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Formulation and Assessment of Gliclazide Solid Dispersions

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Abstract

Gliclazide, a sulfonylurea-class oral hypoglycemic agent, suffers from poor aqueous solubility, limiting its bioavailability and therapeutic efficacy. To enhance its solubility & dissolution rate, solid dispersions of Gliclazide were developed using PEG 6000 as hydrophilic carrier through physical mixing and kneading methods. Spectrophotometric analysis in pH 6.8 phosphate buffer confirmed linearity and reproducibility within a 2-10 µg/mL range. Flow property evaluations revealed good flow characteristics, with angle of repose (23.45–25.88°), compressibility index (13.22–14.11%), and Hausner's ratio (1.10–1.25). Dissolution studies demonstrated significantly improved drug release from solid dispersions compared to pure Gliclazide. Among all formulations, GK2 (kneading method, 1:2 drug-to-polymer ratio) showed the fastest release, achieving 99.68% drug release within 45 minutes and exhibiting favorable kinetic parameters (T_{50} = 2.5 min, T_{90} = 20 min, R^2 = 0.999). Accelerated stability studies confirmed physical & chemical stability of optimized formulation (GK2), with consistent drug release profiles before and after storage. Overall, the kneading method with a higher polymer ratio proved most effective in enhancing Gliclazide's solubility and dissolution, offering a promising strategy to improve its bioavailability.

Keywords: Gliclazide, Diabetes mellitus, Formulation, Solid dispersion, PEG 6000, Dissolution

Introduction

Drug therapy with Gliclazide operates as an oral hypoglycemic agent from the sulfonylurea class for treating type 2 diabetes mellitus (1,2). The compound works by triggering pancreatic β-cells to produce insulin (3,4). By blocking ATP-sensitive potassium channels Gliclazide stimulates cell depolarization and calcium influx that leads to increased insulin release (5,6). Gliclazide also exhibits antioxidant and hemovascular protective effects, making it beneficial for patients at cardiovascular risk (7). It is usually administered once or twice daily and is often preferred for its lower risk of hypoglycemia compared to older sulfonylureas (8).

Gliclazide is a poorly water-soluble drug, which means its absorption in the gastrointestinal tract can be limited, reducing its therapeutic effectiveness (9). The pharmaceutical compound Gliclazide fits into BCS class-II because it shows poor solubility levels combined with high membrane penetration (10). The pharmaceutical method known as solid dispersion enables researchers to improve solubility together with bioavailability of drugs that demonstrate poor water solubility (11-14). The pharmaceutical technique distributes one or more active drug substances into an inactive matrix or carrier material when in its solid form (15-18). Solid dispersion technique used to overcome this problem by: improving dissolution rate - dispersing Gliclazide in a hydrophilic carrier (like PEG, PVP, or HPMC) increases its surface area and interaction with water, speeding up how quickly it dissolves, enhancing bioavailability - faster dissolution usually leads to better absorption and more consistent blood levels and achieving uniform dispersion – the drug is finely dispersed within a carrier (19-20).

Purpose of this research is to develop solid dispersions of Gliclazide using

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PEG-6000 as a carrier material to improve its dissolution performance. The research establishes solid Gliclazide dispersions with PEG-6000 through physical mixing and kneading techniques before conducting FTIR and DSC characterization of the prepared solid dispersions alongside drug content evaluation and solubility analysis and *in vitro* dissolution testing and identifying the best drug-to-polymer ratio for maximum solubility enhancement.

Materials and Methods

Materials

Gliclazide was obtained from Shree Icon Pharmaceutical Laboratories, Vijayawada, Andhra Pradesh. Polyethylene glycol 6000 was purchased from Yarrow Chem Products, Mumbai, Maharashtra. Sodium hydroxide, ethanol, potassium dihydrogen phosphate was purchased from SD Fine Chem Ltd., Mumbai, Maharashtra.

Methods of preparation

Physical mixtures of Gliclazide PEG 6000 were prepared in two different mass ratios (1:1 1:2), labeled as GP1, GP2, by lightly triturating components in glass mortar for 5 minutes. Solid dispersions were similarly prepared using kneading method, producing batches labeled GK1 GK2. For physical mixing, accurately weighed quantities of Gliclazide PEG 6000 were passed through No. 80 sieve, triturated together in dry glass mortar for 5 minutes, stored in sealed glass container at room temp. For kneading technique, drug & PEG 6000 were sieved triturated individually, then combined in specified ratios with minimal amount of water under high pressure for two minutes to form uniform paste, the mixture was then passed through No. 60 sieve, collected, stored in tightly sealed amber jar.

In vitro dissolution study

Solid dispersion dissolution studies took place in a Labindia dissolution tester equipped with paddles that operated at 50 rpm through USP apparatus II method. A pH 6.8 buffer solution (900 ml) functioned as the dissolution medium during the process. Representative dissolution medium volumes (10 ml) were reserved at gap of 5, 10, 15, 20, 30, 45 mins for replacing them with equivalent volumes of fresh buffer to maintain continuous dissolution medium volume. The dissolution medium was used to dilute all sample collections which were examined through Elico double beam UV spectrophotometer at 228 nm to determine drug amount dissolved. The test conditions were applied thrice to each formulation. The dissolution profiles enabled the calculation of T50, T90 parameters because similar dissolution studies ran for three separate formulation tests.

FTIR spectral analysis

Infrared spectra of pure drug & its formulations were recorded using Bruker 8400S Fourier Transform Infrared Spectrophotometer with KBr pellet method. Samples were prepared by mixing with dried potassium bromide, baseline correction was performed before recording spectra. Samples were prepared by KBr pellet press method.

Differential Scanning Calorimetric analysis

The DSC-60 Differential Scanning Calorimeter by Shimadzu allowed researchers to perform analysis through its thermal analyzer system. Each sample received between 5-10 mg and was placed into hermetically sealed aluminum pans which experienced heating from 60 to 250°C at a rate of 15°C/min under nitrogen gas flowing at 20 ml/min. A plain aluminum reference pan rested inside the instrument.

Accelerated study

Accelerated stability examinations were conducted on formulations exhibiting promising *in vitro* results. Scientists performed investigations that examined temperature impacts on tablets' physical attributes and drug compound stability. Stability testing of optimized formulation GK2 included storage of preparations in petri dishes under controlled oven conditions at 25±2ºC with 60±5% RH exposure for 6

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months and 40±2ºC coupled with 75±5% RH exposure for 3 months. Physical assessment involved testing each formulation type's sample samples. Additional drug release studies identified and evaluated the products.

Results and Discussion

In vitro dissolution study

The physical mixing and kneading methods were found to be suitable for the preparation of Gliclazide solid dispersions, with dissolution studies performed using the USP paddle method (Apparatus II) operated at 37°C and 50 rpm. Drug release from all solid dispersions was significantly quicker compared to the pure drug. Among the formulations, GP1 and GP2, prepared by the physical mixing method using PEG 6000 in 1:1 & 1:2 ratios respectively, released 90.11% & 93.28% of the drug within 45 minutes. In contrast, the kneading method yielded even more effective results; GK1 (1:1 PEG 6000) released 94.28%, while GK2 (1:2 PEG 6000) achieved the highest release of 99.68% within the same time frame. These results, illustrated in Figure 1, demonstrate that increasing the polymer ratio and using the kneading method significantly enhance drug release performance, with GK2 being the most efficient formulation. The release kinetics of all formulations followed first-order behavior, as depicted in Figure 2, indicating a concentration-dependent release pattern. Furthermore, the optimized formulation GK2 showed minimal variation in drug release after storage under different conditions, confirming its stability over time, as shown in Figure 3.

FTIR studies

Drug spectra and its formulations were measured through the KBr pellet technique by using a Fourier Transform Infrared (FTIR) Spectrophotometer. The investigators performed baseline correction on dried potassium bromide before recording the spectra from dried drug-inclusion complex mixtures with potassium bromide. The FTIR spectrophotometer analyzed both pure drug chemicals and its formulations for detection purposes. The FTIR spectrum for

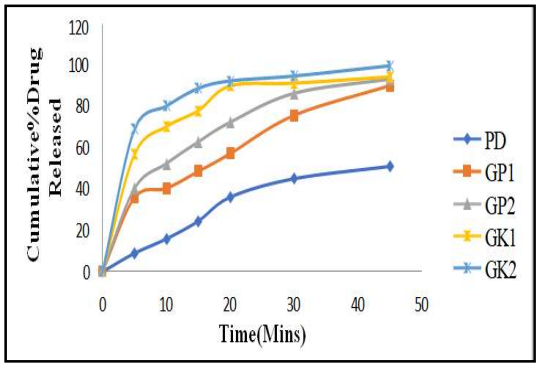

Figure 1: *In vitro* drug release profile of Gliclazide

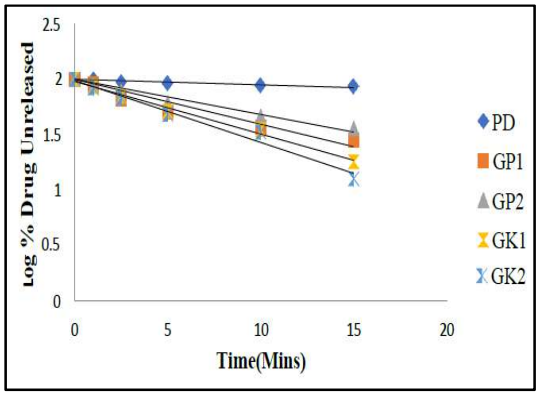

Figure 2: First order plot of Gliclazide

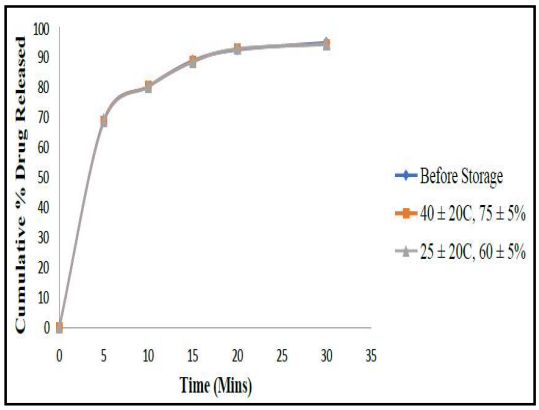

Figure 3: Drug release profile of Gliclazide (GK2) before after storage at different conditions

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the pure drug Gliclazide is shown in Figure 4**,** the FTIR spectrum for the polymer PEG-6000 is displayed in Figure 5, and the FTIR spectrum for the optimized formulation GK2 is shown in Figure 6. The interpretation of these FTIR spectra is provided in Table 1.

DSC analysis

The pure drug and polymer samples alongside solid dispersions got analyzed through DSC and it created heat uptake curves. The standard open aluminum pans received 10 mg of each material for scanning within 20–450°C at 10°C/min under nitrogen gas purging at 60 ml/min. The DSC thermogram for the pure drug Gliclazide is shown in Figure 7, for the polymer PEG-6000 in Figure 8, and for the optimized formulation (1:2 ratio) of Gliclazide in Figure 9. The thermogram for the combination of the drug and polymer formulation is displayed in Figure 10. A detailed interpretation of the DSC thermograms was shown in Table 2.

Compositions of Gliclazide Solid Dispersions

The formulations of Gliclazide solid dispersions were prepared using two different

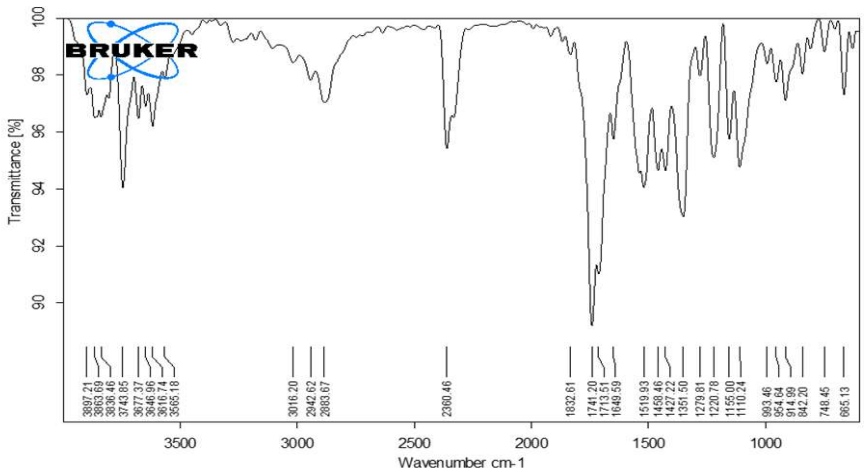

Figure 4: FTIR Spectrum for Gliclazide

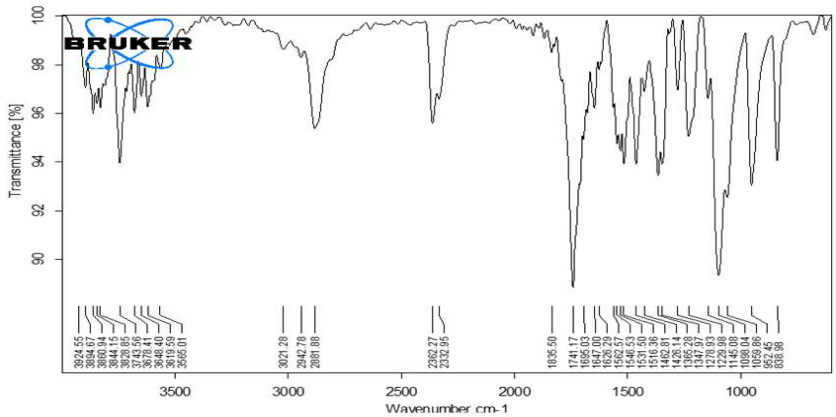

Figure 5: FTIR Spectrum for polymer PEG-6000

Formulation and Assessment of Gliclazide

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methods: physical mixing and kneading. Table 3 outlines the composition of each formulation. The physical mixing method was employed to prepare two solid dispersions: GP1 (1:1 ratio of Gliclazide to PEG 6000) and GP2 (1:2 ratio). Similarly, the kneading method was used for GK1 (1:1 ratio) and GK2 (1:2 ratio). These compositions were designed to evaluate the effects of different polymer ratios on the drug release characteristics.

In vitro dissolution profile

Dissolution behavior of Gliclazide solid dispersions was assessed over a period of 45 minutes. As shown in Table 4, all

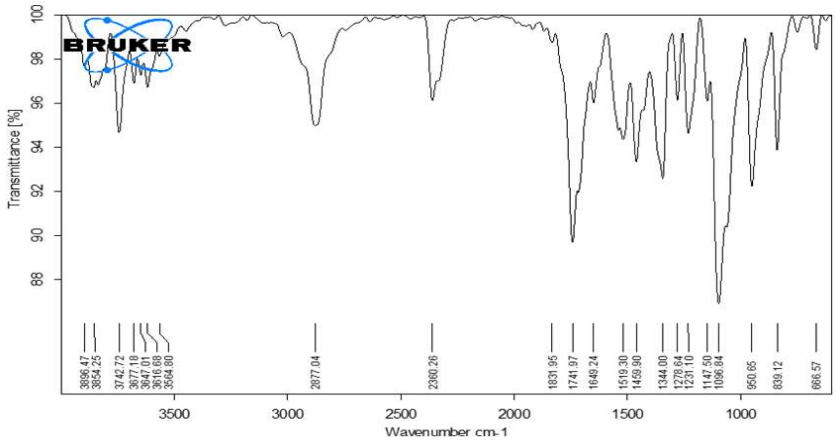

Figure 6: FTIR Spectrum for optimized formulation GK2

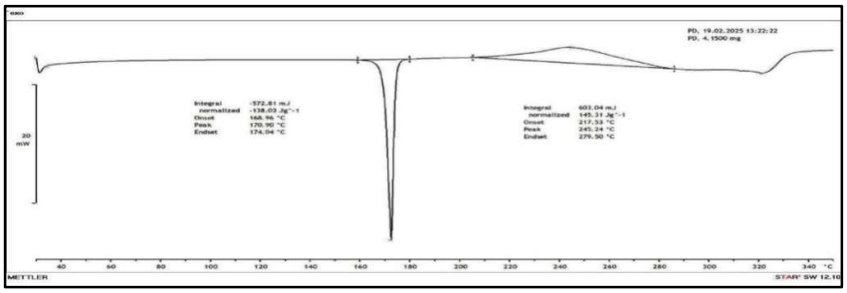

Figure 7: DSC Thermogram of Gliclazide

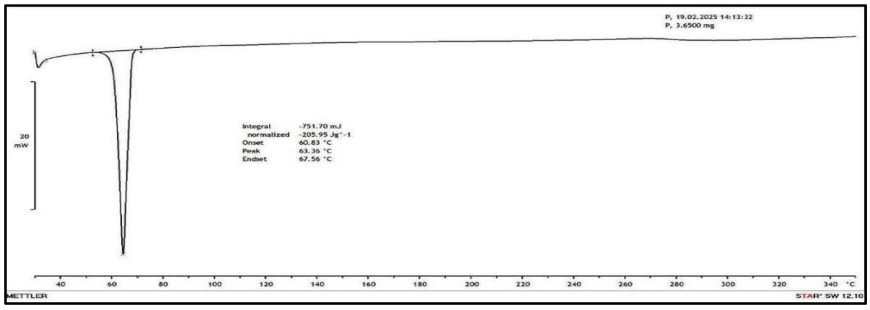

Figure 8: DSC Thermogram of polymer PEG-6000

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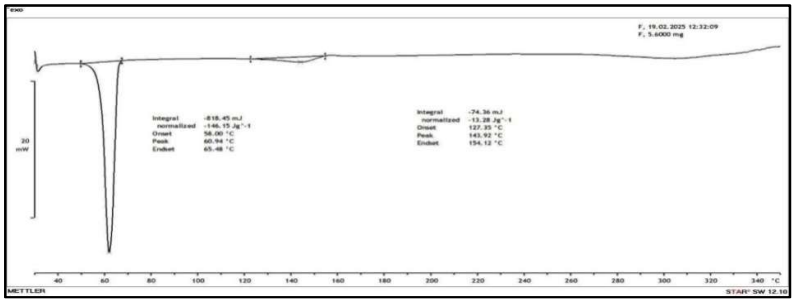

Figure 9: DSC Thermogram of optimized formulation (1:2 ratio) of Gliclazide

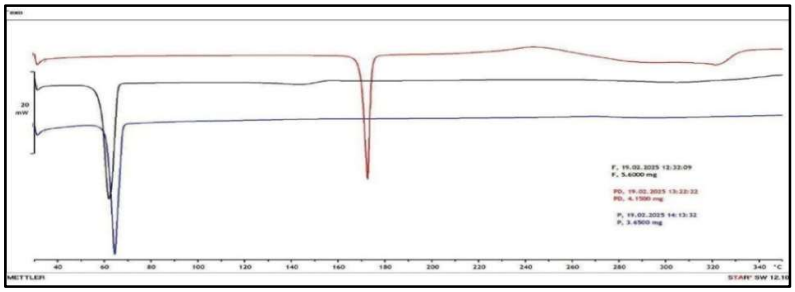

Figure 10: DSC Thermogram for combination of drug, polymer formulation

Table 1: FTIR Interpretation results

Functional groups	Drug (Gliclazide) (cm^{-1})	Polymer (PEG-6000) (cm^{-1})	Optimized Formulation (cm^{-1})
C=O (Ketones)	1741.20	1741.17	1741.97
C=C (Alkenes)	-	-	1649.24
N-H (Bending)	1519.93	1562.14	1519.30
-CH2 (Bending)	1427.22	1462.14	1459.90
S=O	1110.24	1145.08	1147.50
C-H (Aromatic stretch)	914.99	952.45	950.65

Table 2: DSC Thermogram results

S. No.	Drug (Gliclazide)	Polymer(PEG-6000)	Optimized formulation
1	173℃	65℃	62℃
2	Sharp Endothermic	Sharp Endothermic	Sharp Endothermic

dispersions demonstrated significantly quicker drug release compared to pure drug (PD). Notably, release of Gliclazide from GK2 (prepared with the kneading method and a 1:2 ratio of PEG 6000) was the highest, achieving 99.68% release within 45 minutes, while GP1 and GP2 released 90.11% and 93.28%, respectively. The kneading method, especially at higher polymer concentrations, notably enhanced drug release.

Dissolution Parameters

Dissolution characteristics of various Gliclazide solid dispersions were further analyzed through key parameters, as presented in Table 5. The fastest drug release was observed in the GK2 formulation, which had a T50 of 2.5 minutes, and a T90 of just 20 minutes. In contrast, the other formulations showed longer release times (e.g., T50 of 20 minutes for GP1). The

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dissolution rate constant (K) was highest for GK2, confirming its superior performance, and correlation coefficient (R^2) was closest to 1 (R^2 = 0.999), indicating excellent linearity of the release profile.

Stability and drug release profile of GK2 under different storage conditions

The stability of the optimized GK2 formulation was evaluated under various storage conditions. Table 6 summarizes the drug release data of GK2 stored at 25±2°C with 60±5% RH & at 40±2°C with 75±5% RH. Results showed minimal variation in drug release after storage, with 99.54% released at 25°C and 99.74% at 40°C after 45 minutes. These findings suggest that GK2 maintains its release characteristics even under accelerated storage conditions, highlighting the stability of the formulation.

Accelerated study

The selected solid dispersions based on Gliclazide underwent accelerated stability testing because of their demonstrated *in vitro* performance. GK2 formulations using PEG 6000 at the ratio of 1:2 underwent accelerated stability assessment which included physical property testing and drug release investigation from solid dispersions. Stored products exhibited no detectable physical modifications according to stability

Table 3: Different compositions of Gliclazide

Method	Solid dispersion Code	Composition	Ratio	Concentration
Physical mixing method	GP1	G+PEG6000	1:1	40:40
	GP2	G+PEG6000	1:2	40:80
Kneading method	GK1	G+PEG6000	1:1	40:40
	GK2	G+PEG6000	1:2	40:80

Table 4: *In vitro* dissolution data

Time (min)	Cumulative % drug released				
	PD	GP1	GP2	GK1	GK2
5	8.9	35.86	40.33	56.84	68.99
10	15.9	40.35	52.36	70.25	80.14
15	24.5	48.56	62.87	77.94	88.74
20	36.1	57.18	72.36	89.96	92.36
30	45	75.69	86.36	91.26	94.75
45	51	90.11	93.28	94.28	99.68

Table 5: *In vitro* dissolution parameters

Formulation	T50 (min)	T90 (min)	K (min^{-1})	R^2
GP1	20	45	0.0011	0.944
GP2	10	40	0.0013	0.969
GK1	5	25	0.0211	0.984
GK2	2.5	20	0.0377	0.999

Table 6: Drug release data of Gliclazide (GK2) before after storage at different conditions

Time (min)	Before storage	25±2ºC, 60±5%RH	40± 2ºC, 75± 5%RH
5	68.99	68.74	68.47
10	80.14	80.19	80.1
15	88.74	88.54	88.36
20	92.36	92.58	92.66
30	94.75	94.26	94.21
45	99.68	99.54	99.74

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test results. All solid dispersions showed consistent dissolution profiles both before and after multitechnique Gliclazide solid dispersions showed no substantial changes in their drug release patterns during the duration of the study. The designed Gliclazide solid dispersion systems proved to show consistent drug release properties.

Conclusion

The study concluded that solid dispersion using PEG 6000 effectively enhanced solubility dissolution rate of Gliclazide. Spectrophotometric analysis in pH 6.8 buffer was accurate reliable for drug estimation. Solid dispersions prepared by physical mixing kneading showed good flow properties consistent drug content. All formulations improved drug release compared to pure drug, with GK2 (kneading method, 1:2 ratio) achieving highest release (99.68% in 45 mins) fastest kinetics (T50 = 2.5 mins, T90 = 20 mins) release followed linear kinetics (R^2 = 0.984–0.999). GK2 also demonstrated stability under accelerated conditions, making it most promising formulation for enhancing Gliclazide bioavailability.

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Conflicts of Interest

The research author states they have no conflicts involving this study.

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