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DESIGN, DEVELOPMENT AND CHARACTERIZATION OF MOUTH DISSOLVING FILMS FOR BETTER THERAPEUTIC EFFICACY

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ABSTRACT

Aim: Formulation and characterisation of mouth dissolving film. **Objective:** Fast dissolving drug delivery system offers a solution for those patients having difficulty in swallowing tablets/capsules etc. The present investigation was undertaken with the objective of formulating of fast dissolving oral thin films allowing fast reproducible drug dissolution in the oral cavity thus bypassing first pass metabolism, to enhance the convenience and compliance by the elderly and pediatric patients. **Materials and Methods:** Fast dissolving oral thin films were prepared by solvent casting method with using different film-forming agents like HPMC, PVP, PEG 400, glycerol as a plasticizer and mannitol as filler and sweetener. Thin oral films were tested for weight loss, density, high pH, rolling tolerance, drug content, dispersion time, and *in vitro* termination studies. **Results:** Oral thin films based on evaluation studies HPMC showed optimum performance against other formulations. The prepared films were clear, transparent, and had a smooth surface. **Conclusion:** It was concluded that the fast dissolving oral thin films can be made by solvent casting technique with enhanced dissolution rate, better patient compliance and effective therapy.

KEYWORDS

Solvent casting, Mechanical properties, *In-vitro* dissolution and Oral thin films.

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INTRODUCTION

Mouth dissolving films offers an elegant route for systemic drug delivery. The improved systemic bioavailability results from bypassing first pass effect and better permeability due to a well-supplied vascular and lymphatic drainage. Also, large surface areas of absorption, easy ingestion and swallowing, pain avoidance make the oral mucosa an incredibly attractive and selective site for systemic drug

delivery. Recent developments in the technology have presented viable dosage alternatives from oral route for wide variety of group of patients. Buccal drug delivery has lately become an important route of drug administration. Various Bio adhesive mucosal dosage forms have been developed. Fast dissolving drug-delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for paediatric and geriatric patients who experienced difficulties in swallowing traditional oral solid-dosage forms. The new technology of oral fast-dispersing dosage forms is also known as fast dissolve, rapid dissolve, rapid melt, or quick dis-integration. However, the function and concept of all these dosage forms are similar. By definition, a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water, is known as an oral fast-dispersing or fast-dissolving dosage form[1].

Montelukast sodium is a leukotriene receptor antagonist used in maintenance treatment of asthma and to relieve symptoms of seasonal allergies. It shows high hepatic first pass metabolism and low bioavailability and is effective at low dose. It is usually administered orally. Levocetirizine dihydrochloride is an orally active, third generation, non-sedating selective peripheral H1-receptor antagonist used in seasonal allergic rhinitis, perennial allergic rhinitis, and chronic urticaria. It shows high hepatic first pass metabolism and low bioavailability and is effective at low dose. Allergy is a frequent problem among all age groups. These diseases require rapid onset of action to supply fast relief[2].

MATERIAL AND METHODS

Methods

Preparation of the fast-dissolving oral films of HPMC K4Mand Gelatine (Formulation batch) method the fast-dissolving oral films of montelukast sodium and levocetirizine dihydrochloride were prepared by solvent casting technique. The calculated amount of film forming polymer was soaked in three fourth volume of phosphate buffer of pH. 6.8 solution with continuous stirring for about 8 hours to get uniform dispersion. The required amount of montelukast sodium and levocetirizine dihydrochloride was incorporated in the polymeric solutions. Crosspovidone, menthol and saccharin were added to the polymeric solution. To the above mixture citric acid, PEG 400 was added and the final volume was adjusted up to 12ml using phosphate buffer of pH 6.8 solution. Now this solution was kept aside for 3 hours for expulsion of air bubble. Sonicate for a cycle of 10 min if required. The film was casted by pouring the solution in mould of glass and allowed to dry at room temperature. The dried film was peeled off from mould and cut into 2×2cm 2wrapped in aluminium foil and kept in desiccator for further studies.

Evaluation parameters of oral fast dissolving film 51, 52, 53

Appearance

The formulated films should be checked for their appearance. Film should be checked visually for their appearance.

Dryness/Tack test

Tack is the tenacity with which strip adheres to an accessory or a piece of paper that has been pressed into contact with the strip

Thickness of films

The thickness of the film was measured by micro-meter screw gauge at 3 unusual places and average of 3 values were calculated. This is essential to find uniformity in the thickness of the film which is related to the accuracy of dose in the film.

Weight of films/weight variation

Oral fast dissolving films were weighed on analytical balance and average weight can be figured out for each film. It is desirable that films should have constant weight. It is useful to ensure that a film contains the proper number of excipients and API.

Folding endurance

Folding endurance of the film is essential to study the elasticity of the film during storage and handling. The folding endurance of the film films was figured out by repeatedly folding one film at

the same place till it broke. This is considered to reveal the good film properties. A film (2 X 2 cm) was cut evenly and repeatedly folded at the same place till broken. The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance. All determination were performed in triplicate.

pH value

The pH value was figured out by dissolving one oral film in 10ml distilled water and measuring the pH of the obtained solution. All determinations were performed in triplicate. It is necessary that strip should have uniform pH value.

Content uniformity

Drug content was figured out by dissolving the film having 10mg of drug in 100ml water to get 100µg/ml solutions. An aliquot of 01ml sample was withdrawn and diluted to 10ml with water. Then solution was filtered through Whatman filter paper and analysed by UV-spectrophotometer at 230 and 285nm against blank prepared by using dummy film treated in same manner. Content uniformity studies were carried out in triplicate for each batch of the film. Limit of content uniformity is 85-115%.

Disintegration time

It was figured out visually in a glass beaker filled with 25ml distilled water with swirling every 10seconds. The time at which film started to break or disintegrate was recorded as the in-vitro disintegration time. It was performed in triplicate

***In-vitro* dissolution studies**

The *In-vitro* dissolution study was carried out in 500ml pH 6.8 phosphate buffer using (USP) XIV basket apparatus II at 370 ±0.50C and at 50rpm. Each square cut film sample (dimension: 2cm x2cm) was submerged into the dissolution media and proper aliquots were withdrawn at 1, 2, 3, 4, 5, 6, 7-, 8-, 9- and 10-minute time intervals and again replaced with same volume of dissolution media. The sample were filtered through Whatman filter paper for all the batches and analysed spectrophotometrically at 230nm and 285nm (Model UV-1800 UV-Visible spectrophotometer, Shimadzu, Japan). Sink conditions were kept throughout the experiment. The dissolution test was performed in triplicate per batch.

Kinetic study

The matrix systems were reported to follow the zero-order release rate and the diffusion mechanism for the release of the drug. To analyse mechanism for the release rate kinetics of the dosage form, the data obtained was fitted into, zero order, First order, Higuchi matrix and Peppa's model. Thus, by comparing the R-values obtained, the best fit model was selected.

Accelerated Stability Study

In any rationale design and evaluation of dosage forms for drugs, the stability of the active component must be major criteria in figuring out their acceptance or rejection. During the stability studies the product is exposed to normal conditions of temperature and humidity. However, the studies will take the longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions of temperature. In the present study, stability studies were carried out in optimized formulation. The films were stored at 40 ± 20C/75 ± 5% RH for duration of 45 days, sample was withdrawn and tested for drug entrapment, and drug release study.

RESULTS AND DISCUSSION

Appearance

From the study it was found that all films have good, better, and best film forming capacity and transparent to turbid in appearance. F1, F2, F4, and F8 passes the test.

Disintegration time

The disintegration of mouth dissolving film was calculated found in between 26.6±0.57sec. To 47.3±0.57sec and f1, f2, f3, f4 and f7 disintegrated within limit F2 is best.

Folding endurance

Tablet folding endurance was figured out and was found in between 14.3±0.57 to 58.6±0.57. The values of f2 films were of good mechanical strength.

Drug content

The drug content was found to be almost uniform along all formulations and ranged from 2.48- 2.52 and 2.36-2.80 as per standards.

Weight variation

In weight variation test, percent deviation of all tablets was found to be within the limit with exception of F3, F7, F4, F9 .and hence F1, F2, F5, F6 and F8 formulations pass the weight variation tests

Film thickness

Thickness of mouth dissolving film from each batch was found between 0.8 to 1.1 and F2, F3, F4 and F7 passes the test.

pH

From the study it was found that the pH range of all batches lies between 6.26±0.011 to 6.81±0.03 and passes the test

***In-vitro* Drug Release Studies**

The results revealed that release profile of mouth dissolving film of levocetirizine dihydrochloride shows drug release as given in the table. Batch F2 Showed drug release as 99.81±0.09 and 98.55±0.05 respectively, and passes the test.

Kinetic Modeling Data of Optimized Batch

The mathematical models are used to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation coefficient (r) value in various models. The model that gives high 'r' value is considered as the best fit of the release data. The optimized batch follows the Higuchi plot.

Evaluation Parameter of optimized formulation after stability study

The stability study was carried out on optimized formulation F2. The formulation was stored at 40 ±20C/75±5% for one month. After 30 days sample were withdrawn and retested for thickness, hardness, drug content and in vitro drug release studies.

Material

Table No.1: Materials

S.No	Name of the ingredient	Name of supplier / manufacturer
1	Levocetirizine HCL	Ajanta Pharma Aurangabad, Leben Pharmaceutical, Akola
2	Montelukast Sodium	Ajanta Pharma Aurangabad
3	Gelatine	Themis Laboratory, Mumbai.
4	Hydroxypropyl methylcellulose E-15	Themis Laboratory, Mumbai.
5	Hydroxypropyl methylcellulose K-4M	Themis Laboratory, Mumbai
6	Hydroxypropyl methylcellulose K-15	Themis Laboratory, Mumbai
7	Polyethylene glycol 400	Themis Laboratory, Mumbai
8	Glycerol	Thomas Baker, Mumbai
9	Saccharin	Thomas Baker, Mumbai
10	Citric acid	Thomas Baker, Mumbai
11	Crospovidone	Themis Laboratory, Mumbai

Formulation table

Table No.2: Formulation Table

S.No	Batches Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Levocetirizine Hcl (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
2	Montelukast sodium (mg)	5	5	5	5	5	5	5	5	5
3	HPMC K4M (mg)	6.25	6.25	-	6.25	-	-	4.16	10.41	-
4	HPMC K15M (mg)	-	-	6.25	6.25	6.25	-	4.16	2.08	10.41
5	Gelatin (mg)	-	6.25	-		6.25	6.25	4.16	-	2.08
6	PEG 400 (ml)	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
7	Tween 80 (ml)	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
8	Citric acid (mg)	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62
9	Saccharin (mg)	1.65	1.65	1.65	1.65	1.65	1.65	1.65	1.65	1.65
10	Menthol (ml)	0.31	0.31	0.31	0.31	0.31	0.31	0.31	0.31	0.31
11	Ethanol (ml)	Q.s.	Q.s.	Q.s.	Q.s.	Q.s.	Q.s.	Q.s.	Q.s.	Q.s.
12	Water (ml)	Q.s.	Q.s.	Q.s.	Q.s.	Q.s.	Q.s.	Q.s.	Q.s.	Q.s.
13	Crosspovidine (mg)	3.12	3.12	3.12	3.12	3.12	3.12	3.12	3.12	3.12

Table No.3: Evaluation Parameter

S.No	Formulation batch	Tack test	Appearance
1	F1	Tacky	Transparent
2	F2	Non tacky	Transparent
3	F3	Non tacky	Non-Transparent
4	F4	Tacky	Transparent
5	F5	Non tacky	Non-Transparent
6	F6	Non tacky	Non-Transparent
7	F7	Non tacky	Turbid
8	F8	Non tacky	Transparent
9	F9	Non tacky	Non-Transparent

Table No.4: Evaluation parameter

Batch	Disintegration time (Sec)	Folding endurance	% Drug content		Weight variation (mg)	Film thickness (mm)	pH
			Levocetirizine 2HCL	Montelukast sodium			
F1	26.6±0.57	45±1	2.49	2.40	22	0.9	6.26±0.011
F2	21.3±0.57	42.3±0.57	2.5	2.49	16	0.8	6.81±0.03
F3	20.6±0.57	58.6±0.57	2.49	2.56	13	0.8	6.7±0.015
F4	26±1	14.3±0.57	2.52	2.80	13	0.8	6.33±0.02
F6	30±1.73	41.3±0.57	2.48	2.36	16	0.9	6.38±0.015
F3	30.3±0.57	51.6±0.57	2.51	2.49	22	1	6.73±0.06
F7	27±1	15.3±1.15	2.52	2.57	13	0.8	6.32±0.11
F8	39±0	37.3±0.57	2.48	2.44	18	1	6.47±0.017
F9	47.3±0.57	56±0	2.49	2.50	27	1.1	6.75±0.02

Table No.5: Kinetic modeling data of optimized batch F2 (Levo)

S.No	R^2				
	Zero Order	**First Order**	**Hixon Crowell**	**Korse Meyer Peppas model**	**Higuchi Plot**
1	0.9979	0.8324	0.9482	-0.4754	0.9580

Table No.6: Kinetic modeling data of optimized batch F2 (montelukast)

S.No	R^2				
	Zero Order	**First Order**	**Hixon Crowell**	**Korse Meyer Peppas model**	**Higuchi Plot**
1	0.9835	0.7797	0.9075	-0.5146	0.9810

Table No.7: Evaluation Parameter of optimized formulation before and after stability study

S.No	Parameters	Observation	
		Before	**After**
1	pH	6.81±0.03	6.81±0.05
2	Folding endurance	42.3±0.57	42.3±0.59
3	Thickness	0.8	0.8
4	Weight variation	16 ±0.48	16±0.50
5	Disintegration time	21.3±0.57	21.3±0.59
6	Drug content	Levo 2.5±0.05 Monte 2.49±0.04	Levo 2.5±0.06 Monte 2.49±0.05

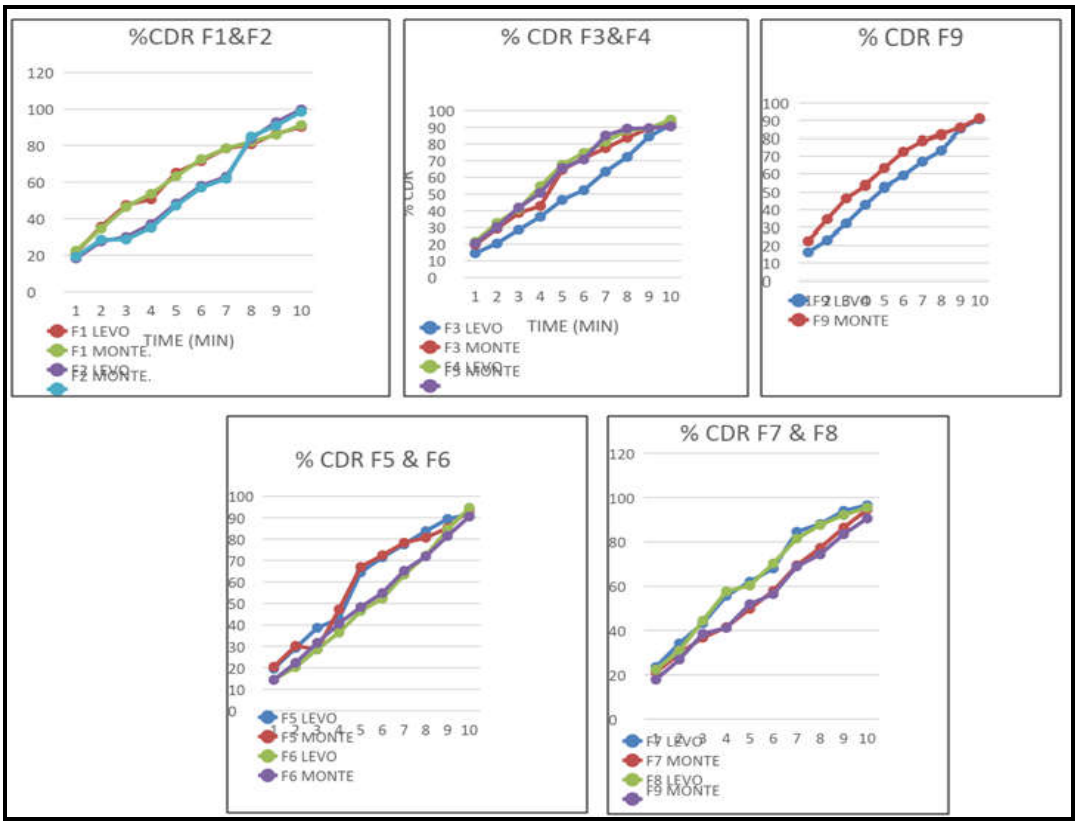

Figure No.1: Percent cumulative drug release

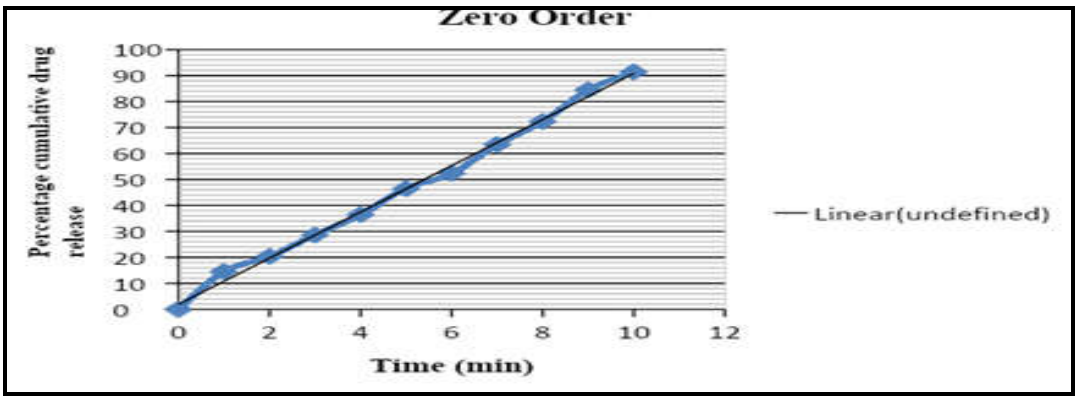

Figure No.2: Graph showing Kinetic Modeling Data of Optimized Batch F2 (Levo)

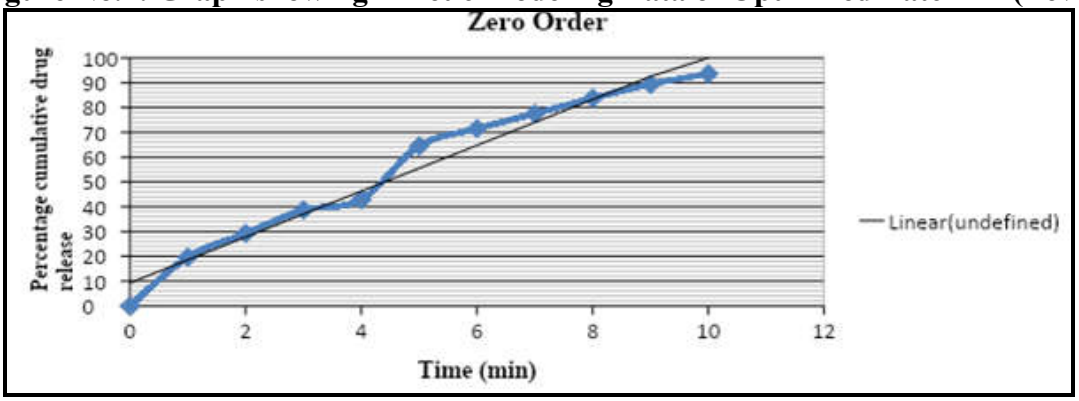

Figure No.3: Graph showing Kinetic Modeling Data of Optimized Batch (F2) (Montelukast)

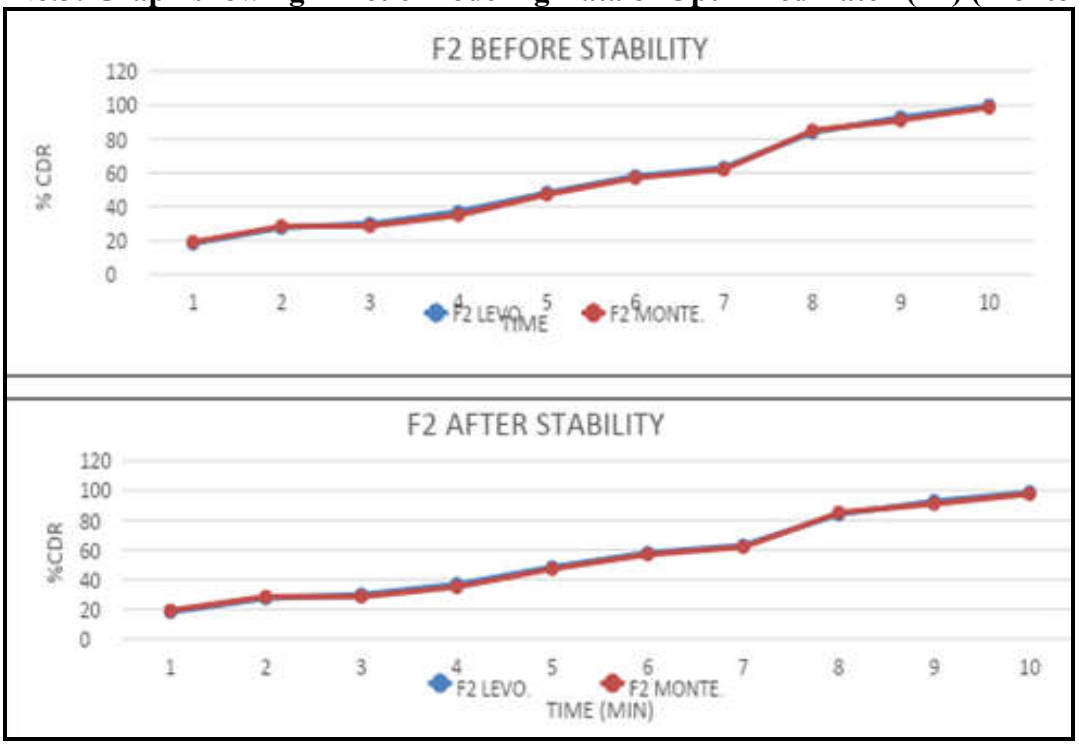

Figure No.4: Evaluation Parameter of optimized formulation before and after stability study

CONCLUSION

The developed formulation which disintegrates in oral cavity in less than 60 seconds without the need of drinking water; and improved patient compliance particularly for those who have difficulty in swallowing. A Pre-formulating study was carried out during the first stages of this work. It has found that, Levocetirizine dihydrochloride, Montelukast sodium are having maximum absorption at wavelength 230nm and 280nm, respectively. The drug-polymer compatibility study was done and stability study is also done. The Fast-dissolving films were formulated by solvent casting technique. Different polymers were screened for the preparation of Fast dissolving films. Amongst all the formulations, formulation having HPMCK4M combine with Gelatine and PEG-400 as plasticizer has shown excellent in vitro disintegration time and in vitro cumulative percent dissolution, compared to other formulations. Formulation F2 (HPMCK4M, PEG-400, Gelatine) disintegrated in 21 seconds and released 99.8% of drug within 10 minutes and was considered as the best formulation. As the concentration of film forming polymers gets increased it also increases the film forming ability of the films. From above discussion, it can be concluded that the successful formation and optimization of fast dissolving films of Levocetirizine dihydrochloride and Montelukast sodium using HPMC K4M and gelatine as film forming polymer and PEG-400 as a plasticizer Hence Levocetirizine dihydrochloride, Montelukast sodium can be conveniently administered orally in the form of films. Hence the objective of this study is achieved.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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