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Formulation and Evaluation of Co-Amoxiclav 228 and 312 mg Dispersible Tablets

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A B S T R A C T

Dispersible tablet is a new form of tablet which any dose of it is dispersed in a small amount of water to create a uniform suspension. The advantage of this formulation is its better and faster effect, no need to swallow, more stability compared to suspension, better taste and greater acceptance by the patients especially kids and elders. This study aimed to design and formulize dispersible tablets including Co- Amoxiclav 228 and 312 mg for enhancement of stability and easier usage and consumption. Co amoxiclav dispersible pill was made by dry granulation method using superdisintegrants ingredients such as crospovidone, croscarmellose sodium and sodium starch glycolate and effervescent materials such as citric acid and sodium bicarbonate. The mixed powder was tested in terms of compressibility, particle size distribution and powders flowability. Some tests were performed for determination of assay, content uniformity, hardness and friability of tablet, weight variation, wetting time, water absorption ratio and disintegration of tablets. Prepared granules had good flowability, compressibility and the hardness and friaibility of tablets were in an acceptable range in most formulations. Formulations made by effervescent bases E_3 and E_4 had disintegration time of 25 and 35 seconds and S_1, S_4 and S_5 formulations made from superdisintegrants materials showed the disintegration time of 260, 262 and 275 seconds. E_4 formulation containing amoxicillin trihydrate, potassium clavulanate, citric acid, sodium bicarbonate, manitol, aspartame and PEG 6000 had 25 sec disintegration time and 40 N hardness.

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Introduction

There are different methods of drug delivery systems to body and make their systemic effects. The most common method is oral consumption that is mostly accepted by the patients. Solid products consumed orally are tablets and capsules. The disadvantages of these products are their slow absorption and delayed effect and also difficult ingestion and swallow. Especially kids, elderly individuals, hospitalized patients and those suffering from mental retardation have difficulty in swallowing pills and capsules [1]. On the other hand, the suspension of antibiotics like Co- Amoxiclav has little stability against moisture and heat and should be kept in refrigerator. Besides, it is difficult to carry suspension bottles and it is costly to produce, keep and transfer them [2]. Formulations with advantages of solid products and sufficient stability, early effect and easy consumption are welcomed by patients and can be beneficial for them. Recent advances in Novel Drug Delivery System (NDDS) aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One of the forms designed with this purpose is dispersible or disintegrable tablet. Dispersible tablets (DTs) are uncoated pills which are quickly diffused in a little amount of water and create uniform suspension. These pills can make a suspension in less than three minutes in 5 ml of water [3].

DTs have early effect since they are consumed in the form of suspension and they are faster and better absorbed than regular pills. Furthermore, the probability of digestive problems is less. This product is welcomed by patients especially kids since they should not be swallowed and have good taste. Besides, these products maintain their taste for a long time after consumption [4-6]. These tablets are offered in small, light and portable packs and can be a good alternative for syrups and suspensions in heavy glass bottles. The main feature of these tablets is their sustainability and stability since any dose is put in water at the time of consumption, so there is no need to keep them in refrigerator and there is no concern on deterioration of drug at trips or inaccessibility to refrigerator. On the other hand, processing is easier in addition to the lower costs of packaging, maintenance and transfer, and they are economical. These products are sensitive to moisture. Humidity must be controlled at the time of production and packed in aluminum and PVC packages [4].

Dispersible tablets need decomposing ingredients for fast disintegration. These ingredients lead to increase the decomposition speed of tablets and their disintegration in aqueous media. Thus, they increase the accessible area and speed of drug release. In recent years, several new agents have been developed known as “Superdisintegrants”. These new substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the superdisintegrants swell and hydrate and its volume increase and produce a disruptive change in the tablet. Efficient superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs [7]. The superdisintegrants such as crospovidone, croscarmellose sodium and sodium starch glycolate can be mentioned [8]. Furthermore, effervescent materials such as sodium bicarbonate, citric acid and tartaric acid can be used as disintegrants. In addition to these ingredients, dispersible tablets contain flavors, lubricants like PEG6000, magnesium stearate and manitol as filler [1, 4, 9].

Co- Amoxiclav is an antibiotic composed of amoxicillin and clavulanic acid. Clavulanic acid is the inhibitor of bacterial Betalactamas which leads to increase spectrum of action of this antibiotic. Co- Amoxiclav is used in the treatment of upper respiratory tract infection such as sinusitis, otitis media, lower respiratory tract infections such as chronic bronchitis and urinary tract infections [10]. This medicine is available in the form of 375 and 625 mg tablets and 156, 228, 312 and 457 mg powder for suspensions. Co- Amoxiclav suspensions are very instable and sensitive to temperature and moisture. After reconstitution with water, they should be kept in refrigerator in 2-8ºC and in this way they could be consumed for seven days. If this suspension is kept in room

temperature, its color will change in less than 2 hours and it is no longer usable [11]. Such instability and certain keeping requirements sometimes make treatment not to be fully done in kids and might have some consequences like microbial resistance and the need to use new antibiotics. The advantage of dispersible tablets is that each dose of this drug is added to water so it is easy to consume it and there is no need to keep it in refrigerator.

The aim of this study is to design and formulate the 228 and 312 mg Co- Amoxiclav dispersible tablets to increase stability and easier consumption. Co- Amoxiclav dispersible tablets of 228 and 312 mg contain crospovidone, croscarmellose sodium, sodium starch glycolate, citric acid and sodium bicarbonate as disintegrating materials. These tablets are prepared through direct compression.

Materials and methods

Materials

Amoxicillin trihydrate, Clavulanate potassium, Sodium starch glycolate, Crospovidone, Croscarmellose sodium were provided from Farabi Pharmaceutical Company (Isfahan, Iran). Citric acid anhydrous, Sodium bicarbonate, Aspartam, PEG 6000, Magnesium stearate were purchased from Merck Company (Germany). Flavoring agents are gifted from Farabi Pharmaceutical Company (Isfahan, Iran).

Spectrophotometeric analysis

First 10 mg amoxicillin powder was added to 100 ml volumetric flask and also phosphate buffer pH 5, and then the mixture was stirred for five minutes and using phosphate buffer. The resulting solution had a concentration of 100 µg per ml. From this solution, concentrations of 10 to 80 µg per ml were made and their absorbancies were measured with UV Spectrophotometry at a wavelength of 229.8 nm. This experiment was repeated three times a day for three consecutive days. The results were plotted as a standard curve [12].

Evaluation of powder mixture

Compressibility index of powders

Using bulk and tapped density, the compressibility index of powders was calculated and compared with the results of USP standard tables and then the compressibility index of powders was interpreted.

At this point, if the powder mixture has not proper compressibility and flowability, these specifications will be modified using excipients or combination of powder and granule [13].

Particle size distribution

The mean particle size of the powders was determined applying sieve analysis and drawing normal distribution charts [13].

Determination of particles flow

To measure the flowability of powder mixture, angle of repose, compressibility index and Hausner's ratio were calculated. To calculate the angle of repose of mixed powder, particles are poured through a funnel onto a flat surface. The angle formed between the powder mass and surface has been calculated using $tan\, a = —$; where H is the height of powder mass and D is the diameter of the powder cone surface. Moreover, powder flowability was interpreted through USP standard tables. By determining bulk density and tapped density by graduated cylinder and putting those in the related formulas, the compressibility index and Hausner's ratio were also calculated and these indices were interpreted using USP standard tables [13].

Preparation of tablets by dry granulation method

Amoxicillin soft powder and clavulanate potassium were compacted to slug and later crushed and passed through a sieve 20. Then the remaining material was weighted, mixed and added to the powder of amoxicillin and clavulanate potassium to obtain a homogeneous powder mixture. Finally, lubricant was added and then the powders was subsequently pressed in a

single punch machine (Kilian & Co, Germany) with a punch number 14 [14].

Characterization of dispersible tablets

Assay

A tablet was entered into a 100 ml volumetric flask and solved in phosphate buffer with pH, 5 and stirred for five minutes and then its volume was increased and filtered. After preparing proper concentrations of this solution, the absorbance of drug was read by UV spectrophotometery in wavelength of 229.8 nm. This test was done for ten tablets of each formula [12, 15].

Content uniformity

Ten tablets were randomly weighed and powdered. Then some powder equal to the weight of a tablet was entered to the volumetric flask and then the assay procedures were calculated. This test was acceptable when the coefficient of variation of 10 samples was 6 or less. If the coefficient of variation was above 6, the number of samples should be increased to reach acceptable range of coefficient of variation [12].

Thickness

In this test, the thickness of 10 tablets was measured by Collis. The variation range of thickness should not exceed 5% of its common thickness [2].

Friability test

10 tablets were weighed and placed on friabilator (Erweka, TAP, Germany). This instrument is set on Erweka motor and rotates by the speed of 25 rpm for 4 minutes. The tablets were reweighed. Tablets were de-dusted using a soft muslin cloth and reweighed. The friability of tablets percentage was calculated as:

$$\frac{initial\ weight\ of\ tablets\ -\ final\ weight\ of\ tablets}{initial\ weight\ of\ tablets} \times 100$$

The acceptable friability was determined as less than 1% [13, 16].

Hardness test

The hardness of tablets is determined by hardness tester (Erweka, 24-TB, Germany) in terms of Newton. This value in the dispersible tablets is usually less than usual tablets [13, 16].

Weight variation

20 tablets are weighed one by one and the mean weight is calculated. If the weight of each tablet is more than 324 mg, maximum ±5% error is considered. Two tablets may be out of this limit and if we double the percentage, no tablet must be out of this range [13, 16].

Wetting time

A paper tissue is folded twice and put into 10 ml water. A tablet is placed on the tissue and waited for wetting. The time for tablet to become fully wet is reported [17].

Water absorption ratio

A piece of paper tissue is folded twice and placed in 6 ml water. A tablet is placed on it and waited for wetting, then the weight of tablet is measured again to calculate water absorption ratio [18-20]:

$$R=Wa - Wb/ Wb$$

- R= water absorption ratio
- Wa= weight after water absorption
- Wb= weight before water absorption

pH test

Just after the complete disintegration of the tablets in the water, pH of the mixture is determined by pH meter [19] (Metrohm, 632, Switzerland). This test is performed for 3 tablets of each formulation and the average values are reported.

Disintegration Time

The device used for this test consists six constant baskets containing six cylindrical glass tubes, the bottom of each tube is connected to a stainless steel basket with certain mesh. Six tablets are placed in the baskets and then the basket is

soaked in 19-21 ºC water baths and the basket is moved. The tablets move up and down in the cylinder without any contact to the basket and without any friability too. The test is done until there is no material remained in the basket and the time is recorded in this condition [19].

Taste Evaluation

The inexperienced volunteers were selected to evaluate the taste of formulations. People were requested to arrange formulations from best to worst. Volunteers were not aware of what differences exist in formulations, and then formulations were given to them randomly. 40 healthy volunteers were selected and divided into four groups: the first group, respectively were given lemon (A), cherry (B), orange (C) and tutifruti (D) flavors. The second group B, C, D and A, third C, D, A and B, and the fourth group was the D, A, B and C. Taste of the following criteria: 1=Bad, 2=Poor, 3=Average, 4=Good, 5=Excellent [21].

Results

Amoxicillin standard curve has been drawn and the line equation was obtained as,
$y= 0.0078x + 0.0126$ ($R^2= 0.996$).
E1- E4 formulations have been designed by effervescent materials such as citric acid anhydrous and sodium bicarbonate as disintegrant.
S1-S6 formulations were prepared by superdisintegrants including sodium starch glycolate, crospovidone and croscarmellose sodium. The last category of formulations including ES1-ES3 was prepared through the combination of effervescent and superdisintegrant materials. Hardness, friability, content uniformity, weight variation, thickness, disintegration time, wetting time and water absorption ratio have been done on all formulations. Weight variation is accepted in the range of ±5% and all tablets were in this range. The friability of tablets was between 0.64 to 0.82%. The hardness of tablets was measured by hardness testing instrument. In the dispersible tablets, the hardness was in the range of 40 - 80 N. The thickness of tablets was 2.4 - 2.85 mm. The pH was in the range of 5.5 to 7. The disintegration time of tablets was between 25 to 275 seconds. The specification of powder mixture has been investigated and the results have been presented in table 4. The results of tests on the mixture of powders and tablets have been presented in tables 4 and 5.
The results of evaluate the taste are shown in Fig.1. According to this chart, the highest score are the fruit flavors of tutifruti, cherry, orange and lemon respectively.

Table 1. Final formulations using effervescent ingredients.

Ingredients (mg)	Formulations			
	E_1	E_2	E_3	E_4
Amoxicillin trihydrate	230	230	278	278
Clavulanat potassium	34	34	74	74
Citric acid	22	54	42	90
Sodium bicarbonate	32	63	54	102
Mannitol	52	39	67	21
Aspartame	20	20	25	25
PEG 6000	10	10	10	10

Table 2. Final formulations using superdisintegrants ingredients.

Ingredients (mg)	Formulations					
	S_1	S_2	S_3	S_4	S_5	S_6
Amoxicillin	230	230	230	278	278	278
Clavulanat potassium	34	34	34	74	74	74
Sodium starch glycolate	28	-	-	36	-	-
Crospovidone	-	17.5	-	-	22.5	-
Croscarmellose	-	-	21	-	-	27
Magnesium stearate	3	3	3	3	3	3
Mannitol	35	45.5	42	35	47.5	43
Aspartame	20	20	20	25	25	25

Table 3. Final formulations using effervescent and superdisintegrants ingredients.

Ingredients (mg)	Formulations		
	ES_1	ES_2	ES_3
Amoxicillin	230	230	278
Clavulanat potassium	34	34	74
Citric acid	22	54	42
Sodium bicarbonate	32	63	54
Sodium starch glycolate	36	-	-
Croscarmellose	-	27	-
Crospovidone	-	-	27.5
Mannitol	66	12	39.5
Aspartame	20	20	25
PEG 6000	10	10	10

Table 4. Evaluation of mixed powders physical specification.

Flowability Characteristics	Formulations												
	E_1	E_2	E_3	E_4	S_1	S_2	S_3	S_4	S_5	S_6	ES_1	ES_2	ES_3
Tapped density (g/ml)	0.62	0.61	0.68	0.60	0.64	0.62	0.63	0.65	0.61	0.60	0.65	0.59	0.63
Bulk density (g/ml)	0.53	0.52	0.59	0.53	0.55	0.53	0.54	0.57	0.52	0.51	0.59	0.51	0.55
Compressibility index (%)	14.5	14.7	13	11.6	14	14.5	14.2	12.3	14.7	15	13	13.5	12.6
Hausner's ratio	1.14	1.17	1.15	1.13	1.16	1.16	1.16	1.14	1.17	1.17	1.15	1.15	1.14
Angle of repose	28.2	27.8	28.9	27	29.3	30.4	32.2	29.5	27.1	28	32.3	30.2	29

Table 5. Evaluation of physicochemical specifications of Co-amoxiclav dispersible tablets.

Physicochemical Properties	Formulations												
	E_1	E_2	E_3	E_4	S_1	S_2	S_3	S_4	S_5	S_6	ES_1	ES_2	ES_3
Assay(mg)	200.01	200.04	250.3	249.8	198.1	200.2	199.2	251.2	250.3	248.2	198.4	200.5	199.5
Content uniformity(mg)	201.2	201.5	248.3	250.4	202.3	205.2	198.6	253.6	248.2	253.1	203.3	201.7	197.1
Hardness(N)	47	45	56	40	45	47	43	48	50	48	58	42	51
Friability (%)	0.82	0.81	0.64	0.88	0.80	0.78	0.77	0.74	0.71	0.73	0.70	0.83	0.77
Thickness (mm)	2.42	2.65	2.73	2.80	2.40	2.42	2.42	2.64	2.65	2.65	2.64	2.65	2.72
Weight variation (mg)	0.402	0.448	0.558	0.593	0.346	0.355	0.342	0.445	0.452	0.454	0.458	0.356	0.547
Wetting time (sec)	147	155	160	166	140	138	140	148	150	152	145	148	163
Dispersion time(sec)	37	35	35	25	260	210	185	262	275	180	70	45	38
pH	5.8	5.82	5.86	5.81	6.7	6.44	6.58	6.68	6.40	6.5	5.88	5.70	5.68
Water absorption ratio	0.125	0.11	0.145	0.116	0.14	0.141	0.141	.120	0.111	0.121	0.123	0.122	0.144

Discussion

Co- Amoxiclav is a broad spectrum antibiotic and is mostly used for respiratory system infections especially in children. This drug is available in the form of oral tablets and powder for suspensions. Co- Amoxiclav suspensions should be kept in refrigerator as it is prepared. They are unstable in the room temperature and are no longer usable. Furthermore, it is difficult to swallow the tablets for elderly people. Fast disintegrating tablets are added to water at the time of consumption which is easy for kids and other individuals. The aim of this study was to design and formulate dispersible tablets of 228 and 312 mg Co- Amoxiclav to remove the problem of suspension instability and easier consumption for patients.

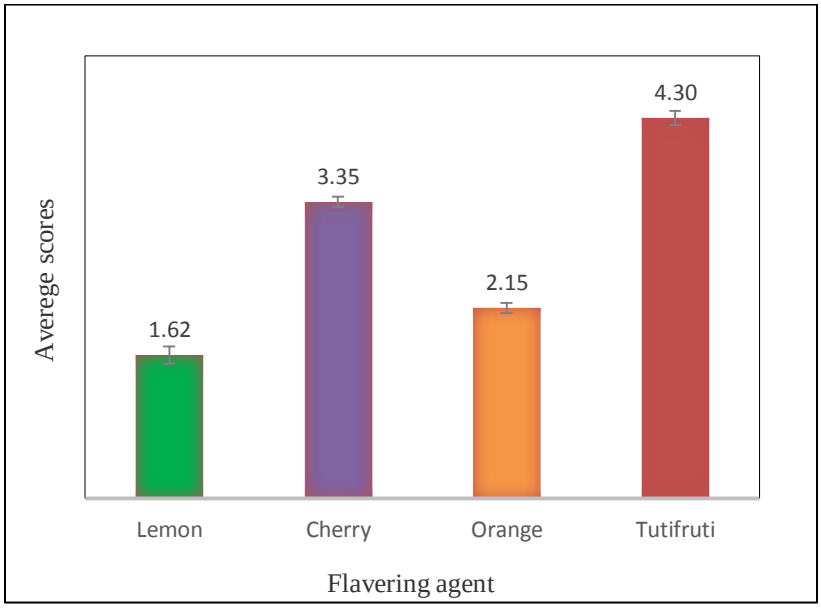

Fig. 1. The results of taste evaluation of Co-amoxiclav dispersible tablets in panel tests by Latin-square method

Amoxicillin standard curve in phosphate buffer with pH 5 was plotted by UV spectrophotometery at λ_{max} of 229.8 nm. The results of this curve were used in determination of the assay and content uniformity test.

In dispersible tablets with effervescent base, citric acid with concentration of 6-18% and sodium bicarbonate with 8-24% concentration were used. Four formulations (E_1- E_4) were prepared by acid and base in this concentration range. Maximum permitted amount for sodium starch glycolate, croscarmellose sodium and crospovidone were 8, 5 and 5% respectively. S_1 to S_6 formulations were prepared in different amounts by using superdisintegrant materials. To achieve the minimum disintegration time of tablets, effervescent and superdisintegrant materials were used in ES_1 to ES_3 formulations. The selected formulations have the best disintegration time in 5 ml water.

The powders particle size distributions are effective in its flow and compressibility. Particle size curve had normal distribution and the size of particles was in the range of 150 – 840 µn (Figure 2).

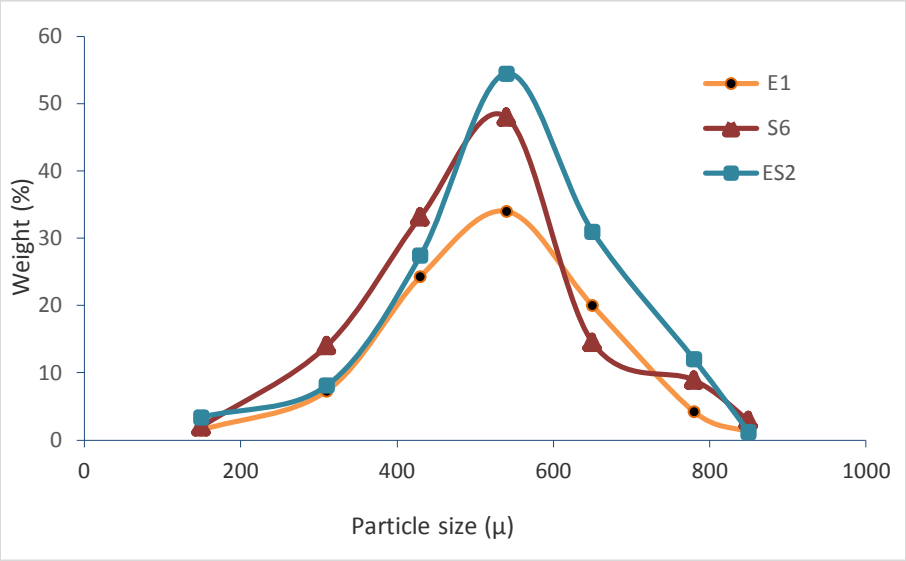

Fig. 2. Particle size distribution curves.

Compressibility index and Haunser's ratio obtained from bulk and tapped density indicated the powders flow. Slug making from the initial powder mixture led the powder have bigger particles, so the powder had better compressibility due to having porous space [21].

The angle of repose, compressibility index and Hausner's ratio showed the flowability of powder. In our study the angle of repose of all formulations was between 27- 32.3. The compressibility index was between 11.6 to 14.7 and the Hausner's ratio was 1.13-1.17 (Table 4). The bigger particles had better drop due to less friction between particles. The granulation of powder helped better flowability. In a similar study on dispersible tablet metformine, the angle of repose between 26 and 30 showed good flowability of powder and the compressibility index between 11-16 indicated good compressibility of powder mixture [20].

Hardness and friability shows physical resistance of the tablet. Hardness of dispersible tablets is less than other tablets and in range of 40 to 58 N. All prepared tablets were in this range. The friability of tablets was between 0.64 and 0.88%. In a similar study, the friability of tablets has been reported between 0.05 and 0.95 [18].

The thickness of tablets varied based on their different weights and it was between 2.4 and 2.8 mm. The same thickness in each weight showed that the imposed force on powder has almost been the same at the time of compression. In the same study thickness has been reported 4.22 mm [19].

According to Pharmacopoeia, the weight variation for tablets weighting 324 mg and more is acceptable in the range of ±5%. The weight variations of prepared tablets were in this range.

The content uniformity assessment was for the determination of fixed dose of medicine in individual tablets and it was acceptable for all formulations.

Disintegration time is the most important test in the preparation of dispersible tablets. The shorter the disintegration time and uniform suspension, the better it would be accepted by patients. Concerning E_1-E_4 formulations, the disintegration time was proper and desired. In S_1- S_6, the disintegration time was longer than desired time. ES_2 and ES_3 made suspensions at 45 and 38 sec, respectively. The use of effervescent showed shorter disintegration time. The more the amount of acid and base, the less the disintegration time. In a similar study the disintegration time has been reported 2.45 min [19].

The acceptable pH range for oral drugs is 5.5-7 and all formulations were in this range.

The wetting time was longer than disintegration time since the tablet remained in plate level and was not soaked in water. In a similar study the

wetting time has been reported between 123 to 144 seconds [18].

The water absorption ratio was about 0.1 % in all formulations. In the same study absorption ratio has been reported between 0.5 – 1.9 % [20].

According to panel test results, the tutifruties flavor was selected by volunteers at the first level of evaluating the taste of the products, according to the average assigned scores.

Conclusion

Co- Amoxiclav tablets were prepared through direct compression method and by the use of effervescent and superdisintegrant materials. The results indicates that the specification of powder mixture and prepared tablets were desirable; however, disintegration time of the prepared tablets by effervescent materials was significantly less than those made from superdisintegrant materials. The use of acid and base as the disintegrating materials made disintegration time of tablets shorter and produced a uniform suspension. To achieve the least disintegration time, the quantity of acid and base can be increased. These tablets have desired specifications.

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Conflict of interest

Authors certify that there is no actual or potential conflict of interest in relation to this article.

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