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FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF REPAGLINIDE USING HYDROPHILIC NATURAL AND SYNTHETIC POLYMERS

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Keywords:

Repaglinide, Type 2 Diabetes mellitus, *Ocimum basilicum* seed mucilage, HPMC K4M, Sustained release Tablet

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ABSTRACT: Repaglinide is used in the treatment of type 2 Diabetes mellitus and has very short half life. The patient compliance can decrease when larger doses are administered two to three times a day. Sustained release formulation which maintains a plasma level of 8-10 h might be recommended for daily administration of repaglinide. The main objective of the present study was to develop sustained release formulation using hydrophilic release retardant natural and synthetic polymers *i.e.*, *Ocimum basilicum* seed mucilage and HPMC K4M alone and in combinations respectively. Direct compression technique was used to prepare tablets which were evaluated for precompression and postcompression parameters. Nine formulations were prepared in which F1-F3 were prepared using Basil seed mucilage, F4-F6 by HPMC K4M and F7-F9 using both the polymers (Basil seed mucilage and HPMC) at 1:3, 1:6 and 1:9 to the drug and polymer ratios respectively. F8 was selected as the best formulation which sustained the drug release upto 98.61% in 10 h out of nine formulations (F1-F9). The selected formulation which was subjected to accelerated stability studies at Rh 75% ± 5% and 40 ºC ± 2 ºC for one month was found to be stable.

INTRODUCTION: Demand of natural excipients increased over synthetic excipients due to its easy availability, ecofriendly nature, biodegradability, low cost. *Ocimum basilicum* plant is well known for its medicinal properties like expectorant, antibacterial, antifungal, carminative, digestive, stimulant, antispasmodic, carminative *etc.* and was widely used as traditional medicine since years [1].

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Sustained release drug delivery systems (SRDDS) are designed to increase the concentration of in the systemic circulation for prolonged period of time [2]. Repaglinide is a drug used to treat type 2 Diabetes mellitus has a short half-life of 2 h. The present study involves formulation and evaluation of sustained release formulation using hydrophilic natural and synthetic polymers such as *Ocimum basilicum* seed mucilage and hydroxy propyl methyl cellulose K4M (HPMC K4M) as release retardants [3].

MATERIALS AND METHODS

Materials: Basil seeds were procured from the Ayurvedic pharmacy. Repaglinide was obtained as gift sample from Aurobindo laboratories.

HPMC K4M, magnesium stearate, Talc, Micro-crystalline cellulose and Lactose were obtained from Kerry laboratories.

Methods:

Isolation of Mucilage from *Ocimum basilicum* Seed mucilage: [4, 5, 6] To remove the foreign particles, basil seeds were taken in clean bowl and rinsed with adding required amount of water. The rinsed seeds were soaked in water for 20 - 40 min at the ratio of 1:10 to the basil seeds and water. The soaked seeds were homogenized at high agitation speed of 1500 rpm to separate the seeds and gel layer.

The obtained gel layer was filtered using muslin cloth to remove the unwanted particles and precipitated by using required amount of acetone. The precipitate was dried in Hot air oven at 40 ºC. The dried mucilage was powdered using motor and pestle, sieved using 60 mesh and stored in airtight container.

Characterization of *Ocimum basilicum* Seed Mucilage: [7] The mucilage was evaluated for organoleptic characters, physicochemical and phytochemical characters, flow properties, pH and morphology.

1. Organoleptic Evaluation: The isolated mucilage was evaluated for its colour, odour and taste.

2. Physicochemical Evaluation: Physicochemical evaluation is useful to determine the purity of the compound. Basil seed mucilage was evaluated for the contents of total ash, water soluble ash, acid soluble ash, swelling index, alcohol soluble extract, ether soluble extract and Loss on drying.

3. Phytochemical Evaluation: The solution of 1% w/v extract was prepared using distilled water and evaluated for carbohydrates, gums and mucilage.

4. Flow Properties: Flow properties were evaluated by angle of repose, Carr's index and Hausner's ratio.

5. pH: pH of 1% w/v solution of *Ocimum basilicum* seed mucilage was determined using pH meter.

6. Morphology: Morphology was determined by X-ray diffraction (XRD) and Scanning Electron Microscopy (SEM).

X-Ray Diffractometer was used to record XRD of powder (PXRD). SEM was used to determine the surface topology and morphology.

Solubility Studies: Distilled water, Ethanol, 0.1N HCl, pH 6.8 Phosphate buffer solution were used to determine the solubility of Repaglinide.

Fourier Transform Infrared Spectrophotometer (FTIR): [8, 9] FTIR spectrophometer (Bruker alpha) is used to determine the compatibility of drug with the excipients. Pellets were prepared by using KBr and sample at high compaction pressure at the ratio of 1:100 by Disc method. The prepared pellets were subjected for IR Spectral studies in the wave number range of 4000 - 400 cm^{-1}. The spectra obtained for repaglinide and the excipients were compared.

Preparation of Repaglinide Tablets: Direct compression technique was used to prepare different tablet formulations. Prior to the formulation, all the powders were passed through 60 mesh and required amounts of repaglinide and polymers were mixed thoroughly with the diluent MCC. After proper mixing, the lubricant magnesium stearate, the glidant talc and the filler lactose were added slowly to the above mixture and mixed properly for few minutes in a polybag. Finally the above blend was subjected to compression using Rotary Tablet Machine.

TABLE 1: PREPARATION OF REPAGLINIDE SUSTAINED RELEASE TABLETS

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Repaglinide	2	2	2	2	2	2	2	2	2
OBSM	6	12	18	-	-	-	3	6	9
HPMC K4M	-	-	-	6	12	18	3	6	9
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
MCC	20	20	20	20	20	20	20	20	20
Lactose	87	81	75	87	81	75	87	81	75
Total	120	120	120	120	120	120	120	120	120

Note: OBSM-*Ocimum basilicum* seed mucilage, MCC-Microcrystalline cellulose.

Evaluation: [10, 11]

Pre-compression Parameters: All the powders of tablet were evaluated for angle of repose, bulk density, tapped density, carr's index and hausner's ratio.

Post-compression Parameters: The prepared tablets were evaluated for thickness, weight variation, hardness, friability, water uptake and drug content.

***In vitro* Drug Release Study:** [12, 13] Dissolution test was used to determine the drug release for which USP type-II dissolution apparatus at 50 rpm. The dissolution medium was kept for first two hours with 0.1N HCl which was prepared by taking 8.5ml of HCl in 1000 ml water. Later the medium was replaced with pH 6.8 Phosphate buffer solution which was prepared by using 6.8g of potassium dihydrogen phosphate and 0.8g of sodium hydroxide. At predetermined intervals, 5ml of sample was withdrawn, filtered and analyzed spectrophotometrically using UV spectrophotometer. Immediately equal amount fresh dissolution medium was replaced after every withdrawal of test sample. Percentage drug release was calculated.

Model Fitting for Drug Release Kinetics: [14] The *in-vitro* drug release data was determined by using various mathematical models to know the drug release kinetics and drug release mechanism from its dosage form. Depending on the following estimates, the suitable mathematical model was determined to describe the dissolution profiles.

The plots made were as below:

1) Zero Order kinetic model: Cumulative percent drug release versus Time.

2) First Order kinetic model: Log cumulative percent drug release versus Time.

3) Higuchi model: Cumulative percent drug release versus Square root of Time.

4) Korsmeyer-Peppas model: Log cumulative percent drug release versus log Time.

Accelerated Stability Studies: [14] The selected formulation is said to be stable when it remains the same in a specific container within its physical, chemical, therapeutic and toxicological specifications. The accelerated stability studies provide an evidence on the quality of drug substance which varies with time under different environmental factors like humidity, temperature, recommended storage conditions and light. In the present study, the FDT is stored in specific conditions of Rh 75% at 40 ºC. After a period of one month, the tablets were analyzed for thickness, weight variation, hardness, friability, drug content and dissolution studies.

RESULTS AND DISCUSSION:

Characterization of *Ocimum basilicum* seed mucilage:

TABLE 2: CHARACTERIZATION OF *OCIMUM BASILICUM* SEED MUCILAGE

S. no.	Test	Observation
1.	Organoleptic evaluation	
	Colour	Brownish yellow
	Odour	Characteristic
	Taste	Tasteless
2	Physico-chemical evaluation	
	Total ash	3.564% w/w
	Water soluble ash	1.5% w/w
	Acid insoluble ash	0.3% w/w
	Ethanol soluble extractive	4% w/w
	Ether soluble extractive	4.3% w/w
	Loss on drying	2%
	Swelling index	1817.5
3	Phyto-chemical evaluation	
	Test for carbohydrates : Molisch Test: Few drops of alcoholic α- napthol and concentrated sulphuric acid are added to the test solution along the sides of the test tube	Purple to violet color ring appeared at the junction
	Test for Gums: Treat the test solution with Ruthenium red solution.	Pink color was observed
	Test for mucilage: The extract is treated with 25ml of absolute alcohol, and filtered	Swelling of extract was observed
4	Flow properties	
	Angle of repose	18.98"
	Bulk density	0.845g/CC
	Tapped density	0.769g/CC
	Compressibility index	12.85%
	Hausner's ratio	1.15
5	pH	7.8

Morphology of *Ocimum basilicum* seed mucilage powder: X-ray Diffraction: X- ray diffraction shows that basil seed mucilage is amorphous.

Scanning Electron Microscopy (SEM): SEM photographs of Basil seed mucilage shows that the mucilage powder is irregular in shape and has porous nature.

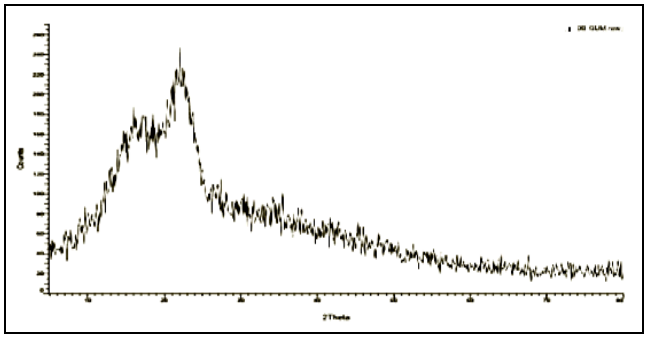

FIG. 1: XRD OF BASIL SEED MUCILAGE

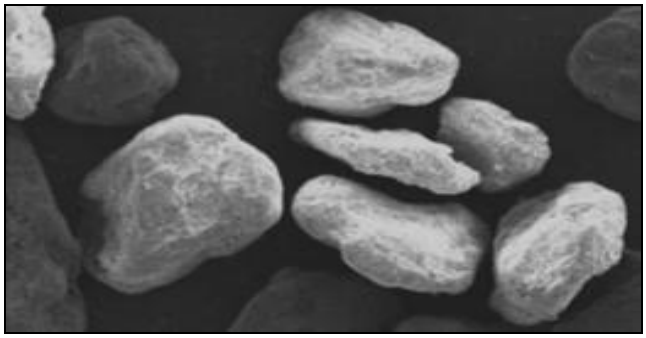

FIG. 2: SEM OF *OCIMUM BASILICUM* SEED MUCILAGE

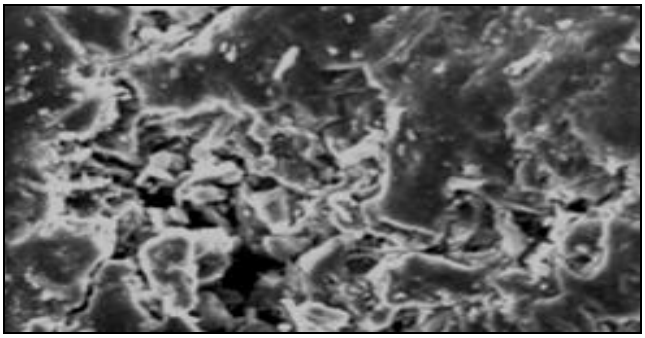

FIG. 3: SEM SURFACE VIEW OF *OCIMUM BASILICUM* SEED MUCILAGE

FT-IR (Fourier Transform Infrared Spectro-photometer): The FTIR spectrum showed that all the principle peaks of the pure drug repaglinide were retained in the physical mixture of repaglinide with Basil seed mucilage and HPMC which were prepared at 1:1 ratio. It was observed that the drug and polymers were compatible. The drug and the combination of excipients showed negligible variation when compared to to the pure drug which shows good compatibility of drug and excipients.

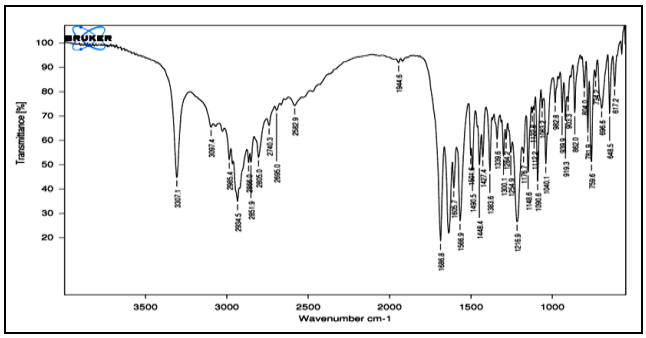

FIG. 4: FTIR SPECTRUM OF REPAGLINIDE

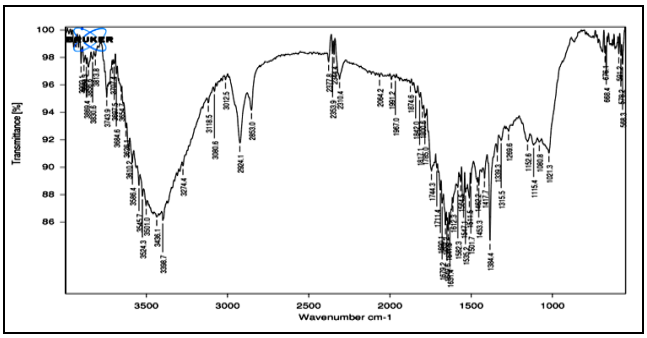

FIG. 5: FTIR OF *OCIMUM BASILICUM* SEED MUCILAGE

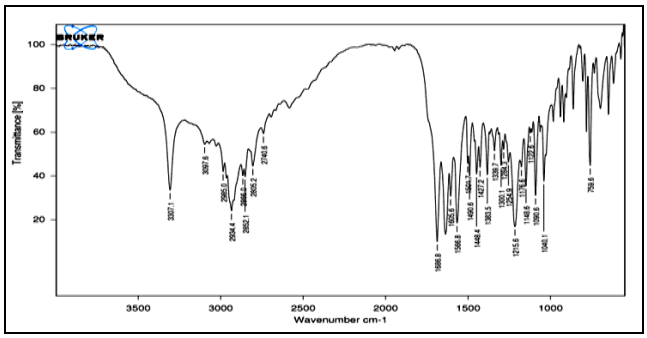

FIG. 6: FTIR SPECTRUM OF REPAGLINIDE + OCIMUM BASILICUM SEED MUCILAGE

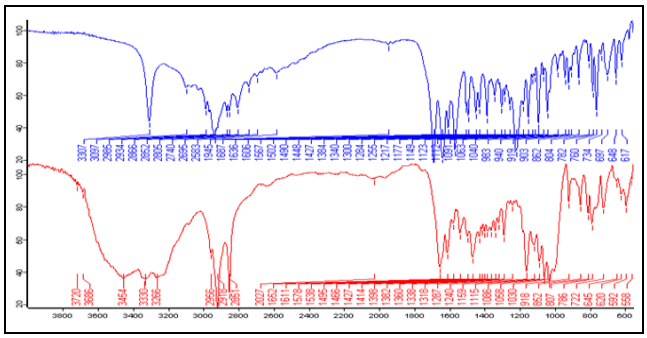

FIG. 7: FTIR SPECTRUM OF DRUG AND OPTIMIZED FORMULA

Evaluation of Powders: All the powders exhibited good flow properties with the Angle of repose values ranging from 26.06 ± 0.18 to 29.76 ± 0.49, Bulk density ranging from 0.32 ± 0.02 gm/cm^3 to 0.39 ± 0.09 gm/cm^3, Tapped density ranging from 0.39 ± 0.01 gm/cm^3 to 0.49 ± 0.04 gm/cm^3, Carr's indexes ranging from 12.19 ± 1.45% to 25.58 ± 1.12%. Hausner's ratio of all the formulations of powders were between in 1.13 and 1.39. The results were represented in **Table 3**.

TABLE 3: EVALUATION OF POWDERS

Formulation code	Angle of repose (θ) ±SD	Bulk density (gm/cm^3) ±SD	Tapped density (gm/cm^3) ±SD	Carr's index (%) ±SD	Hausners ratio
F1	28.56±0.51	0.32±0.02	0.39±0.01	17.94±1.45	1.21
F2	28.65±0.63	0.35±0.06	0.43±0.02	18.60±1.24	1.22
F3	28.31±0.58	0.35±0.08	0.41±0.05	14.63±1.18	1.17
F4	29.76±0.49	0.32±0.04	0.43±0.06	25.58±1.21	1.34
F5	27.49±0.62	0.39±0.09	0.49±0.04	20.44±1.32	1.25
F6	28.61±0.47	0.33±0.04	0.46±0.03	17.44±1.26	1.39
F7	26.91±0.36	0.34±0.06	0.42±0.01	16.46±1.36	1.23
F8	26.06±0.18	0.36±0.03	0.41±0.06	12.19±1.45	1.13
F9	28.75±0.24	0.36±0.04	0.44±0.04	18.18±1.64	1.22

Evaluation of Tablets: Different polymers were used alone and in combinations in different ratios to compress the formulations (F1-F9). The results were shown in table 4 below. All the formulations were found to be in the limits where the thickness was 1.69 mm to 2.54 mm, weight variation was 119 ± 0.10% to 121 ± 0.37%, hardness was 6.1 kg/cm^2 to 6.91 kg/cm^2, Friability was 0.53% to 0.75% showing enough resistance, the water uptake was between 20.2% - 26.4% and the drug content was found to be 96.68% to 99.03%.

TABLE 4: EVALUATION OF TABLETS

Formulation Code	Thickness (mm)	Weight variation (%) ±SD	Hardness (Kg/Cm^2) ±SD	Friability (%) ±SD	Water Uptake (%)	Drug content (%)
F1	1.91	120±0.14	6.5±0.28	0.63±0.06	20.5	98.75
F2	2.08	119±0.23	6.2±0.67	0.66±0.05	22.4	98.56
F3	2.19	121±0.37	6.2±0.65	0.66±0.08	25.9	98.52
F4	2.26	119±0.65	6.1±0.53	0.68±0.05	24.5	97.95
F5	1.67	120±0.43	6.2±0.74	0.75±0.75	20.2	96.68
F6	2.19	119±0.10	6.9±0.61	0.65±0.06	26.4	97.23
F7	2.54	120±0.38	6.4±0.53	0.53±0.03	22.6	97.69
F8	1.89	120±0.63	6.3±0.71	0.70±0.08	23.4	99.03
F9	2.34	119±0.93	6.9±0.65	0.65±0.06	25.7	98.89

***In vitro* Drug Release Study:** Different formulations (F1-F9) were prepared using different polymers like Basil seed mucilage and HPMC alone and in combinations at different ratios. Formulations F1-F3 were prepared using Basil seed mucilage at the ratio of 3%, 6% and 9% which showed the drug release about 74.15%, 82.16% and 80.97%.

TABLE 5: CUMULATIVE % DRUG RELEASE OF FORMULATIONS F1-F9

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	11.74	13.15	13.11	23.78	22.97	19.56	08.44	09.61	09.11
2	20.53	21.67	20.28	34.65	33.67	21.65	17.92	18.06	24.91
3	39.56	42.89	35.83	39.17	40.23	30.28	33.76	34.59	36.89
4	46.50	48.32	41.92	45.43	44.98	35.69	39.45	41.78	49.62
5	52.91	53.71	52.89	57.54	56.78	51.65	47.18	68.50	64.95
6	56.51	62.84	57.16	61.21	62.91	57.31	53.72	77.52	69.12
7	64.59	68.73	67.61	71.66	74.17	66.73	68.91	87.08	79.42
8	68.15	71.97	71.72	76.43	78.49	74.91	77.29	92.51	87.67
9	70.24	76.29	74.38	81.98	82.76	80.72	86.98	95.89	91.95
10	74.15	82.16	80.97	88.53	89.89	86.91	91.63	98.61	97.17

Formulations F4-F6 were prepared using HPMC K4M at the ratio of 3%, 6% and 9% with the drug release of 88.53%, 89.89% and 86.91% and the formulations F7-F9 were prepared by using equal amounts of both polymers at the ratio of 3%, 6% and 9% showed the drug release of 91.63%, 98.61% and 97.17% at the end of 10 h. Among all these formulations F8 was selected as the best ideal formulation which exhibited 98.61% of drug release in 10 h.

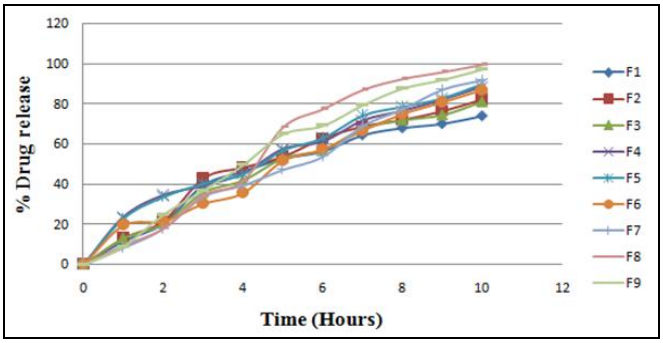

FIG. 8: PERCENTAGE DRUG RELEASE FROM DIFFERENT FORMULATIONS (F1-F9)

Model Fitting for Drug Release: Drug release kinetic equations were used to fit the results of dissolution data. Regression coefficient (R^2) value was found to high for Korsmeyer-peppas release equation in F8 formulation and the mechanism of drug release was diffusion. The results were tabulated in **Table 6**.

TABLE 6: RESULTS OF KINETIC MODELS

S. no.	Kinetic model	R^2 value	n value
1	Zero Order	0.958	10.92
2	First Order	0.934	0.58
3	Higuchi	0.917	37.15
4	Korsmeyer-Peppas	0.967	1.08

Accelerated Stability Studies:

TABLE 6: ACCELERATED STABILITY STUDIES

S. no.	Parameters	Before Stability Studies	After Stability Studies
1	Thickness	2.49 mm	2.56 mm
2	Weight Variation	120±0.63 mg	119±1.32 mg
3	Hardness	6.3±0.71 kg/cm²	6.2±0.38 kg/cm²
4	Friability	0.70±0.02%	0.68±0.03%
5	Drug Content	99.03%	98.84%
6	Percentage Drug Release	98.61%	97.86%

Formulation F8 was subjected to various stability studies under the conditions of 40 ± 2 ^{o}C/75 ± 5% RH for 30 days. It was tested for general appearance, weight variation, hardness, friability, drug content and percentage drug release after a period of 30 days. The formulation showed no considerable variations, hence the formulation F8 was found to be stable.

CONCLUSION: The aim of the present study was to formulate and evaluate the sustained release tablets of repaglinide by using hydrophilic natural and synthetic polymers to achieve prolonged therapeutic effect by continuously releasing the medication over an extended period of time after administration of single dose. The basic goal of therapy is to achieve steady state blood levels that is therapeutically effective and non toxic for a prolonged period of time. The design of proper dosage regimen is an important element in accomplishing this goal.

A fixed dose of 2 mg of repaglinide was used in the formulation. Various formulations like Basil seed mucilage and HPMC K4M were used as release retardants to study the effect on drug release. The total weight of the tablet was 120 mg. All the formulations (F1-F9) passed the evaluation parameters and were found to be in limits. Among all the formulations F8 with 6% polymer content (3% Basil seed mucilage and 3% HPMC K4M) showed the drug release of 98.61% in 10 h and was selected as the ideal formulation.

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CONFLICT OF INTEREST: Nil

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