

Short Communication

**ALTERATION OF PHARMACOKINETIC PARAMETERS OF PROTON PUMP INHIBITORS USING
TRANSDERMAL DRUG DELIVERY SYSTEM**

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ABSTRACT

Objective: The present study was aimed to find out the effect of transdermal patches of proton pump inhibitors pantoprazole and esomeprazole on the alteration of pharmacokinetic parameters of these drugs.

Methods: The transdermal patches were formulated by the solvent evaporation technique using polymers HPMC E₅ with PVP K 30 and HPMC E₅ with Eudragit L100 in different ratios. The best formulation from each of the drug pantoprazole and esomeprazole was selected and administered to rabbits and the plasma drug concentration was compared with the marketed formulation. The pharmacokinetic parameters such as maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}), area under the curve (AUC), area under first moment curve (AUMC), elimination rate constant (λ_e), biological half-life (t_{1/2}), and mean residence time (MRT) were determined.

Results: The plasma drug concentration vs time curve shows the extended-release of the drugs pantoprazole and esomeprazole when compared with the marketed formulation. The results show that there is no change in the peak plasma concentration, but a significant difference was observed in all the pharmacokinetic parameters. The AUC showed 6 fold increase for pantoprazole from 8.91 to 55.20 µg*h/ml and 3.5 fold increase for the drug esomeprazole from 7.86 to 28.53 µg*h/ml, and the mean residence time also showed 2 fold increase for the transdermal patches when compared with the marketed formulations.

Conclusion: The increase in t_{max}, AUC, and MRT values of the formulated transdermal patches with the values of the marketed formulation of both the drugs, revealed that the transdermal patches can be used to deliver the drug for an extended period and also can alter the pharmacokinetics of pantoprazole and esomeprazole.

Keywords: Transdermal patches, Pantoprazole sodium, *Esomeprazole magnesium*, Pharmacokinetics

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The transdermal drug delivery system (TDDS) is a widely accepted mode of drug delivery, and transdermal patches are designed for the treatment of different diseases [1]. Transdermal deliveries lead to more compliance with the patient and avoidance of the first-pass metabolism via injectable and oral routes. They can even avoid gastrointestinal issues and low absorption associated with medicines [2]. The objective of the transdermal system of the delivery of medicines is to maximize skin flow to the systemic circulation while simultaneously reducing skin retention and metabolism [3–5]. These therapeutic benefits reflect the higher marketing potential of TDDS [6]. The role of permeating or penetrating enhancers in TDDS is therefore, essential as they reduce the barrier resistance to stratum corneum reversibly without damaging viable cells [7]. The FDA in 1981, approves the first transdermal patch developed by Alza corp, California and because of its constant success, 35 TDDS patches for various conditions are currently on the market [8].

A peptic ulcer forms a sore when the lining of the digestive system wears off digestive juices and may occur in the stomach lining, duodenum, or lower part of the esophagus. That is why peptic ulcer is considered both morbid and mortal as a complicated disease and a major health hazard [9].

Overall, up to 10 % of adults are estimated to be affected at least once in life by peptic ulcers. Patients who test negative for *H. pylori* are prescribed conventional proton pump inhibitor (PPIs) tablets. There is a lack of bioavailability with *H. pylori* infection, showing a lower drug availability at the site of action in peptic ulcers (GERD), which does not, in turn, provide the therapeutically required efficiency. Treatment usually takes 1-2 mo, but treatment may continue longer if the ulcer is severe [4, 10, 11]

Pantoprazole is a substituted benzimidazole sulphoxide for the treatment of acid-related gastrointestinal diseases such as reflux

esophagitis, duodenal and gastric ulcers. Pantoprazole, administered as a 40 mg enteric-coated tablet, is quantitatively absorbed. Its absolute bioavailability is 77% and does not change upon multiple dosing [12]. Pantoprazole shows linear pharmacokinetics after both i. v. and oral administration. Pantoprazole is extensively metabolized in the liver, and to overcome these problems the current study was aimed to formulate a transdermal drug delivery system for it.

Esomeprazole magnesium trihydrate has been approved by the FDA for the treatment of gastroesophageal reflux disease, short-term treatment, and the maintenance of erosive esophagitis, as standard PPIs. Esoméprazole is an omeprazole S-isomer that has been developed as an optical isomer as the first PPI [13]. The pharmacokinetic profile of the medication has improved, leading to greater systemic exposure and lower interpersonal variability than omeprazole, and a better suppression of the production of gastric acid in comparison with other PPIs. It is 89 % bioavailable, and the elimination half-life is 1.5h [14]. With the corresponding reduction in pH of the media, the stability of the esomeprazole magnesium trihydrate decreases.

The acidic contents of the stomach would therefore lead to significant degradation of the medicament and lower bioavailability with esomeprazole magnesium trihydrate exposure [13].

PPIs in the form of parenteral are used to get maximum bioavailability by avoiding first-pass hepatic metabolism through an invasive route with certain limitations. In this study, an attempt was made to formulate a transdermal therapeutic system for pantoprazole and esomeprazole in the form of transdermal patches to release the drug through the skin at a controlled rate into the systemic circulation and to maintain drug concentration within the therapeutic window, thereby reducing the adverse effects of the drug.

Pantoprazole and Esomeprazole were obtained as a gift sample from Dr. Reddy's Laboratories Ltd, Hyderabad. PVA and Sodium

hydroxide are purchased from Thomas Baker (Chemicals) Pvt Ltd, Mumbai. HPLC-grade Potassium dihydrogen phosphate (KH_2PO_4), acetonitrile (purity not less than 99.80%), methanol and triple distilled water, and o-phosphoric acid were used as received from Merck India Ltd. (Mumbai, India). HPMC E₅ was purchased from Loba Chemie Pvt Ltd, Mumbai. PVP, Methanol, Chloroform, Dibutyl phthalate, DMSO are purchased from Research-Lab Fine Chem Industries, Mumbai. Eudragit L100 was purchased from Rohm Pharma, Germany. All the other reagents are all of the analytical grades obtained from Shaimil Laboratories Ltd., Baroda, India. (99.69–99.99% quality).

Every six batches of transdermal films containing Pantoprazole sodium and Esomeprazole magnesium were cast on a petri dish by a solvent evaporation method using different polymers (HPMC E₅:PVP K30 and HPMC E₅:Eudragit L 100) [15]. The drug to polymer ratio was fixed as 1:1 and the polymer to polymer ratio was fixed as 1:1, 1:2, and 2:1 [16]. Three different concentrations of HPMC E₅ were

used in all six formulations and another two polymers PVP K 30 and Eudragit L100 were used in every three formulations at varying concentrations (table 1). N-dibutyl phthalate and propylene glycol were used as a plasticizer. 1% DMSO was used as a permeation enhancer in all the formulations [17].

The polymers were accurately weighed and dissolved in 10 mL of ethanol and in the case of Eudragit L 100, the chloroform: methanol (1:1) solution was also used and kept aside to form a clear solution. Drug pantoprazole sodium was dissolved in the above solution and mixed until a clear solution was obtained. Then the plasticizer and the permeation enhancers were added to the formulation step by step and mixed uniformly. The resulted uniform solution was cast on the petri dish, which was lubricated with glycerin and dried at room temperature for 24 h. An inverted funnel was placed over the petri dish to prevent fast evaporation of the solvent. After 24 h the dried patches were taken out and stored in a desiccator for further studies [18].

Table 1: Formulation details of pantoprazole sodium and esomeprazole magnesium transdermal patches

Ingredients	Formulations											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Pantoprazole Sodium (mg)	635	635	635	635	635	635	-	-	-	-	-	-
Esomeprazole Magnesium	-	-	-	-	-	-	635	635	635	635	635	635
HPMC (E ₅) (mg)	300	200	400	300	200	400	300	200	400	300	200	400
PVP K 30 (mg)	300	400	200	-	-	-	300	400	200	-	-	-
Eudragit L 100 (mg)	-	-	-	300	400	200	-	-	-	300	400	200
Ethanol (ml)	10	10	10	10	10	10	10	10	10	10	10	10
Chloroform: Methanol (1:1) (ml)	-	-	-	6	6	6	-	-	-	6	6	6
n-Dibutyl Phthalate (ml)	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5
Propylene glycol (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
DMSO (ml)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

(All quantities are in mg/ml)

The prepared transdermal drug delivery system of Pantoprazole sodium and Esomeprazole magnesium using different polymers HPMC E₅, PVP K30, and Eudragit L100 were evaluated and had shown good promising results for all the evaluated parameters. From the *in vitro* studies, it was confirmed that the formulations F1 and F7 formulated with HPMC E₅: PVP K30 in the ratio of 1:1 released the drugs pantoprazole 98.99 % and Esomeprazole 95.93 % respectively at 24 h [16]. So, these two formulations were selected for the pharmacokinetic studies on rabbits.

Female New Zealand white rabbits of either sex and approximately the same age, weighing about 1.5 to 1.75 kg, procured from Sri Venkateswara Enterprises, Bengaluru (Reg No. 237/99), were used for the study [19]. They were housed in separate metallic cages and fed with a standard chow diet and water ad libitum. The animals were exposed to an alternate cycle of 12 h of darkness and light each. Before each test, the animals fasted for at least 12 h. The experimental protocols were subjected to the scrutinization of the Institutional Animal Ethics Committee and were cleared by the same (Approval No. P. COL/25/2021/IAEC/VMCP). The animals were divided into 4 groups, each consisting of three. The first group was administered with the transdermal batches of pantoprazole (F1) and the second group was treated with the transdermal patches of esomeprazole (F7). The third and fourth groups were administered with marketed pantoprazole 40 mg and esomeprazole 40 mg tablets, respectively, along with 100 ml of water.

Before the patches were applied, the abdominal site of the rabbit was shaved and cleaned with saline. The skin of the rabbits was checked carefully in case of any skin breakage. The blood samples were collected into heparinized vacuum tubes at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 h following the Pantoprazole or Esomeprazole administration. After collection, the blood samples were centrifuged at 1000 rpm for 10 min at room temperature (25 °C); followed by direct transfer into microcentrifuge tubes and stored at -70 °C until analysis. The amount of food and water intake for each animal was standardized during the sampling day.

The stock solution was prepared by weighing pantoprazole (40 mg) and esomeprazole (40 mg) separately in a 100-ml volumetric flask, dissolved in methanol, and diluted to volume with the same solvent. Of these solutions, 1.0 ml was further diluted to 100 ml with mobile phase to obtain (4,000 ng ml⁻¹) and esomeprazole (4,000 ng ml⁻¹). The standard working solutions of pantoprazole and esomeprazole were produced by diluting the stock solutions with blank rabbit plasma (1:1).

Pantoprazole and esomeprazole were used as an internal standard for each other. Esomeprazole was used as IS for the determination of pantoprazole and pantoprazole was used as IS for the determination of esomeprazole. The internal standard solution was prepared by weighing pantoprazole (4 mg) and esomeprazole (4 mg) in a 100-ml volumetric flask, dissolved in methanol and diluted to volume with the same solvent. Of these solutions, 1.0 ml was further diluted to 100 ml with mobile phase to obtain a concentration of pantoprazole (400 ng ml⁻¹) and esomeprazole (400 ng ml⁻¹). Solutions were freshly prepared before use.

The Phosphate Buffer Solution was prepared by using KH_2PO_4 (6.8 g), previously dried for 2 h at 120±5 °C, was dissolved in triple distilled water, diluted to 1,000 ml with the same solvent, and adjusted to pH 4.70±0.1 with 85% orthophosphoric acid.

The calibration curve was prepared by an accurately measured standard working solution of Pantoprazole and Esomeprazole (1.0, 2.0, 4.0, 6.0, 8.0, 10.0 ml) were transferred in a series of 10 ml of volumetric flask and diluted to the mark with the mobile phase. Calibration curves were plotted over the concentration range of pantoprazole and esomeprazole (400, 800, 1,600, 2,400, 3,200, 4,000 ng ml⁻¹). Twenty microliters of each solution were injected under the operating chromatographic conditions described above. Each solution was injected five times. The least-squares method was used for the calculation of slope, intercept, and correlation coefficient (r). For all the compounds, the correlation between the peak area and substance concentration was described by linear regression equations with high values of correlation coefficient (r).

The plasma samples were prepared by taking 1 ml of the plasma samples transferred to a 15 ml glass tube and 4-ml of tert-butyl methyl ether was added to the pantoprazole samples and 5 ml of dichloromethane was added to the esomeprazole samples. The mixtures were vortexed for 3 min then centrifuged at 3,000 rpm for 15 min. The 4 ml of the organic phase was transferred to another tube and evaporated at 37 °C under a stream of nitrogen. The residue was reconstituted with 100 μ l mobile phase [potassium dihydrogen phosphate buffer-acetonitrile, 72:28 (v/v)], and injected into the chromatographic system [20–22].

An HPLC instrument of LC-10AT VP series (Shimadzu Corporation, Switzerland) consisting of a UV-Visible detector, manual injector with 20 μ l loop, and Hypersil BDS C18 column (250 mm \times 4.6 mm i.d., 5 μ m particle size) was used. A Beckman Instruments (Fullerton, CA, USA) U50 pH meter was used for pH control; the instrument has previously been calibrated against standard buffer solutions of pH 1.68, 3.56, 4.01, and 6.86.

Chromatography was performed on a Hypersil C18 (2) reverse-phase column (250 mm \times 4.6 mm i.d., 5 μ m) base deactivated silyl bonded amorphous silica. The mobile phase was potassium dihydrogen phosphate buffer-acetonitrile, 72:28 (v/v). Flow-rate was 1.0 ml min⁻¹. The column was kept at 25.0 \pm 0.1 °C during the analysis; the detection wavelength was 210 nm and the injection volume was 20 μ l.

The method exhibited linearity of response over a range of 400–4000 ng/ml for both pantoprazole and esomeprazole. The limit of detection and limit of quantification was found to be 147.51 and 399.63 ng/ml for pantoprazole and 131.27 and 397.79 ng/ml for esomeprazole. The within-batch precision ranged from 0.74–1.73 % for pantoprazole and 0.43–0.65 % for esomeprazole. The accuracy ranged from 99.91–100.20 for pantoprazole and 98.96–99.85 % for esomeprazole. The stability of the samples under frozen conditions, at room temperature, and during the freeze-thaw cycle was also determined. The accuracy and precision for calibration curve standards and quality samples in all bioanalytical methods met the acceptance criteria as per FDA guidelines.

Pharmacokinetic evaluation non-compartmental modeling was used to estimate the pantoprazole and esomeprazole pharmacokinetic parameters after single-dose administration. The plasma concentration vs time data was evaluated by using PKSolver. Pharmacokinetic parameters such as maximum drug concentration (C_{max}) in plasma, the time that C_{max} occurred (t_{max}), area under the plasma concentration-time curve from 0 to 24 h (AUC_{0-24}) and 0 to infinity ($AUC_{0-\infty}$), elimination rate constant (λ_z), biological half-life ($t_{1/2}$), Apparent volume of distribution during terminal phase after non-intravenous administration (V_z/F), Apparent total clearance of the drug from plasma after oral administration (Cl/F) and mean residence time (MRT) were determined.

The area under the plasma concentration versus time curve from 0 to 24 h (AUC_{0-24}) was assessed using the linear trapezoidal methodology and was extrapolated to infinity ($AUC_{0-\infty}$). The maximum plasma concentration (C_{max}) and time to reach C_{max} (t_{max}) for pantoprazole and esomeprazole were directly obtained from the individual observed data. The terminal phase elimination rate (λ_z) was estimated using a log-linear regression of the observed plasma concentration point in the terminal phase, and the elimination half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$. The apparent total clearance (Cl/F) and volume of distribution (V_z/F) were calculated using the formula's dose/ $AUC_{0-\infty}$ and dose/ $(\lambda_z * AUC_{0-\infty})$, respectively.

Each experiment was repeated at least three times. The results are expressed as the mean \pm SD. One-way analysis of variance was used to test the statistical significance of differences among groups. Statistical significance of the differences of the means was determined by Student's t-test.

Proton-pump inhibitors (PPIs) have emerged as the drug class of choice for treating patients with acid-related diseases, including gastroesophageal reflux disease (GERD), duodenal ulcer, and gastric ulcer. Patients with Barrett's esophagus and Zollinger-Ellison syndrome benefit from PPIs as well. The gastric acid pump, H⁺, K⁺-

adenosine triphosphatase (ATPase), in the canalicular membrane of the parietal cell is targeted by these drugs, which reduce gastric acid secretion [23]. Acid secretion regulation is a complicated process involving a variety of cell types, hormones, and mediators, *yet al.* of these processes converge in a final common phase involving H⁺, K⁺-ATPase. As a result, PPIs effectively inhibit acid secretion in a manner independent of the processes that stimulate the parietal cell [24].

PPIs in the form of tablets are widely prescribed by medical practitioners, but the oral route of administration is reducing the bioavailability due to the first-pass hepatic metabolism. So, in this present study, an attempt was made to study the effect of transdermal patches on the alteration of pharmacokinetic parameters of some selected PPIs such as pantoprazole and esomeprazole.

The transdermal patches were formulated by a solvent evaporation method using different polymers. The drug to polymer concentration was fixed as 1:1 and the polymer to polymer concentration was 1:1, 1:2, and 2:1. The transdermal patches were formulated and evaluated for various parameters. The *in vitro* studies confirmed that the formulations F1 and F7 formulated with HPMC E5: PVP K30 in the ratio of 1:1 released the drugs pantoprazole 98.99 % and Esomeprazole 95.93 % respectively at 24 h. So, these two formulations were selected for the *in vivo* pharmacokinetic studies on rabbits.

Female New Zealand white rabbits of either and the same age, weighing about 1.5 to 1.75 kg were used for the study. The rabbits of the first and second groups were administered with the transdermal patches of F1 and F7. The third and fourth groups were administered with the respective marketed formulations along with 100 ml of water. The drug concentrations in plasma after the administration of pantoprazole and esomeprazole in all four groups were followed for 24 h. The PPIs concentrations in plasma were assayed using a validated high-performance liquid chromatography with the RP-HPLC method. The mean plasma concentration versus time profiles for PPIs after a single oral dose of PPIs is shown in fig. 1. The pharmacokinetic parameters were calculated by using PKSolver. The results are shown in table 2.

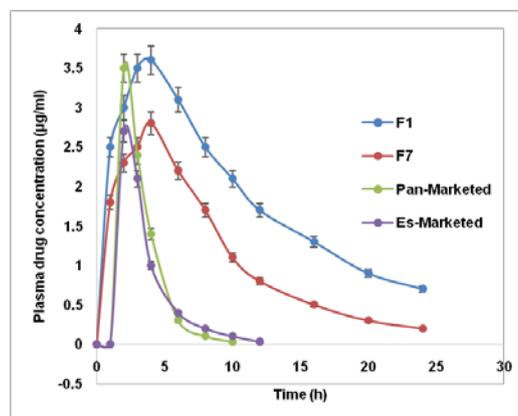


Fig. 1: Mean plasma concentration of PPIs after a single oral administration and transdermal patches ((mean \pm SD; n=3)

The absorption of pantoprazole and esomeprazole was rapid in marketed formulation than the formulated transdermal patches; the mean t_{max} of the marketed pantoprazole and esomeprazole was found to be 2 h, while in the tested transdermal patches F1 and F7, the mean t_{max} was around 4 h. This shows that the formulated transdermal patches were effective in delaying the peak plasma concentration of pantoprazole and esomeprazole. The time to achieve maximum plasma concentrations of PPIs following administration of the marketed tablets used in this study showed relatively 2 h post-dose between the subjects studied. This is probably a result of the use of an enteric-coated formulation. A similar study was conducted by Pue *et al.*, which showed the relative variability of 2–4 h in the subjects treated with pantoprazole [25].

Table 2: Non-compartmental extravascular pharmacokinetic parameters after single-dose administration of pantoprazole and esomeprazole on rabbits

Parameters	Values			
	F1	F7	Pantoprazole marketed formulation	Esomeprazole marketed formulation
λ_z (h^{-1})	0.0693203	0.115611	0.615131	0.4401033
$t_{1/2}$ (h)	9.997071565	5.99426	1.126589	1.57463032
T_{max} (h)	4	4	2	2
C_{max} ($\mu g/ml$)	3.6	2.8	3.5	2.7
AUC_{0-t} ($\mu g^*h/ml$)	45.1	26.8	8.86	7.79
$AUC_{t-\infty}$ ($\mu g^*h/ml$)	10.09805209	1.729945	0.04877	0.068165815
$AUC_{0-\infty}$ ($\mu g^*h/ml$)	55.19805209	28.52995	8.90877	7.858165815
$AUMC_{0-t}$ ($\mu g^*h^2/ml$)	409.8	200.7	28.4	28.78
$AUMC_{t-\infty}$ ($\mu g^*h^2/ml$)	1.533057851	0.438017	0.04898	0.050625
$AUMC_{0-\infty}$ ($\mu g^*h^2/ml$)	411.3330579	201.138	28.44898	28.830625
MRT (h)	7.451948797	7.050067	3.193368	3.668874605
V_z/F (L)	10.2215618	11.93707	2.89806	6.066378709
Cl/F (L/h)	0.708561731	1.380052	1.782688	2.669833289

(All values are calculated from the mean of Plasma drug concentration; n=3)

The peak plasma concentrations (C_{max}) were 3.6 and 3.5 $\mu g/ml$, respectively for the formulated transdermal patches and the marketed formulation of pantoprazole and 2.8 and 2.7 $\mu g/ml$, respectively for the formulated transdermal patches and the marketed formulation of esomeprazole. It indicates there is no significant change in the peak plasma concentration when it was given as a controlled release formulation of transdermal patch or a conventional marketed release formulation, which assures both the formulations F1 and F7 were in the same therapeutic window of the marketed formulations. The K_{el} values were found to be 0.0693, 0.1156, 0.6151, and 0.4401 h^{-1} , respectively, for the formulations F1 and F7 and the marketed formulations of pantoprazole and esomeprazole, calculated from the slope of the plasma concentration-time data. A decrease in the elimination rate constant of formulations F1 and F7 indicated the slow/sustained release of the drug pantoprazole and esomeprazole in rabbits

$AUC_{0-\infty}$ in plasma were 55.198, 28.530, 8.909, and 7.858 $\mu g \cdot h/ml$, respectively, for the formulations F1, F7, and marketed formulations of PPIs pantoprazole and esomeprazole, respectively, which indicated the increased bioavailability of the transdermal formulation. The AUC of the formulation F1 and F7 was increased almost 4-6 fold when compared with their respective marketed formulations, which shows the sustained release of the drug pantoprazole and esomeprazole for an extended period. The elimination rate of both the PPIs was relatively fast with a $t_{1/2}$ of 9.99 and 5.99 h for the test formulations and 1.127 and 1.574 h for the marketed formulations. The $t_{1/2}$ values were found to vary widely; similar results were reported by Hassan *et al.* and Kamdi *et al.* [26, 27]. The other parameters, like AUMC were also found to be higher in the F1 and F7 formulations. The controlled release characteristics of the formulated transdermal patches of PPIs were reflected in the MRT. The MRT was noticeably increased (2 fold) following oral administration of the PPIs formulations (7.45, 7.05 h) for the formulations F1, F7, and (3.19, 3.66 h) for the marketed pantoprazole and esomeprazole formulations.

In this present study, each animal was administered with 40 mg of either pantoprazole or esomeprazole transdermal patches or the marketed formulations of the same for the evaluation of alteration of pharmacokinetic parameters of these two PPIs. A significant difference was observed in all the pharmacokinetic parameters between both the formulations when compared with the marketed formulation. Thus, the results of the present study indicated the applicability of transdermal patches in the alteration of pharmacokinetic parameters of the PPIs pantoprazole and esomeprazole. The study was concluded that enhancement in the bioavailability of studied PPIs would suggest that the transdermal formulation could be used to improve the bioavailability of both the PPIs positively.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICTS OF INTERESTS

All authors have none to declare

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