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Development and Validation of Stability Indicating UPLC Method for Simultaneous Determination of Olmesartan Medoxomil and Chlorthalidone in Bulk and Pharmaceutical Dosage Form

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KEYWORDS

Chlorthalidone, Olmesartan, flow rate, UPLC, retention time, %RSD, regression equation.

ABSTRACT:

Aim: The establishment and validation of simultaneous determination of Olmesartan medoxomil and chlorthalidone by UPLC according to ICH guidelines ensure that the analytical method meets regulatory standards and can be used effectively for quantitative analysis of these compounds.

Objectives: To develop a new UPLC method for simultaneous estimation of Chlorthalidone and Olmesartan to develop a validated method according to ICH guidelines. To apply a validated technique for the estimation of Chlorthalidone and Olmesartan in pharmaceutical formulation.

Methods: The analysis employs an ACQUITY UPLC HSS C18 column with dimensions of 2.1 mm x 50 mm and a particle size of 1.8 µm. The mobile phase consists of a 60:40 mixture of orthophosphoric acid (OPA) and acetonitrile (ACN). This mobile phase is passed through the column at a flow rate of 0.4 mL/min, with the column temperature held constant at 30.0°C. The detection of Olmesartan and Chlorthalidone is optimized at a wavelength of 235 nm.

Results: **:** Retention time of Olmesartan and Chlorthalidone was found to be 1.134 min and 1.535 min. %RSD of the Olmesartan and Chlorthalidone was and found to be 0.1 and 0.6 respectively. %Recovery was Obtained as 99.95 % and 99.38% for Olmesartan and Chlorthalidone. LOD, LOQ values were obtained from regression equations of Olmesartan and Chlorthalidone were 0.08ppm, 0.25ppm and 0.09ppm, 0.26ppm respectively. Regression equation of Olmesartan is y = 29829x + 9806.4, and Chlorthalidone is y = 32492x + 2718.1.

Conclusions: The newly developed method shows to be simple and economical, with shorter run durations and lower retention times. This makes it appropriate for regular quality control testing in industrial settings.

1. Introduction

A prodrug called Olmesartan medoxomil (figure 1) hydrolyzed to become Olmesartan during absorption. It is an angiotensin II receptor antagonist used to treat hypertension. Telmisartan, candesartan, losartan, valsartan, and irbesartan are all part of the angiotensin II receptor blocker (ARB) class of medications, just like Olmesartan. ARBs are commonly used to treat conditions like high blood pressure (hypertension) and heart failure. They work by blocking the action of angiotensin II, a hormone that causes blood vessels to constrict, thereby helping to lower blood pressure and reduce the strain on the heart. Each ARB has its own unique properties and may be chosen based on specific patient needs or tolerability.

Journal of Chemical Health Risks
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Angiotensin II protein cannot bind to angiotensin receptor 1 (AT1) and cause hypertension because ARBs attach to AT1 specifically. Angiotensin II is the main pressor of the renin-angiotensin system, causing vasoconstriction, aldosterone production and release stimulation, cardiac stimulation, and salt reabsorption through the kidneys. Through the specific inhibition of angiotensin II's binding to the AT1 receptor in vascular smooth muscle, olmesartan inhibits the vasoconstrictor effects of angiotensin II. As a result, its activity is unaffected by the pathways involved in the production of angiotensin II.

A diuretic called Chlorthalidone (figure 2) is used to treat edema or hypertension brought on by hepatic cirrhosis, heart failure, renal failure, estrogen medication, and other disorders. Chlorthalidone prevents the reabsorption of sodium and chloride by blocking the Na+/Cl- symporter in the cortical diluting portion of the ascending limb of the loop of Henle. Although the precise mechanism underlying the anti-hypertensive action of chlorthalidone is yet unknown, it is believed that enhanced diuresis leads to a decrease in the amount of plasma and extracellular fluid, which in turn reduces the need for cardiac output and ultimately decreases blood pressure.

The article examined the ways in which UPLC might enhance sample analysis during the development and production of pharmaceuticals. In comparison to UPLC, special attention has been paid to the question of whether UPLC can shorten analysis times without sacrificing the amount or caliber of analytical data produced. Ultra Performance Liquid Chromatography (UPLC) has proven highly effective in enhancing the detection of drug metabolites, improving both the quality of the spectra obtained and the efficiency of separation[1,2].

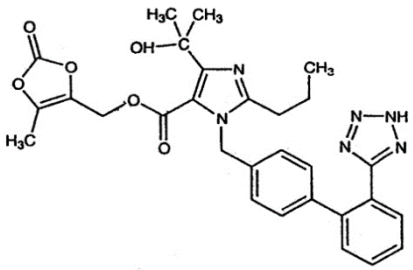

Figure 1: Olmesartan medoxomil

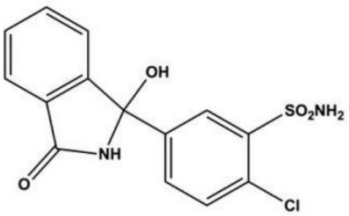

Figure 2: Chlorthalidone

2. Objectives

- To develop a new UPLC method for simultaneous estimation of Chlorthalidone and Olmesartan to develop a validated method according to ICH guidelines.
- To apply a validated technique for the estimation of Chlorthalidone and Olmesartan in pharmaceutical formulation.
- The simultaneous estimation of drugs refers to the process of analyzing and quantifying multiple drugs or compounds in a single analytical run. This is particularly important in pharmaceutical analysis and environmental monitoring.
- The goal of simultaneous estimation of drugs is to provide a comprehensive, efficient, and accurate analysis of multiple drugs or compounds, meeting both practical and regulatory needs.

3. Methods

Chemicals required: Distilled water, CH_3CN, Phosphate buffer, CH_3OH, KH_2PO_4, H_3PO_4

Active ingredients: Olmesartan and Chlorthalidone pure drugs (API), Combination Chlorthalidone and Olmesartan Tablets (**Namzaric**)

Intsruments used: pH meter, Electronics Balance-Denver, Ultrasonicator, Acquity TUV detector of Software Empower 2, WATERS UPLC SYSTEM, UV-VIS spectrophotometer

3.1 Methods:

Diluent: A 60:40 v/v mixture of methanol and water was selected as the diluent based on the drugs' solubility.

Buffer preparation:

0.01N KH_2PO_4 Buffer: weigh 1.38g of KH_2PO_4 in a 1000 ml v.f. Approximately 900ml of milli-Q water was then added, and the flask was allowed to degas and

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JCHR (2024) 14(5), 775-783 | ISSN:2251-6727

sonicate before adding water to fill up the volume and using dil. OPA to correct the pH to 4.8.

Buffer: (0.1% OPA)

In a 1000ml v.f, add 1ml of Ortho phosphoric acid solution. Then, add about 100ml of milli-Q water to get the total volume up to 1000ml with milli-Q water.

Standard stock solution preparation: 10mg of olemesartan and 6.25mg of chlorthalidone were precisely weighed, transferred, and filled into a 50ml v.f . These flasks were then filled with 3/4 th of diluents and sonicated for 10minutes. Add the diluents and named as "Standard (std) stock solution." (200µg/ml of Olmesartan and 125µg/ml of Chlorthalidone)

Standard working solution preparation (100% soln): Pipette out 1ml of std stock soln in10ml volumetric flask (v.f) and makeup with the same solvent. (20µg/ml Olmesartan of and 12.5µg/ml of Chlorthalidone)

Sample stock solution preparation: A 100ml v.f was filled with the weight equivalent of one tablet (20 mg/12.5 mg) after 10 tablets were weighed and their average weights were determined. 5 milliliters of diluent were then added, and the flask was sonicated for 25minutes. The volume was then increased with diluent and filtered using HPLC filters. (200µg/ml of Olmesartan and 125µg/ml of Chlorthalidone)

Sample working solution preparation (100% solution): Take 1ml of sample stock soln in 10ml v.f and makeup the volume. (20µg/ml of Olmesartan and 12.5µg/ml of Chlorthalidone).

3.2 METHOD VALIDATION:[4-21]

System suitability parameters (SSP): The SSP were established by creating std soln of Olmesartan (12.5ppm) & Chlorthalidone (12.5ppm). Six injections were made into each solution in order to assess several characteristics, including USP plate count, resolution, and peak tailing. For the region containing the six standard injections, the percentage RSD should not exceed 2%.

Specificity: To ensure the accuracy of the optimized method, it is crucial to verify the absence of interfering peaks in both placebo and blank samples at the retention time corresponding to the drugs being analyzed. This criterion is essential for confirming the method's specificity, indicating its ability to selectively detect the target drugs without interference from other substances present in the samples. Thus, the method is considered specific based on this validation.

Precision: Precision was evaluated by preparing sample solutions containing Olmesartan (12.5 ppm) and Chlorthalidone (12.5 ppm). Inject the soln for 6 times for each of them & the % RSD of the peak areas from these injections should not exceed 2%.

Linearity: 50% Standard soln: Pipette 0.5ml of std stock solution and make it upto 10ml. (10µg/ml of Olmesartan and 6.25µg/ml of Chlorthalidone)

100% Standard soln: Pipette 1ml of std stock solution and make it upto 10ml. (20µg/ml of Olmesartan and 12.5µg/ml of Chlorthalidone)

150% Standard soln: Pipette 1.5ml of std stock solution and make it upto 10ml. (30µg/ml of Olmesartan and 18.75µg/ml of Chlorthalidone)

Accuracy: Accuracy is the degree to which a measurement, calculation or specification confirms to the correct or true value, often considered in comparison to a known or accepted standard. For determination of accuracy, prepare the sample stock solution and std working solution (100%) according to the above mentioned. Prepare the spiked solutions that for 50% take the 0.5ml of sample stock soln and 1ml of std stock soln diluted in 10ml v.f, for 100% take the 1ml of sample stock soln and 1ml of std stock soln diluted in 10ml v.f and for 150% take the 1.5ml of sample stock soln and 1ml of std stock soln diluted in 10ml v.f respectively.

Acceptance criteria: For every stage, the percentage recovery should range from 98.0 to 102.0.

Robustness: Even though the temperature, mobile phase ratio, and flow rate were deliberately changed, the results did not change and were within the acceptable range as stated by the ICH guidelines. Robustness conditions, for flow rate 0.3ml/min should be ± 0.03ml/min, mobile phase temperature should be 30℃± 3℃ were maintained, and samples were injected in duplicate.The system suitability parameters showed minimal impact, with every parameter passing. %RSD was not over the threshold.

Preparation of LOD sample: Pipetting 2 std stock solns into two different 10ml volumetric flasks, each holding

Journal of Chemical Health Risks
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JCHR (2024) 14(5), 775-783 | ISSN:2251-6727

0.25ml, and diluents were added to make the mixture. 0.3ml of the Olmesartan and Chlorthalidone solutions respectively, taken from the aforesaid solutions and added to 10ml v.f with the diluents.

Preparation of LOQ sample: Separately two, 10ml v.f were taken then, pipetted out of two standard stock solutions, containing 0.25ml each, and then makeup volume with same diluent. Transferring 0.9ml of the Olmesartan and Chlorthalidone solutions, respectively, from the aforesaid solutions into 10ml volumetric flask, then makeup using the same solution.

Degradation studies: Degradation studies refer to scientific investigations that explore how materials, substances change over time under specific conditions like oxidation, acid and alkali degradation, dry heat degradation studies, photo stability studies and natural degradation studies. To conduct degradation studies, take 1.0ml of the stock solutions of Olmesartan and Chlorthalidone & add 1ml of the specified reagent to each. Incubate the solutions at 60°C for 30minutes. Next, inject 4 µL of each prepared solution into the chromatographic system. After injection, record the resulting chromatograms to assess the stability of the samples. Evaluate the chromatograms by comparing them for consistency in peak shape, retention times, and peak areas to determine if there are any signs of degradation or instability in the samples.

4. Results and Discussion

Optimized Chromatographic conditions:

Column : UPLC ACQUITY HSS C_{18} Column 1.8 µm, 2.1 mm X 50 mm.

Mobile phase : 0.1% OPA: Acetonitrile (60:40)

Flow rate : 0.3ml/min

Wavelength : 235 nm

Temperature : 30 ℃

Injection Volume : 1.0µl

Run time : 10.0 Minutes

Both peaks have good theoritical plate, resolution and tailing factor. It suggests that both peaks are well-separated, have good peak symmetry, and the column is performing efficiently. This generally indicates a well-optimized chromatographic method (shown in figure 3).

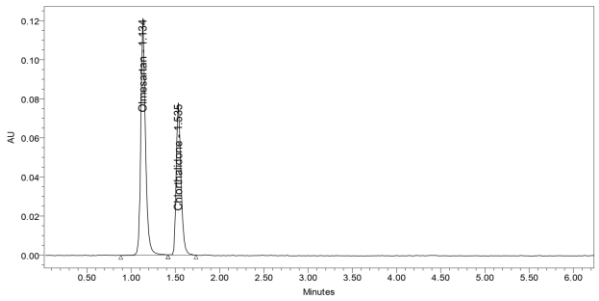

Figure 3: Optimized chromatogram of Chlorthalidone and Olmesartan

System suitability: Every system suitability parameter (represented in table 1) appears within the allowable range and complies with ICH guidelines.

Specificity: Retention times of Olmesartan and Chlorthalidone were eluted at 1.134 min and 1.535 min. respectively. We did not find and interfering peaks in blank and placebo at retention times of these drugs in this method. So, this method was said to be specific shown in figure 4 and 5.

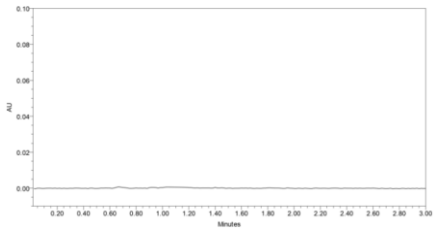

Figure 4: Chromatogram of blank

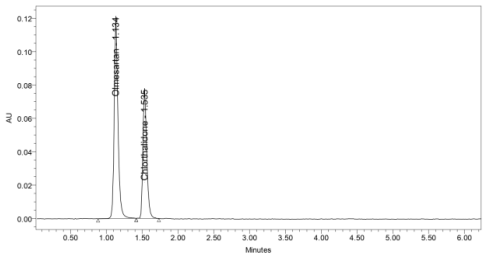

Figure 5: Typical chromagram

Linearity: To construct the calibration curve (shown in figure 6 and 7) by using conc. on the X-axis and response on the Y-axis. The regression equation for Chlorthalidone and Olmesartan was found to be y = 32492x + 2718.1 and y = 29829x + 9806.4, respectively. The regression coefficient was calculated to be 0.999. The calibration data (represented in table 2).

Journal of Chemical Health Risks

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JCHR (2024) 14(5), 775-783 | ISSN:2251-6727

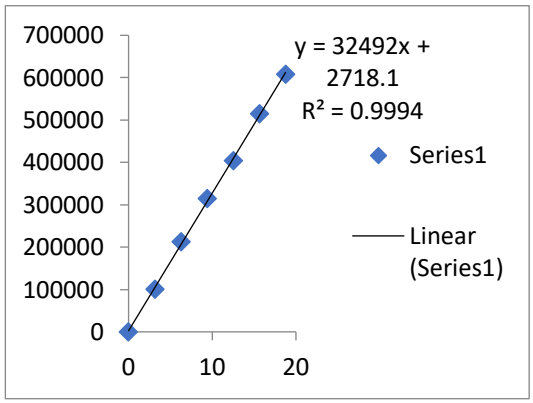

Figure 6: Calibration curve of Chlorthalidone

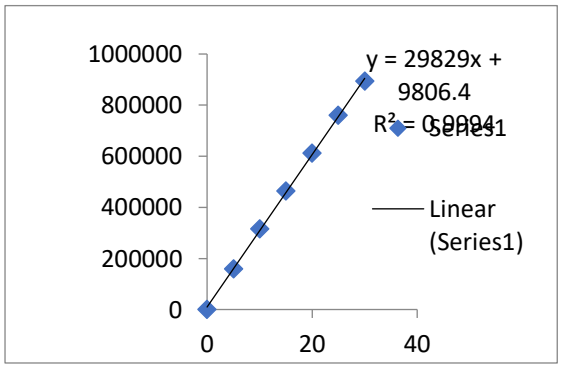

Figure 7: Calibration curve of Olmesartan

Precision: Following Method precision repeatability (represented in table 3), the %RSD for Chlorthalidone and Olmesartan were 0.6% and 0.1% respectively.

Interday precision (Intermediate Precision): Based on inter day precision (represented in table 4), attained with a 10 hours time lag. The %RSD of both Chlorthalidone and Olmesartan was 0.9% and 0.5% respectively.

Accuracy: Three injections of 50%, 100%, and 150% of the concentration were made in triplicate and the amount recovered and mean % recovered was found to be 99.65% and 99.38% (represented in table 5 and 6).

LOD and LOQ:

- LOD (figure 8) for Chlorthalidone was 0.09 and Olmesartan was 0.08 respectively.
- LOQ (figure 9) for Chlorthalidone was 0.26 and Olmesartan was 0.25 respectively.

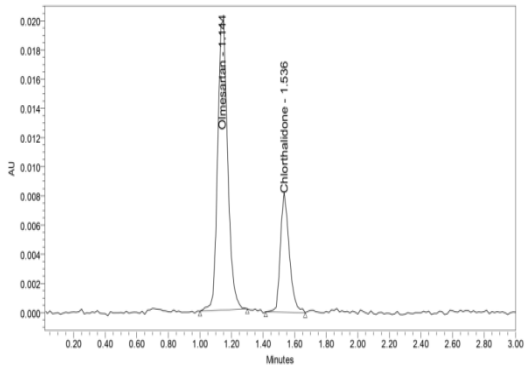

Figure 8: LOD Chromatogram of Chlorthalidone and Olmesartan method

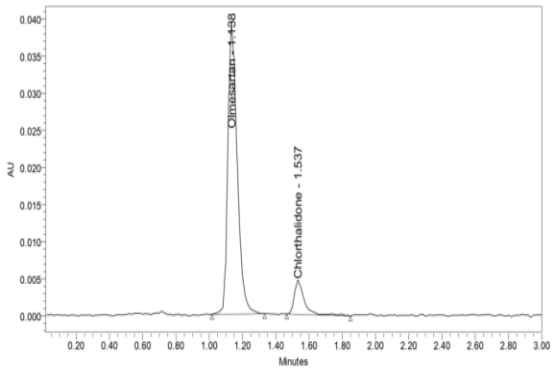

Figure 9: LOQ Chromatogram of of Chlorthalidone and Olmesartan method

Robustness: Although intentional changes of the flow rate, temperature and mobile phase ratio but outcomes did not shows any changes in the result. The results maintained within the permitted range according to ICH guidelines (represented in table 7).

Assay: For standard preparations, the API is utilized, while for sample preparations, formulation is employed. Both the sample and the standard are injected using 6 identical samples. The standard was utilized as a reference for the drug composition of the formulation. Calculations indicated that the mean assay % (represented in table 8) for Chlorthalidone and Olmesartan was found to be 99.29% and 99.99% respectively.

Degradation data: Different types of degradation was performed %recocery (represented in table 9) was noted.

Journal of Chemical Health Risks
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JCHR (2024) 14(5), 775-783 | ISSN:2251-6727

Table 1: System suitability studies of Chlorthalidone and Olmesartan method							
Sl.no	**Olmesartan**			**Chlorthalidone**			
Injections	**RT (min)**	**USP Plate Count**	**Tailing**	**RT (min)**	**USP Plate Count**	**Tailing**	**Resolution**
1	1.133	2197	1.23	1.502	3821	1.29	3.8
2	1.135	2195	1.23	1.519	3771	1.3	3.8
3	1.136	2248	1.21	1.519	3795	1.29	3.9
4	1.136	2248	1.21	1.519	3811	1.29	3.8
5	1.137	2210	1.21	1.521	3845	1.32	3.8
6	1.137	2242	1.22	1.531	3853	1.3	3.9

Sl. no	**Conc. of Chlorthalidone (µg/ml)**	**Response**	**Conc. of Olmesartan (µg/ml)**	**Response**
1	0	0	0	0
2	3.125	99608	5	159427
3	6.25	212100	10	314292
4	9.375	314188	15	462438
5	12.5	403818	20	612349
6	15.625	514294	25	759776
7	18.75	607330	30	892457

Table 2: Calibration data of Chlorthalidone and Olmesartan method

Table 3: Repeatability results for Chlorthalidone and Olmesartan.

Sl. No.	**Chlorthalidone**	**Olmesartan**
1	401253	603825
2	401258	605182
3	403262	604268
4	406195	604961
5	403650	603993
6	407495	605660
Mean	403852	604648
Std.	2554.7	729.1
%RSD	0.6	0.1

Table 4: Intermediate precision results for Chlorthalidone and Olmesartan.

Sl. No.	**Olmesartan**	**Chlorthalidone**
1	606232	401990
2	603997	405651
3	610738	409114
4	606748	402884
5	606521	401171
6	611060	409094
Mean	607549	404984
Std. Dev.	2776.6	3530.1
%RSD	0.5	0.9

Table 5: Accuracy results of Olmesartan

% Level	**Amount Spiked (µg/mL)**	**Amount recovered (µg/mL)**	**% Recovery**	**Mean %Recovery**
50%	10	9.9	99.1	99.65%
	10	9.9	99.3	
	10	10	100	
100%	20	20	99.8	
	20	20.4	101.9	
	20	20	99.8	
150%	30	30.1	100.3	

Journal of Chemical Health Risks
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JCHR (2024) 14(5), 775-783 | ISSN:2251-6727

	30	29.9	99.7	
	30	29.9	99.8	

Table 6: Accuracy results of Chlorthalidone

% Level	Amount Spiked (µg/mL)	Amount recovered (µg/mL)	% Recovery	Mean %Recovery
50%	6.25	6.18	98.95	99.38%
	6.25	6.19	98.99	
	6.25	6.2	99.13	
100%	12.25	12.57	100.52	
	12.25	12.36	98.91	
	12.25	12.52	100.14	
150%	18.75	18.73	99.92	
	18.75	18.53	98.8	
	18.75	18.56	99.01	

Table 7: Robustness data of Chlorthalidone and Olmesartan method

Sl.no	Robustness condition	Olmesartan %RSD	Chlorthalidone %RSD
01	Flow minus	0.3	0.5
02	Flow Plus	0.2	0.4
03	Mobile phase minus	0.3	0.7
04	Mobile phase Plus	0.6	1.3
05	Temperature minus	0.4	0.4
06	Temperature Plus	1.0	0.5

Table 8: Assay Chromatogram Table

Sl. No.	Chlorthalidone %Assay	Olmesartan %Assay
1	98.88	99.19
2	98.88	99.41
3	99.38	99.26
4	100.10	99.37
5	99.47	99.22
6	100.42	99.49
Average	99.52	99.32
S.D	0.63	0.12
% RSD	0.63	0.1

Table 9: Degradation data

Degradation type	Chlorthalidone		Olmesartan	
	% RECOVERED	% DEGRADED	% RECOVERED	% DEGRADED
Acid	95.23	4.77	95.01	4.99
Base	96.03	3.97	95.38	4.62
Peroxide	96.51	3.49	95.80	4.20
Thermal	98.25	1.75	97.58	2.42
Uv	99.06	0.94	98.89	1.11
Water	100.00	0.00	99.37	0.63

5. Conclusion

UPLC enhances and broadens chromatography's utility compared to traditional methods by boosting productivity through improved chemical separation capabilities. Its primary advantage lies in delivering greater information efficiency, offering heightened resolution, speed, and sensitivity in liquid chromatography. Sensitivity is notably enhanced, demonstrated by narrower peak widths at half height in UPLC compared to conventional methods. Consequently, UPLC represents a substantial advancement in speed, sensitivity, and resolution over traditional approaches.

Journal of Chemical Health Risks

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JCHR (2024) 14(5), 775-783 | ISSN:2251-6727

6. Acknowledgemnet

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7. Conflict of interest

Authors declares no conflict of interest.

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