glass plate and dried at 60 ± 5°C for about 5 hours until dry. Then the film loaded with metformin HCl was gently peeled out and cut into 20 × 20 $mm^2$ pieces (Figure 1).

*Evaluations*: *Morphological properties*: All films were visually observed for properties such as color, clarity, flexibility, and smoothness.

*Variation of weight*: The weight of 2 × 2 $mm^2$ films were weighted in analytical balance. The mean weight of film and standard deviation was calculated. The results are shown in table 2.

*Film thickness:* Film thickness was determined using the standard pre-calibrated micrometer. Each 2 × 2 $cm^2$ film was measured at three different positions (center and corner) and the mean thickness was calculated and reported separately. The results are shown in Table 2**.**

*Folding endurance*: It was determined by repeatedly folding a film of 2 × 2 $cm^2$ size at the same place until it broke. Ten films of each formulation of size (2 × 2 $cm^2$) were folded at same place until it cracks. The results are shown in table 2.

*Surface pH measurement*: After placing the film to be tested on a petri dish and moistening it with 0.5 ml of distilled water, it was left for 30 seconds. The pH was measured after bringing the pH paper in contact with the surface of the formulation and allowing it to equilibrate for 1 min. table 2 displays the findings.

*Percentage of moisture loss*: The films were kept in a desiccator with anhydrous calcium chloride to calculate the percentage of moisture loss. After three days films were taken out re-weighted and the percentage of moisture loss was calculated by the following formula:

Percentage of moisture loss = {(initial weight-Final weight)/initial weight} ×100.

The results are shown in table 2.

*In vitro disintegration test* (Bhyan *et al.*, 2011): To replicate the *in-vitro* and *in-vivo* settings, the disintegration test was slightly modified. Films of each size (2 x 2 $cm^2$) needed for dosage administration were set up in a beaker with 50 ml of distilled water at 37 ± 2°C for the study. The in vitro disintegration time was the amount of time needed for the film to break down. Only 50 ml of medium was utilized because it is anticipated that the film will dissolve in the mouth when saliva is present. The results are shown in table 2.

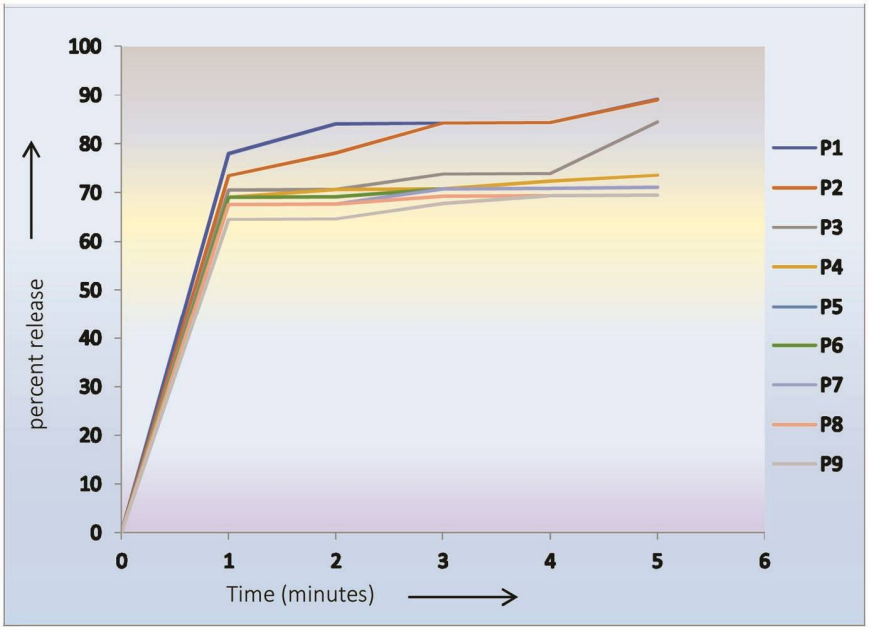


Figure 2. Percent drug release for metformin hydrochloride sublingual films.

*In vitro dissolution test* (Bhyan *et al.*, 2011): The dissolution study was performed in 600 ml phosphate buffer (pH 6.8) as a dissolution medium in a dissolution testing apparatus. The temperature was maintained at 37 ± 2°C. The fast-dissolving films were placed in the dissolution tester and 1 ml sample was withdrawn in every minute for 5 minutes and replaced with same amount of fresh phosphate buffer. Further 1 ml sample was adjusted to 10 ml by the medium and was analyzed by Shimadzu -1800 series UV-Visible spectrophotometer at 332 nm. The cumulative percentage of drug release was calculated. The release profile is illustrated in figure 2.

*Trinocular microscopic image of film*: A trinocular microscopic image of the film was taken and assessed. The film's surface and the distribution of the medication and polymer within it were analyzed.

*Content uniformity* (Palepu, 2019): A 20×20 mm² metformin HCl film was placed in a 100 ml volumetric flask. Sixty milliliters of pH 6.8 phosphate buffer were introduced and sonicated for thirty minutes to dissolve the film. Subsequently, pH 6.8 phosphate buffer was used to achieve a total volume of 100 ml. The solution was subjected to filtration with whatman filter paper. Following that, 1 ml of filtrate was extracted with stimulated salivary fluid and diluted to 10 ml using the identical buffer. The solution's absorbance was quantified at $\lambda_{max}$ 276 nm utilizing a UV-VIS spectrophotometer (Alam *et al.*, 2014). The results are shown in table 2.

## Results and Discussion

*Compatibility study by FTIR spectral analysis*: Appropriate quantity of sample were used to analyze the compatibility of API and excipients used in the formulation.

The IR spectrum of the formulation (Figure 4) then compared with those of pure drug (Figure 3) and matching was completed to detect any change in peak.

**Table 1. Formulation of metformin hydrochloride sublingual film.**

| Ingredients/films | Formulation code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | P1 | P2 | P3 | P4 | P5 | P6 | P7 | P8 | P9 |
| Metformin hydrochloride (API) (mg) | 40.13 | 40.13 | 40.13 | 40.13 | 40.13 | 40.13 | 40.13 | 40.13 | 40.13 |
| Polymer A (mg) | 20 | 40 | 60 | 80 | 100 | 120 | 140 | 160 | 180 |
| Plasticize B (mg) | 20 | 20 | 20 | 30 | 30 | 30 | 40 | 40 | 40 |
| Citric Acid (mg) | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Crosspovidone (mg) | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Distilled water (ml) | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |

**Table 2. Various physical properties of metformin hydrochloride sublingual films.**

| Formulation code | Weight variation (mg) | Thickness uniformity (µm) | Folding endurance (Times) | Surface pH | % of moisture loss | Disintegration time (sec.) | Content uniformity (%) |
|---|---|---|---|---|---|---|---|
| P1 | 93.7 ± 1.09 | 221.4 ± .87 | 195 | 6.0 | 1.08 ± 0.09 | 23 | 99.95± 0.98 |
| P2 | 104 ± 0.67 | 287.6± 1.59 | 200 | 6.0 | 1.19 ± 0.08 | 30 | 98.06± 0.97 |
| P 3 | 120.7 ± 1.28 | 309.5 ± 1.68 | 280 | 6.0 | 1.27 ± 0.04 | 46 | 98.10± 0.99 |
| P4 | 141.8 ± 0.50 | 339.0 ± 0.58 | 300 | 6.0 | 1.67 ± 0.05 | 124 | 97.50± 1.00 |
| P5 | 163.96 ± 0.47 | 408.60 ± 0.88 | 327 | 6.0 | 1.95 ± 0.08 | 130 | 97.49± 1.12 |
| P6 | 251.80 ± .56 | 419.2 ± 0.98 | 378 | 6.0 | 2.07 ± 0.07 | 200 | 95.85± 1.16 |
| P7 | 305.60 ± 0.76 | 509.00 ± 1.05 | 482 times | 6.0 | 2.15 ± 0.08 | 280 | 95.58± 1.36 |
| P8 | 229.18 ± 0.26 | 597.60 ± 1.89 | 486 times | 6.0 | 2.98 ± 0.09 | 320 | 95.3± 1.26 |
| P9 | 379.5 ± 0.89 | 605.2 ± 1.58 | 488 times | 6.0 | 3.06 ± 0.09 | 328 | 91.01± 1.53 |

Note: All values are shown as mean ± SD, n = 10; SD denotes standard deviation.

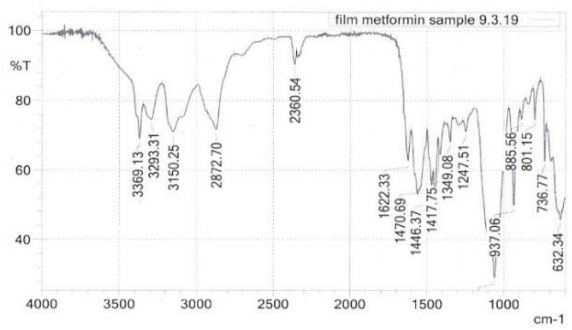


Figure 3. IR spectrum of pure metformin hydrochloride

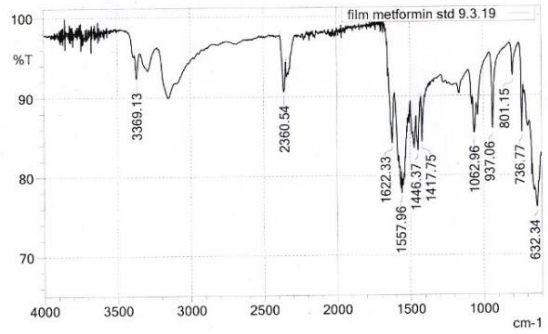


Figure 4. IR spectrum of metformin hydrochloride film

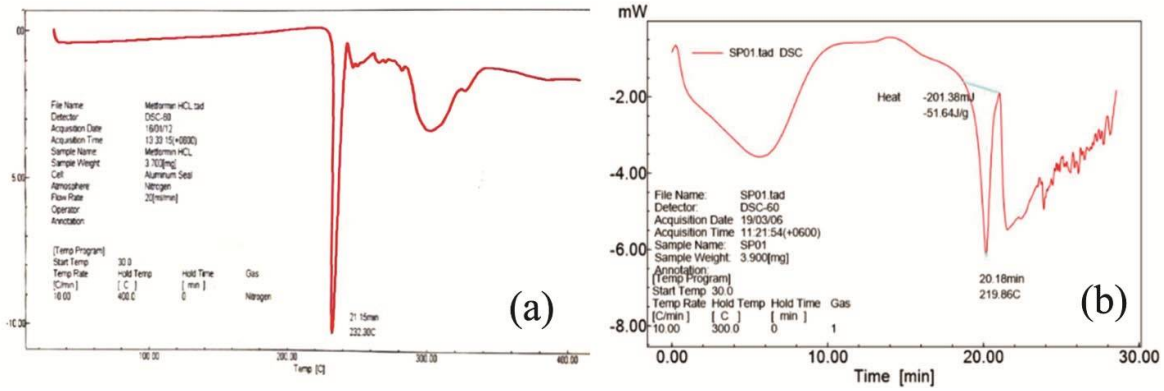


Figure 5. Differential scanning colorimetric spectrum, a) pure metformin hydrochloride, and b) metformin hydrochloride film.

Total of nine batches (P1–P9) of sublingual films were prepared through the use of solvent casting method by using metformin hydrochloride as the API, polymer A as the polymer, plasticizer B as the plasticizer, citric acid as a saliva stimulant, cross-povidone as the super disintegrant, and distilled water as the solvent. The ratios of polymer A to plasticizer B were 1:1, 2:1, 3:1, 2.67:1, 3.33:1, 4:1, 1:3.5, 4:1, and 4.5:1, respectively.

Ten films of each 2×2 $mm^2$ were cut at ten different places from casted films and weight variation was measured. This study reported that the weight variation varies from 93.7 ± 1.09 to 379.5 ± 0.89 mg. The results of weight variations are shown in the table 2. Total nine (09) film formulations were evaluated for weight variation exhibited satisfactory results, as all the measured values in this section of weight variation fall within acceptance limit. However, the mean weight of the formulations (P1 to P9) increased with higher polymer concentrations, which may also be partially attributed to the corresponding increase in plasticizer content. But an exception occurred in the formulation P8 as it is evident that a drastic decrease in mean weight from formulation P7 may be due to variation in casting process, inconsistent film thickness and/or environmental conditions (Avinash, 2024; Cai *et al.*, 2023). The thicknesses uniformity of the drug loaded films were measured with the help of screw gauge. Thickness of film varies from 221.4 ± 0.87 to 605.2 ± 1.58 µm. Results are reported in the table 2. A total of nine (09) film formulations were assessed for thickness uniformity, all of which demonstrated satisfactory results. Typically, the thickness of oral thin films ranges between 0.05 mm and 0.15 mm. However, the ideal thickness may vary based on the intended application, with some formulations extending up to 1 mm or more in the form of thicker films or sheets (Rani *et al.*, 2021). The thickness uniformity of the formulations (P1 to P9) increases gradually as the number of excipients (polymer A, Plasticizer B) increases.

For folding endurance, the no. of film fold until it broke was reported in the table 2. The folding endurance of the films improved with higher polymer concentrations, attributed to the enhanced elasticity of the polymer (Akter *et al.*, 2023a). Formulations (P3 to P9) gained greater flexibility and durability than the formulations (P1 to P2) because films with a folding endurance value of 300 or more are regarded to have excellent flexibility and durability (V. Londhe and Shirsat, 2018a). Since pH of the saliva range from 5.5 to 7 (V. Londhe and Shirsat, 2018b), an attempt was made to keep the surface pH of the film within that range. The surface pH of all the films (P1 to P9) was 6 as shown in table 2 and hence, this film formulations may not cause any irritation in the oral cavity (V. Londhe and Shirsat, 2018a).

The prepared film formulations were analyzed for % drug content and it was noticed that all the formulations (P1 to P8) except the P9 found to contain more than 95% drug content, though formulation P9 to have contained more than 90% suggesting all the formulations to have satisfied the acceptance criteria as per the USP guidelines because a batch is considered acceptable if the individual film dosage units contain 85-115% of the labeled amount of the API and the standard deviation or SD does not exceed 6% (Shen *et al.*, 2014). The data of % drug content alongside SD was shown in table 2. Disintegration time of the film was done by using tablet disintegration test apparatus. A size of two square inch film was subjected for this study. The formulations P1 to P3 from table 2 shows standard DT as sublingual film formulations are designed for rapid disintegration, typically aiming for disintegration times within 10 to 50 seconds (Akter *et al.*, 2023b; Londhe and Shirsat, 2018b). Additionally, changes in the amounts of polymer A and plasticizer B also caused a corresponding change in the disintegration time.

This study examines the development and assessment of sublingual films containing metformin hydrochloride (MH) to improve drug bioavailability and patient adherence, especially for elderly and dysphagic patients. The solvent casting technique was utilized with different polymer-plasticizer ratios to enhance film properties. Of the nine (9) formulations (P1–P9), P1 exhibited superior performance, characterized by quick disintegration (28 seconds), substantial drug release (89.05% within 5 minutes), and optimal folding durability (195 cycles). In contrast to traditional oral metformin tablets, which demonstrate a delayed onset and gastrointestinal adverse effects (Migdadi *et al.*, 2018), the sublingual film presents a promising option. Comparable research on fast-dissolving metformin films, indicated that polymer-bound formulations attained quick dissolution and notable enhancement in bioavailability (Sheela and Haque, 2015). Another study developed fast-dissolving films of telmisartan utilizing hydroxypropyl methylcellulose (HPMC), which disintegrated within 30 seconds (Londhe and Umalkar, 2012). Corroborating the results of the current work. (Karki *et al.* 2016) also asserted that thin-film drug administration improves systemic absorption by circumventing hepatic metabolism, hence reinforcing the methodology of this investigation (Karki *et al.*, 2016). This formulation exhibited favorable physicochemical qualities; nevertheless, subsequent research should investigate *in vivo* pharmacokinetics and stability evaluations for clinical application. In contrast to buccal patches created by Chemate *et al.* (2016), which demonstrated extended drug release, this sublingual film has a quick onset, rendering it beneficial for immediate glucose management. This study provides a robust basis for the development of metformin sublingual films as an effective alternative to conventional oral delivery, requiring more refinement and optimization for commercial use.

**Conclusion**

The advantage of utilizing sublingual drug delivery systems for Metformin HCl over systemic delivery is that a reduced dosage suffices to attain the effective concentration at the targeted region. The current study successfully developed the sublingual films of metformin HCl utilizing various ratios of polymer A and plasticizer B. Based on the comprehensive discussion and findings of the current study, we conclude that Sublingual films of

metformin HCl can be fabricated using the solvent casting method and Both hydrophilic and hydrophobic polymers are suitable for the preparation of sublingual films. Further research on formulation, optimization, compatibility, stability and scale-up studies is essential to substantiate the efficacy of this sublingual film formulation.

**Author contribution**

Sadia Nowshin Islam: Analyzed and interpreted the data; wrote the paper. Sreebash Chandra Bhowmik, Marzia Alam, Abdul Kuddus and Abir Hasan Pranto: Conducted the experiments; Contributed reagents, Analyzed and interpreted the data, and wrote the paper. Md. Saiful Islam Pathan and Tanoy Saha: Conceived and designed the experiments; Reviewed and edited the paper.

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No funds have been received to conduct this study.

**Conflicts of Interest**

There are no conflicts of interest that the authors have disclosed concerning the publication of this paper.

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