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IMPROVEMENT OF DISSOLUTION PROPERTIES OF ALBENDAZOLE FROM DIFFERENT METHODS OF SOLID DISPERSION

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ABSTRACT

Poor aqueous solubility of drugs results in poor absorption and bioavailability. The objective of solid dispersion technology is to increase the dissolution properties of highly lipophilic drugs, by using different hydrophilic carriers thereby improving their bioavailability. This technology is useful for enhancing the dissolution, absorption and therapeutic efficacy of drugs in dosage forms. Albendazole is a broad-spectrum antihelmintic agent used for the treatment of a variety of parasitic worm infestations. It is practically insoluble in water but slightly soluble in solvents like chloroform, methanol, ethyl acetate, and acetonitrile. The aim of our study was to improve the dissolution profile of albendazole using HPMC K 100 LV, Kollidon VA64 and Mannitol as carriers by solid dispersion techniques. From the prepared solid dispersion, formulation code CSF5 showed better result where carrier was HMPC K 100 LV at 1:10 ratio in solvent evaporation method. The HPMC K 100 LV showed better result for both kneading and solvent evaporation methods. Moreover, among the method employed, solvent evaporation method showed better solubility of drug at 60 min also at 1:10 ratio which was 78.86%. Results indicated that current formulation of solid dispersion is a promising approach for enhancing drug solubility and dissolution.

Keywords: Solid dispersion, Albendazole, Solubility, Dissolution, hydrophilic carriers.

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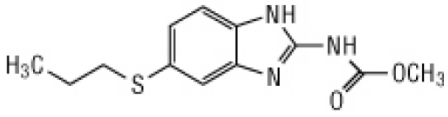
INTRODUCTION

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. Solid dispersions are a useful pharmaceutical technique for increasing the dissolution, absorption and therapeutic efficacy of drugs in dosage forms. The most commonly used hydrophilic carriers for solid dispersions include polyvinyl pyrrolidone, polyethylene glycols (PEGs), Tween-80, sodium lauryl sulphate (SLS) etc. [1,2,3]. The increase in dissolution rate from SDs can be attributed to one or a combination of the following factors: a reduction of particle size of the drug, a solubilizing effect on the drug by the water soluble carrier, enhancement of the wettability and dispersibility of the drug by the carrier material, and the possible formation of a metastable dispersion that has a greater solubility resulting in a quick dissolution rate [4].

The solubility depends on the physical form of the solid, the nature and composition of solvent medium (temperature and pressure) of system [5]. According to Biopharmaceutical classification system (BCS) which is based on the permeability characteristics of the drugs, the poorly aqueous soluble drugs fall under two major classes i.e. class II and IV. The BCS class II drugs represent low aqueous solubility and high permeability

characteristics. Attempts to improve the solubility of the drugs belonging to class II category can result in an enhancement of their bioavailability [6]. Solid dispersion technology is utilized to increase the dissolution rate of highly lipophilic drugs, thereby improving their bioavailability [7].

Albendazole is a broad-spectrum antihelminthic agent of the benzimidazole type. It is a medication used for the treatment of a variety of parasitic worm infestations. It is useful for giardiasis, trichuriasis, filariasis, neurocysticercosis, hydatid disease and ascariasis [8]. Its molecular formula is $C_{12}H_{15}N_3O_2S$ and molecular weight is 265.34. It has the following chemical structure:



Albendazole is a white to off-white powder. Each white to off-white, film-coated tablet contains 200 mg of albendazole. It is soluble in dimethylsulfoxide, strong acids, and strong bases. It is slightly soluble in methanol, chloroform, ethyl acetate, and acetonitrile. Albendazole is practically insoluble in water [9]. Due to the lower solubility in water, the absorption in the GI tract is poor [10]. It is, however, better absorbed than other benzimidazole carbamates [11]. Albendazole concentrations are negligible or undetectable in plasma as it is rapidly converted to the sulfoxide metabolite prior to reaching the systemic circulation.

The systemic anthelmintic activity has been attributed to the primary metabolite, albendazole sulfoxide. Oral bioavailability appears to be enhanced when albendazole is co-administered with a fatty meal (estimated fat content 40 g) as evidenced by higher (up to 5-fold on average) plasma concentrations of albendazole sulfoxide as compared to the fasted state. Maximal plasma concentrations of the drug are typically achieved 2 to 5 hours after dosing and are on average 1.31 mcg/mL (range 0.46 to 1.58 mcg/mL) following oral doses of albendazole (400 mg) in 6 hydatid disease patients, when administered with a fatty meal. Plasma concentrations of albendazole sulfoxide increase in a dose-proportional manner over the therapeutic dose range. The mean apparent terminal elimination half-life of albendazole sulfoxide typically ranges from 8 to 12 hours in 25 normal subjects, as well as in 14 hydatid and 8 neurocysticercosis patients [12].

MATERIALS AND METHODS

Beximco Pharmaceuticals Ltd. was provided the drug Albendazole to conduct this study. The other materials such as Kollidon VA64, HPMC K 100 LV and Mannitol were purchased from local scientific materials suppliers.

Preparation of Solid Dispersions

Albendazole (pharmaceutical grade) and the polymers mentioned above were used for the preparation of SDs. To prepare the solid dispersions of selected polymers (Kollidon VA64, HPMC K 100 LV, Mannitol) were used at different proportion with the drug Albendazole. Then the drug polymer mixtures were homogenized by stirring, pulverized and cooled, the obtaining mixtures were sieved properly and kept in a screw-capped glass vial at desiccator for further use.

Preparation of Solid Dispersion by Physical mixtures

To prepare the solid dispersion formulation was employed by physical mixing of the selected polymer and obtained Albendazole at different ratio (1:2, 1:4, 1:6, 1:8, 1:10) in individual formulation. The mixture was performed by triturating using mortar and pestle for about 15 minutes and then kept in a screw-capped glass vial at desiccator until use [12].

Preparation of Solid Dispersion by Kneading Method

For preparation of solid dispersion by kneading method, a mixture (10 mg) of Albendazole and each of every polymer at a ratio of (1:2, 1:4, 1:6, 1:8, 1:10 by weight, respectively) were wetted with methanol to form the slurry and kneaded thoroughly for 60 min in a glass mortar and then dried in an oven at 35ºC till the constant weight is reached. The dried mass was pulverized and shifted through #60 and obtained product was stored in a desiccator until further evaluation.

Preparation of Solid Dispersion by Solvent Evaporation Method

For this method, about 100 mg of Albendazole was weighed accurately in an analytical balance and taken into dry and clean glass vials. Then methanol was added on each vial [13]. Then each of every polymer were dissolved in the solvent using a vortex mixer to make a polymer solution. Drug, polymer and solvent (methanol) combination was dried by using hair dryer until solid dispersion was formed and the solvent evaporated completely. Finally, the formulations were withdrawn from vials, crushed in mortar and pestle, passed through #60 sieve and the resulted samples were weighed and then transferred in clean vials with proper labelling and its double amount of lactose was added on each vials as adsorbent and mixed well. These formulations were kept also in desiccator until the dissolution started.

Selection of Solvent for solvent evaporation method

Since the drugs which are usually hydrophobic in nature usually chosen for solid dispersions and with them hydrophilic polymers are used to enhance the rate of dissolution. The selection of proper solvent in solvent evaporation method is very much important because its removal rate is critical to the quality of dispersion. For complete removal of solvent lower temperature and reduced pressure can be used. Solvent evaporation method is considered as the effective method for SD_S but the major disadvantage associate with the method is that different polymorphic forms of the same drug may be formed if different solvents are used [17]. Sometimes after selecting a proper solvent it was observed that complete removal of solvent was very much difficult in some SD_S. In some cases, large volume of organic solvent is required to dissolve both drug and carriers. So to avoid multiple complications care should be taken to make proper choice and use of organic solvents during formulations.

Table 1: Drug carrier ratio for different formulations of Physical Mixture

Code	Method	Polymer	Drug-Carrier ratio	Formulation Code
A	Physical Mixture	HPMC K 100 LV	1:2	APF1
			1:4	APF2
			1:6	APF3
			1:8	APF4
			1:10	APF5
		Kollidon VA64	1:2	APF6
			1:4	APF7
			1:6	APF8
			1:8	APF9
			1:10	APF10
		Mannitol	1:2	APF11
			1:4	APF12
			1:6	APF13
			1:8	APF14
			1:10	APF15

Table 2: Drug carrier ratio for different formulations of Kneading Method

Code	Method	Polymer	Drug-Carrier ratio	Formulation Code
B	Kneading Method	HPMC K 100 LV	1:2	BKF1
			1:4	BKF2
			1:6	BKF3
			1:8	BKF4
			1:10	BKF5
		Kollidon VA64	1:2	BKF6
			1:4	BKF7
			1:6	BKF8
			1:8	BKF9
			1:10	BKF10
		Mannitol	1:2	BKF11
			1:4	BKF12
			1:6	BKF13
			1:8	BKF14
			1:10	BKF15

Table 3: Drug carrier ratio for different formulations of Solvent Evaporation Method

Code	Method	Polymer	Drug-Carrier ratio	Formulation Code
C	Solvent Evaporation method	HPMC K 100 LV	1:2	CSF1
			1:4	CSF2
			1:6	CSF3
			1:8	CSF4
			1:10	CSF5
		Kollidon VA64	1:2	CSF6
			1:4	CSF7
			1:6	CSF8
			1:8	CSF9
			1:10	CSF10
		Mannitol	1:2	CSF11
			1:4	CSF12
			1:6	CSF13
			1:8	CSF14
			1:10	CSF15

Evaluation of Albendazole Solid Dispersions

Drug content

For the estimation of drug content, 10 mg Albendazole was transferred into 100 ml volumetric flasks and volume was adjusted to 100 ml with distilled water. The content of Albendazole was determined using UV-vis spectrophotometric at 292 nm against suitable blank.

In vitro dissolution study

Solid dispersions formulation was subjected to *in vitro* dissolution by using USP 23 basket method (apparatus 1). Distilled water was used as a dissolution media with 50rpm and 37°C temperature. 5 ml of sample was withdrawn at regular intervals of time and filtered and replaced with 5 ml of fresh dissolution medium, dilutions were made and analyzed for Albendazole at 292 nm by using UV-vis spectrophotometer.

RESULTS AND DISCUSSION

The solubility of Albendazole increases with using different polymers and also with increasing the concentration of the polymers. Among the polymers used here to conduct our study, HPMC K 100 LV showed better solubility profile compared to other two-kollidon VA64 and mannitol. In physical mixture method, HPMC K 100 LV at 1:10, Kollidon VA64 at 1:10 and mannitol at 1:10 ratio showed the maximum % of drug release against time with 45%, 40.88% and 30.42% (Figure 1).

However, in kneading method exhibited better drug release profile against time which is almost double compared to physical mixture method. HPMC K 100 LV at 1:10, Kollidon VA64 at 1:10 ratio showed 81.96% and 71% where mannitol at 1:10 showed only around 28% drug release (Figure 2).

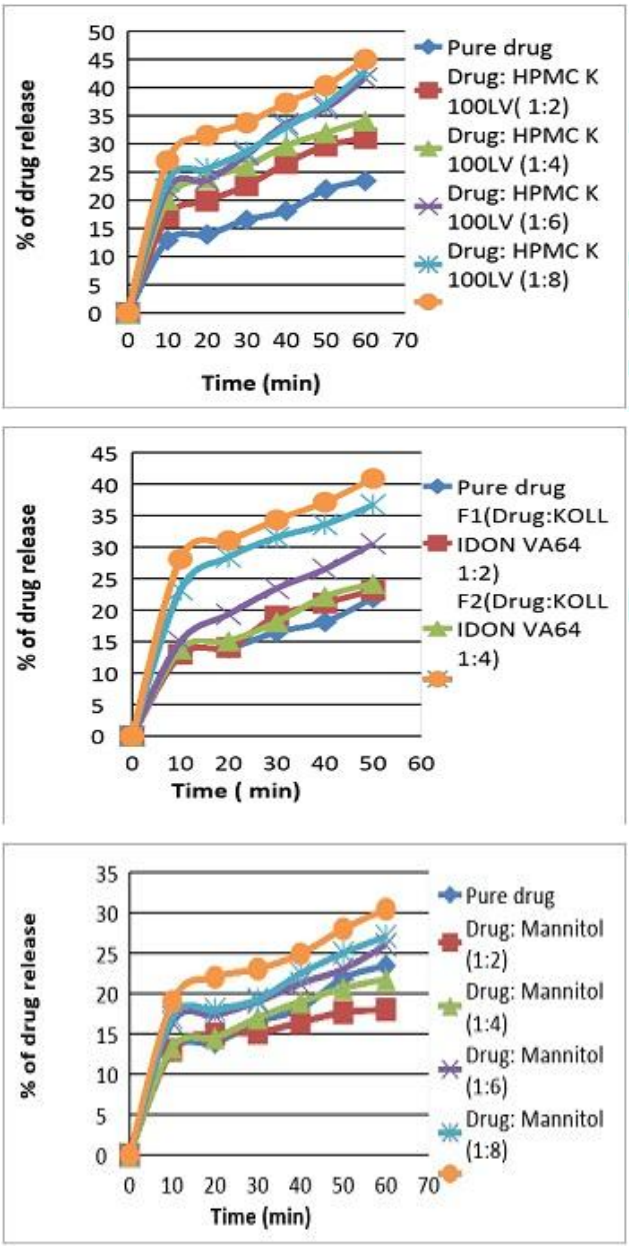


Figure 1: The graphical representation of Time Vs % of drug release profile from physical method.

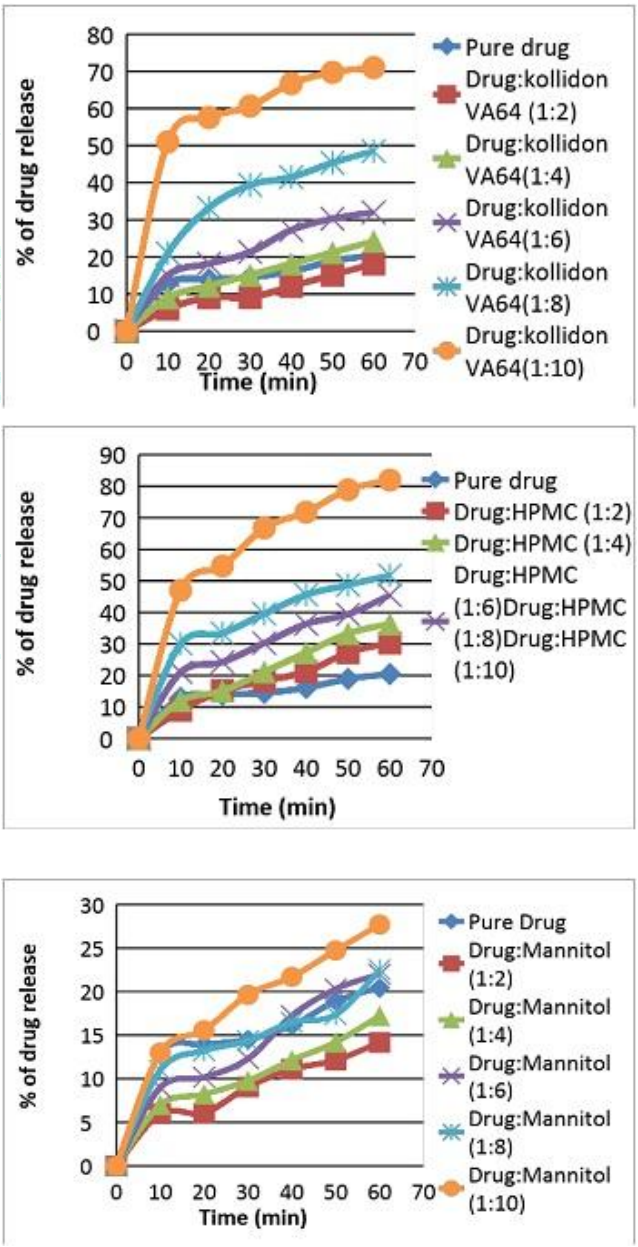


Figure 2: The graphical representation of Time Vs % of drug release profile from kneading method.

Among the three formulation technique, solvent evaporation method gave the best results for the ratio of the polymers of HPMC K 100 LV at 1:10, Kollidon VA64 at 1:10 and mannitol at 1:10. Interestingly, even mannitol at 1:10 showed almost 50% drug release where other two methods around 30% at the same polymer ratio. In addition, HPMC K 100 LV at 1:10 and Kollidon VA64 at 1:10 ratio revealed almost 80% and 70% of drug release which is noticeable.

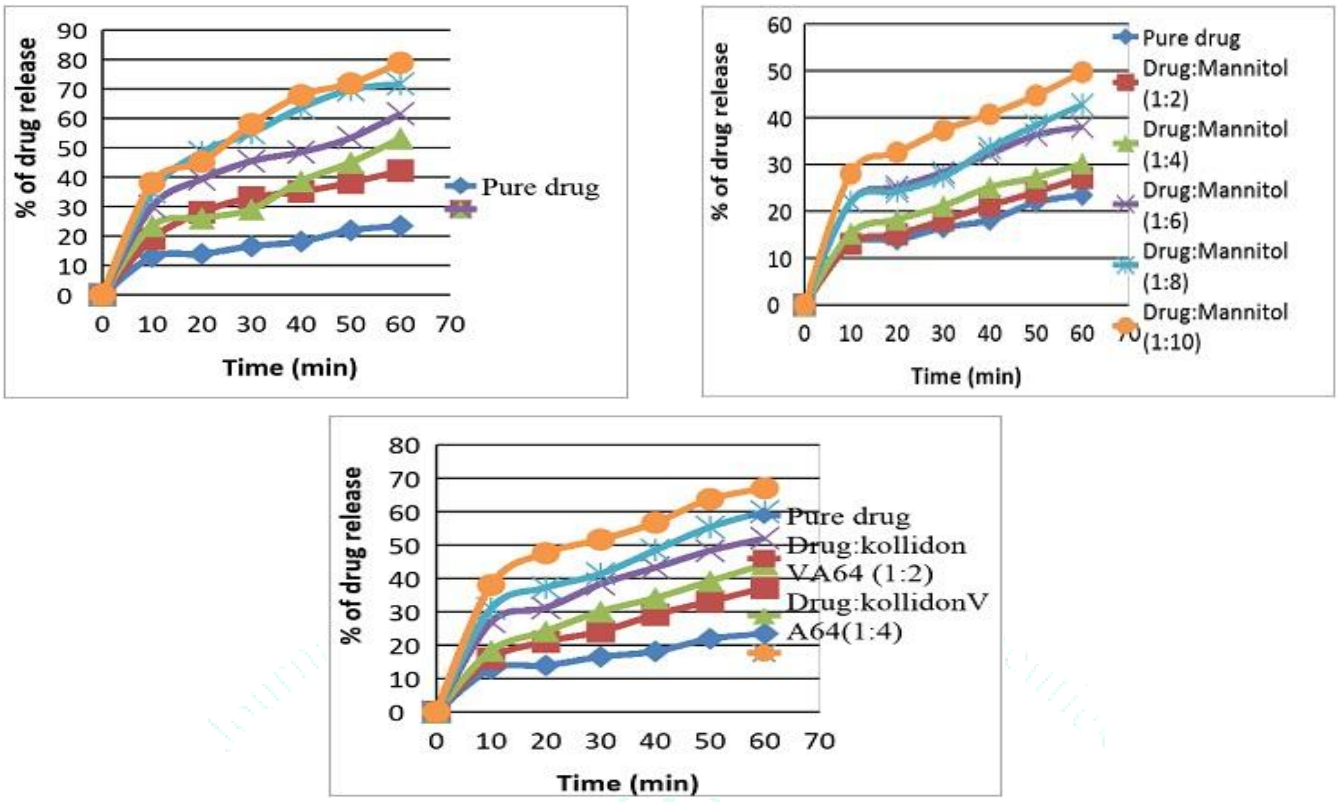


Figure 3: The graphical representation of Time Vs % of drug release profile from solvent evaporation method.

From this study, it is clear that the solvent evaporation method with HPMC K100LV at 1:10 ratio exhibit the best result which can be presented graphically as follows (Figure 4).

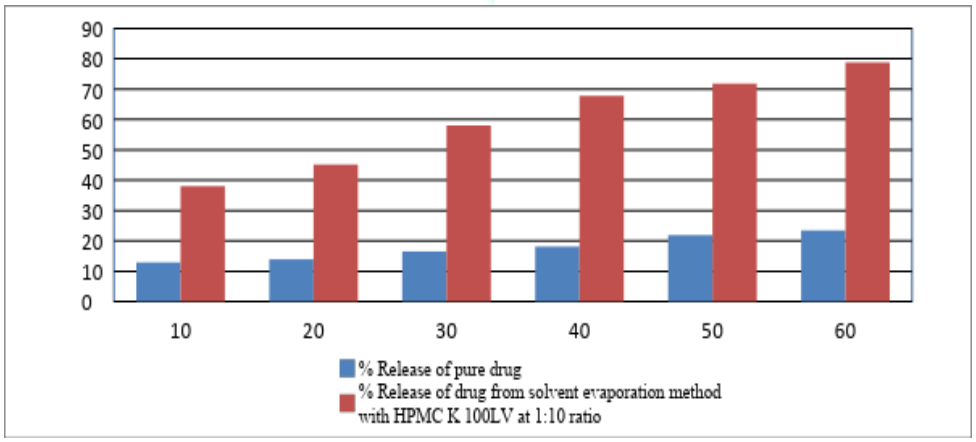


Figure 4: Graphical representation of time Vs % release of pure drug and release of drug from solvent evaporation method with HPMC K 100LV at 1:10 ratio

So it is clear evident that solubility of solid dispersion is higher in solvent evaporation method as compared to other two methods- physical mixtures and kneading method. When % of drug release was plotted against time the graphical representation showed that release of drug from different methods of solid dispersion was faster than release of pure Albendazole. And amongst the different polymer used, HPMC K 100 LV with 1:10 ratio showed maximum drug release in solvent evaporation method which is shown in figure 4. From our discussion we can represent a graphical representation showing the effect of maximum drug releasing polymer HPMC K100LV in different methods employed here to conduct our study. Overall, the employed three methods and their % of drug released have shown in bellow (Figure 5).

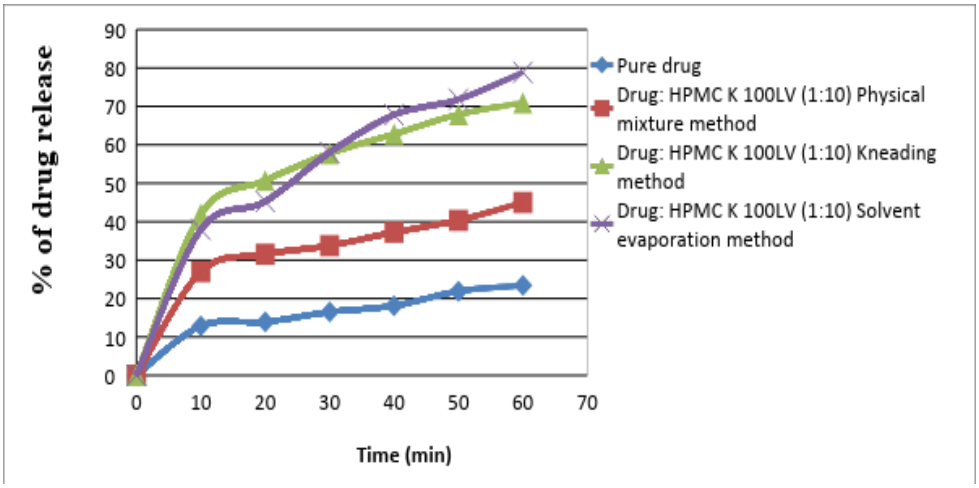


Figure 5: The effects of HPMC K100LV on different methods of SDs for Albendazole.

CONCLUSION

It can be summarized that, by using the three physical method, kneading and solvent evaporation methods, solid dispersion would be the successfully applicable with solvent evaporation technique which have the best drug release of percentage at 1:10 ratio of the employed polymers. Amongst the methods solvent evaporation method showed maximum result as compared to other two – physical method and kneading method. Results indicated that our prepared solid dispersion is a promising approach for enhancing drug solubility and dissolution. Several studies have also been conducted with the drug Albendazole but we have used different polymers here along with different ratios and among the polymers used to conduct our study HPMC K100LV exhibit better dissolution.

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Conflict of Interest: Authors have declared no potential conflict of interest.

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