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Formulation of Pectin-Based Double Layer-Coated Tablets Containing Dexamethasone and Probiotics for Inflammatory Bowel Disease

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ABSTRACT

Inflammatory Bowel Disease (IBD) is a chronic inflammatory condition in the colon that includes ulcerative colitis and Crohn's disease. Dexamethasone is a steroid anti-inflammatory drug that can be used in IBD therapy. This study aims to obtain an optimum formulation of a dexamethasone drug delivery system for IBD treatment and to investigate its release profile based on an *in vitro* dissolution test. Dexamethasone was formulated as a double-coated tablet in combination with a probiotic *L. acidophilus* and *B. longum* mixture (1:1). The core tablets were produced using the wet granulation method, after which they were coated with pectin 4% b/v on the inner coat and a mixture of Eudragit L100 and S100 (1:4) on the outer coat. Three different core tablet formulas were prepared by varying the concentration of probiotics at 0%, 16% and 40% (F1, F2, and F3, respectively). The cumulative drug release of F1, F2 and F3 in HCl 0.1 N pH 1.2 for 2 hours were 42.92 ± 1.55%, 39.41 ± 4.10%, and 39.39 ± 1.63%, respectively, while in the phosphate buffer pH 6.8 they were 102.83 ± 1.56%, 105.08 ± 1.70%, and 98.81 ± 3.37% respectively, after 12 hours. From the results, we conclude that all formulas could be promising candidates for developing colon-targeted drug delivery.

Keywords: *colon-targeted; inflammatory bowel disease*; *eudragit; probiotic; tablet*

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition divided into ulcerative colitis and Crohn's disease (Crowley & Muise, 2018). In 2017, the prevalence of IBD in the world reached 6.8 million cases (Alatab et al., 2020). From 2011 to 2013, the average number of IBD incidents in Indonesia went 0.77 cases per 100,000 population, with ulcerative colitis representing 0.49 cases and Crohn's disease 0.27 cases (Ng et al., 2019).

One of the active substances used in the treatment of IBD is dexamethasone, a corticosteroid drug commonly used to treat mild to severe cases (Oshi et al., 2018). It has a high anti-inflammatory potential and a long duration of action compared to other glucocorticoid drugs. However, peroral administration of the drug can cause systemic side effects, such as hyperglycemia, hypertension and osteoporosis (Zeng et al., 2016). To minimise systemic absorption and to increase treatment locally in the colon, colon-targeted drug delivery systems have been widely investigated (Amidon et al., 2015; Iswandana et al., 2018; Iswandana et al., 2017).

One of the strategies developed for colon-targeted delivery systems is the double layer-coated tablet system. Such a system involves tablets coated with a primary (inner) and a secondary (outer) layer. The outer layer consists of pH-sensitive polymers, which will dissolve depending on the pH of the dissolution medium. The inner layer consists of polymers, such as polysaccharides, which can be degraded by colon microflora, allowing the release of drugs into the colon (Prudhviraj et al., 2015). Previously, the polymers used for colon-targeted drug delivery systems have included alginate/polyvinyl alcohol and alginate-carboxymethyl cellulose (Iswandana et al., 2018); alginate/hydroxypropyl methylcellulose and alginate–chitosan (Iswandana et al., 2018); and chitosan tripolyphosphate (Iswandana et al., 2017).

One of the polysaccharides that is commonly used in drug delivery is pectin. This is non-toxic, biodegradable, biocompatible, and perfectly degraded by microflora enzymes, making it suitable for a colon- targeted delivery system. Furthermore, it has a long retention time in the gastrointestinal (GI) tract. However, pectin has limitations because of its high solubility and because it can swell in an aqueous medium. It is therefore less effective in preventing drug release in the upper GI tract (Maestrelli et al., 2007). Therefore, core tablets coated with polysaccharides are normally re-coated with enteric polymers. This strategy is used to minimise the release of the drug into the upper GI tract before it arrives in the colon. Enteric polymer that are commonly used are Eudragit L100 and Eudragit S100. Eudragit L100 is dissolved at a pH above 6, while Eudragit S100 is dissolved at one above 7 (Thakral et al., 2013).

In a delivery system based on microflora activity, the number of colon microflora must be sufficient to digest polysaccharides in order for the drug to be released into the colon in appropriate quantities. However, some conditions, such as variations in the number of colon microflora between individuals, reduce microbial numbers due to antibiotic use, and the slow process of enzyme degradation inhibits the release of drugs in the colon (Pooja et al., 2011). In addition, ulcerative colitis is always accompanied by an imbalance of microflora in the colon (Kaur et al., 2016). These barriers can be overcome by adding probiotics in different preparations or as excipients in tablet formulations (Ghosh et al., 2010). The addition of probiotics has the advantage of facilitating the release of drugs in the colon. In addition, the process is also more efficient, since probiotics and active substances can be co-delivered in a single dosage form.

Probiotics are known to mimic colon microflora by producing enzymes that can degrade polysaccharides. The genus *Lactobacillus* and *Bifidobacterium* have been reported to degrade pectin (Singh et al., 2015). Additionally, the probiotics *L. acidophilus* and *B. longum* have shown clinical effects as anti-inflammatories (Saez-Lara et al., 2014). This study aims to formulate a double-layer coated tablet containing dexamethasone and to obtain an optimum concentration of probiotics that can enhance the release of dexamethasone into the colon. Double-coated dexamethasone tablet formulations were prepared by incorporating probiotics into the core tablet. Three formulas were formulated, containing 0%, 16% and 40% probiotics, to study their effect on the drug release profile. Pectin was used as the inner coat layer, and a mixture of Eudragit L100 and Eudragit S100 as the outer coat layer.

MATERIALS AND METHODS

The materials used were dexamethasone (Lloyd, Indonesia), dexamethasone BPFI (BPOM, Indonesia), pectin with a degree of esterification of 71% (Danisco, USA), Avicel® PH 102 (Brataco, Indonesia), PVP K-30 (BASF, Germany), talc (Brataco, Indonesia), magnesium stearate (Brataco, Indonesia), *L. acidophilus* (Shandong Zhongke Jiayi Bioengineering, China), *B. longum* (Shandong Zhongke Jiayi Bioengineering, China), Eudragit® L100 (Evonik, Germany), Eudragit® S100 (Evonik, Germany), ethanol (RIV Chemicals, Indonesia), isopropyl alcohol (Brataco, Indonesia), triethyl citrate (Jinan Jinbang Chemical, China), hydrochloric acid (Merck, Germany), sodium hydroxide (Merck, Germany), potassium dihydrogen phosphate (Merck, Germany), and aquadest (Brataco, Indonesia).

Preparation of Core Tablets Using the Wet Granulation Method

Core tablets were prepared according to the formula shown in Table 1. *L. acidophilus* and *B. longum* were mixed homogeneously. Half of the probiotic mixture was then mixed with Avicel® PH 102 and dexamethasone until homogenous. A 9% w/w PVP solution was added, and the mixture blended until a homogenous wet mass was formed; it was then sieved through an 8-mesh sieve to produce damp granules. The moist granules were then dried in an oven at a temperature of 40°C for 2 hours. Subsequently, the dried granules were sifted through an 18-mesh sieve and mixed with the rest of the probiotics, magnesium stearate, and talc. The final granules were then evaluated for their compressibility index, Hausner ratio, repose angle, flow rate (g/second), and moisture content before compression using an Erweka EP-1 (Germany) single-punch tableting machine.

Table 1. Formulation of the core tablet

Composition	Amount per tablet (mg)		
	F1	F2	F3
Dexamethasone	0.5	0.5	0.5
L. acidophilus	-	8	20
B. longum	-	8	20
Avicel® PH 102	93.5	77.5	53.5
PVP	5.9	5.8	5.9
Talk	4	4	4
Magnesium stearate	2	2	2

Tablet Coating with Pectin

The coating solution was prepared by dissolving 4 g pectin in 100 ml aquadest. 1.4 g triethyl citrate was added to the solution and stirred until homogeneous (Table 2). The tablets were coated using a coating pan (Erweka DKM, Germany) equipped with a spray gun (Meiji F-75G, Japan) at a speed of 18 rpm.

Tablet Coating with Eudragit L100 and Eudragit S100

Eudragit L100 and Eudragit S100 (1:4) were dissolved in 100 mL of isopropyl alcohol to make a 10% w/v solution. Triethyl citrate 20% w/w was added to the coating solution and stirred until homogeneous. The second coating formula can be seen in Table 2. The tablets were coated in the same conditions and using the same methods as the inner coating. The tablets were also coated using a coating pan (Erweka DKM, Germany) equipped with a spray gun (Meiji F-75G, Japan) at a speed of 18 rpm.

Table 2. Formulation of coating solution

Composition	Amount
Inner layer	
Pectin	4 g
Triethyl citrate	1.4 g
Aquadest	up to 100 ml
Outer layer	
Eudagrit® L100	2 g
Eudagrit® S100	8 g
Triethyl citrate	2 g
Aquadest	up to 100 ml

Dexamethasone in Tablet Assay

A total of 20 tablets were weighed, then pulverized. The powder equivalent to 1.4 mg of dexamethasone was weighed, then dissolved in the ethanol-water mixture (2:1) in a 100 ml volumetric flask, followed by sonication for 10 minutes. The solution was then filtered with a membrane filter (pore size 0.45 µm). Subsequently, sample absorbance was measured using a spectrophotometer UV-Vis (Shimadzu UV-1800, Japan) at λ_{max} 240 nm.

A calibration curve was made using dexamethasone *BPFI*. 10 mg of dexamethasone *BPFI* was weighed and dissolved in an ethanol-water mixture (2:1) in a 100 ml volumetric flask to create a 100 µg/ml solution. This solution was then diluted to obtain a series of solutions with concentrations of 6, 8, 10, 12, 14, 16 and 18 µg/ml. Each solution was then measured in a spectrophotometer UV-Vis at λ_{max} 240 nm.

Tablet Evaluation

Organoleptic tests were performed by observing shape, size, colour, odour, surface, and physical defects. The surface morphology of the tablets was observed using scanning electron microscopy (Jeol JSM-5310 LV, Japan). The tablet dimension was measured using a vernier caliper.

A weight uniformity test was conducted by weighing ten tablets one by one and calculating their average weight. The dexamethasone content per tablet was calculated and expressed in the percentage of the amount of dexamethasone added to the formulation. A friability test was performed in a friability tester apparatus (Vanguard Pharmaceutical Machinery LIC-2, USA), using 20 tablets at a speed of 25 rpm for 4 minutes. In addition, a hardness test was performed on ten tablets using a hardness tester (Erweka TBH 28, Germany).

Disintegration Time

Tablet disintegration time was investigated using a disintegration tester apparatus (Electrolab ED-2, India) in an artificial gastric fluid LP (HCl pH 1.2) at a temperature of 37±2°C. The disintegration time was also investigated in a simulated intestinal fluid medium (phosphate buffer pH 6.8) at a temperature of 37±2°C.

***In Vitro* Dissolution Test**

An *in vitro* dissolution test was performed using three tablets from each formula in an apparatus 1 (basket) dissolution tester (Electrolab TDT-08L, India), at a speed of 100 rpm and temperature of 37°±0.5°C. The test was conducted in 500 ml hydrochloric acid 0.1 N for the first two hours. After two hours, the medium was replaced with 500 ml phosphate buffer pH 7.2, and the test continued for three hours. After this time, the medium was replaced with 500 ml phosphate buffer pH 6.8, and the test continued for another 7 hours. The phosphate buffer pH 6.8 was heated for 30 minutes and purged with CO_2 for 30 minutes before use to create anaerobic conditions.

An amount of 5 ml of the samples was withdrawn at predetermined time intervals. Each sample was filtered with a 0.45 µm membrane filter before analysis with a spectrophotometer UV-Vis. After each sampling, 5 ml of new dissolution medium was added.

RESULTS AND DISCUSSION

Preparation of Double Layer-Coated Tablets

As mentioned previously, the core tablets were prepared by varying the concentration of probiotics in them. Half of the probiotics were added to the wet granulation to ensure their homogeneity, and the rest were added to the dried granules as the external phase. The granules from the three formulas demonstrated excellent flow characteristics based on the compressibility index, Hausner ratio, and angle of repose (Table 3). These results indicate that although half of the probiotics were added as an external phase, this did not negatively affect the flow characteristics of the granules. Good flow characteristics, which are represented by a low compressibility index and Hausner ratio, were also supported by a low moisture content of below 5%, since high moisture content can negatively influence the characteristics.

The core tablets from all three formulas were white, round with biconvex surfaces, smooth and shiny (Figure 1). Pectin-coated tablets of all formulas also had similar shapes and a yellowish colour. The distinctive colour of pectin probably produced this effect. The double layer-coated tablets were also round, with biconvex surfaces with a yellowish tint. Evaluation of the tablet surface morphology with SEM showed that the whole surface of the core tablets was covered by the coating layer

Table 3. Evaluation of tablet granules

Parameters	F1	F2	F3
Compressibility index	11.48 ± 2.12	14.15 ± 0.80	9.26 ± 2.17
Hausner ratio	1.13 ± 0.03	1.16 ± 0.01	1.10 ± 0.03
Angle of repose (°)	25.56 ± 1.38	27.30 ± 0.69	26.18 ± 1.85

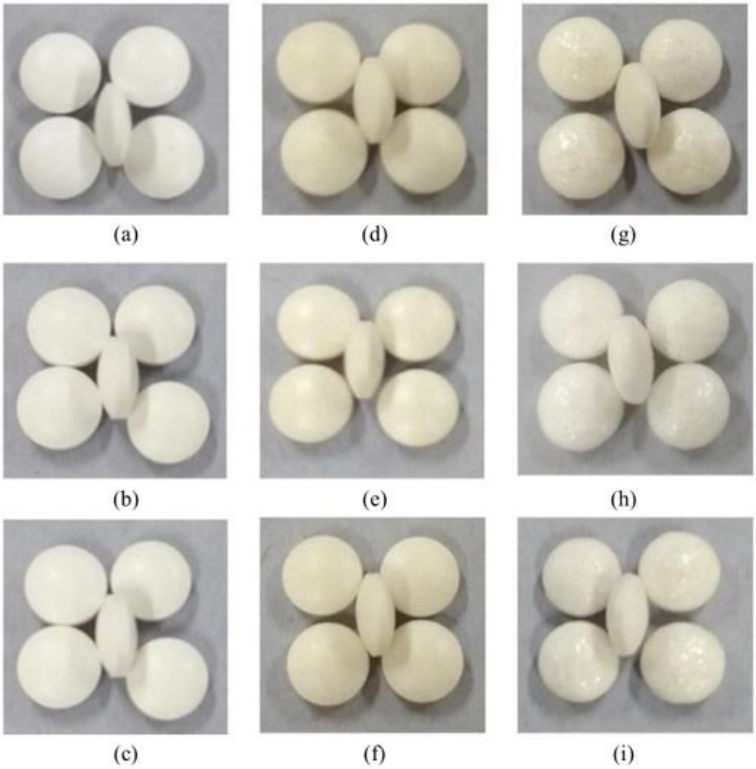

Figure 1. Appearance of the core tablets F1 (a); F2 (b); F3 (c); pectin-coated tablets F1 (d); F2 (e); F3 (f); and of the double layer-coated tablets F1 (g); F2 (h); and F3 (i).

(Figure 2). However, the texture of the coating layer appeared bumpy, with pores which might have been due to the tablet sticking during the second coating process.

The results of the drug assay showed that the dexamethasone content in tablets F1, F2, and F3 was between 90% and 110% (Table 4). These results align with the Indonesian Pharmacopeia requirements for dexamethasone tablet assay. The thickness and diameter were measured for the core tablets, tablets with an inner coat, and those with a double coat. As shown in Table 4, the thickness of the tablets after the first coating showed increases of 7.61%, 5.74% and 4.84%, while the diameter after the first coating showed increases of 2.10%, 2.52% and 2.54% for F1, F2 and F3 respectively. These results indicate that the coating layers were distributed more on the upper and lower surfaces of the tablets, rather than on the side. Similar results were found after the second coating. Among the three formulas, F1 showed the highest increase in thickness, followed by F3 and F2. The highest increase in weight was also shown by F1, in line with the increase in thickness. However, despite the higher gain in diameter shown by F3 compared to F2, F3 showed a lower increase in weight. This is probably because the density of the coating layers on F3 were less than those on F2.

The hardness of the core tablets from the three formulas was found to be similar, between 5-6 kPa (Table 5). The coated tablets showed increased hardness, probably due to the flexibility of the film layer surrounding them. These results meet the optimum criteria of tablet hardness, which are > 4 kP for the core tablet and 10-20 kP for a coated tablet (Allen et al., 2011). The friability of the core tablets from all formulations was less than 0.2% (Table 5), indicating good mechanical characteristics. This value ensures the mechanical strength of the tablets in withstanding the pressure exerted during the coating process. After coating, the friability was even lower for all formulas, possibly due to the compact coating layer.

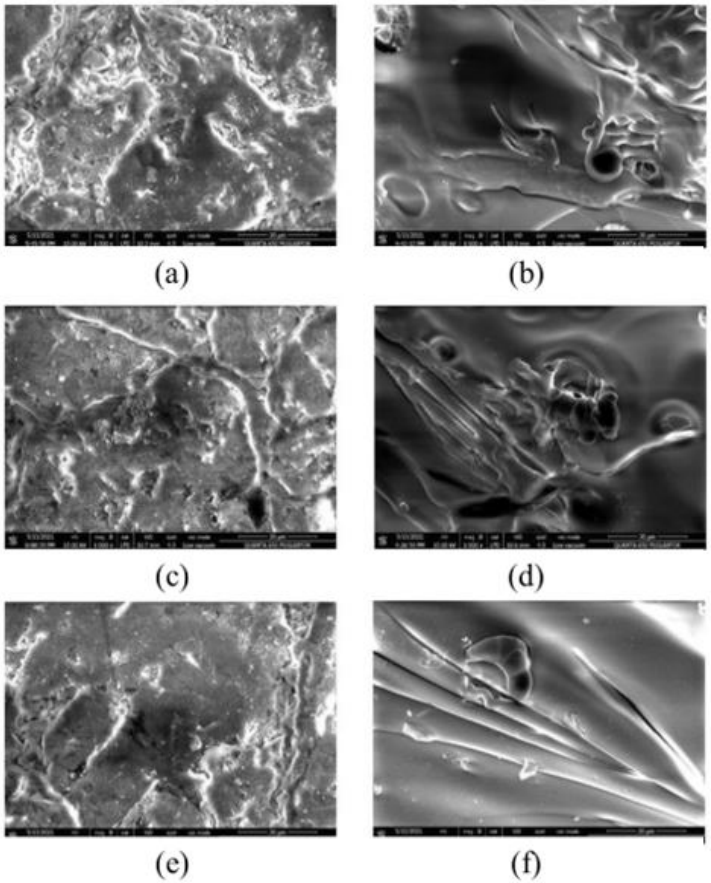

Figure 2. Morphology of the surface of the core tablets and double layer-coated tablets F1 (a and d), F2 (b and e), and F3 (c and f), shown by SEM with 1000 times magnification.

Table 4. Characteristics of the double layer-coated dexamethasone tablets

Formula	Tablet Components	Drug Content (%)	Thickness (mm)	Increase in thickness (%)	Tablet Diameter (mm)	Increase in diameter (%)	Average Weight (mg)	Increase in Weight (%)
	Core tablet	99.55 ± 1.60	3.02 ± 0.03		7.13 ± 0.04		103.29 ± 1.43	
F1	+inner coat		3.25 ± 0.03	7.61	7.28 ± 0.03	2.10	112.23 ± 1.47	8.65
	+outer coat		3.58 ± 0.06	10.15	7.42 ± 0.05	1.92	119.79 ± 1.17	6.74
	Core tablet	98.42 ± 0.57	3.31 ± 0.03		7.13 ± 0.04		106.57 ± 1.91	
F2	+inner coat		3.50 ± 0.04	5.74	7.31 ± 0.04	2.52	115.66 ± 1.78	8.53
	+outer coat		3.76 ± 0.06	7.43	7.49 ± 0.06	2.46	122.59 ± 1.85	6.50
	Core tablet	101.21 ± 0.69	3.08 ± 0.05		7.07 ± 0.04		105.82 ± 2.11	
F3	+inner coat		3.23 ± 0.05	4.87	7.25 ± 0.02	2.54	112.86 ± 1.62	6.65
	+outer coat		3.59 ± 0.07	11.14	7.33 ± 0.06	1.10	120.39 ± 1.36	6.67

Table 5. Evaluation of tablet hardness and friability

Formula	Tablet	Hardness (kP)	Friability (%)
F1	Core tablet	5.22 ± 0.46	0.229
	Double layer-coated tablet	13.14 ± 1.99	0.022
F2	Core tablet	5.01 ± 1.26	0.165
	Double layer-coated tablet	16.36 ± 1.52	0.061
F3	Core tablet	6.01 ± 0.65	0.102
	Double layer-coated tablet	15.80 ± 3.07	0.072

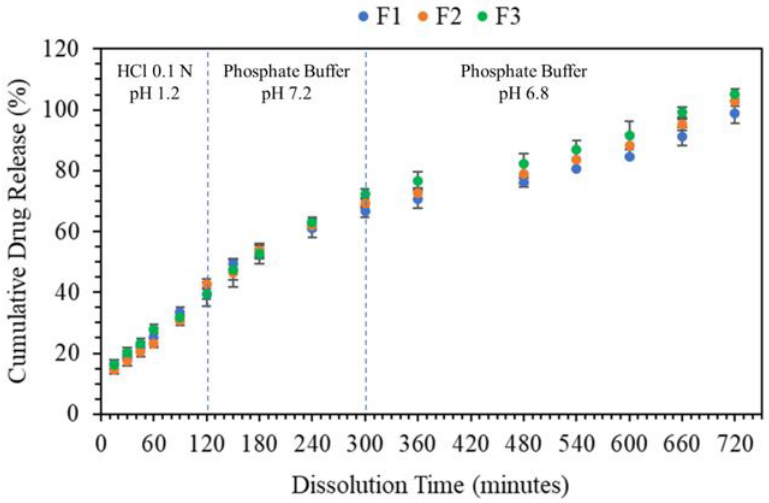

Figure 3. Cumulative drug release of F1, F2 and F3 in different media (mean ± SD, n=3).

The outer layer of the coating consisted of Eudragit® L100 and Eudragit® L100. Eudragit® is a polymethacrylate-based copolymer with carboxylic acid as the pendant group. The carboxylic groups are insoluble in an acidic environment and were therefore expected to protect the tablet from disintegration in the stomach. All of the formulas showed that no disintegration occurred in the pH 1.2 medium, indicating that the coating layer could protect the core tablets from vigorous water infiltration. The tablet dissolution test showed cumulative drug releases of around 39%, 43% and 39% for F1, F2 and F3 respectively in the pH 1.2 medium for the first two hours (Figure 3). This high percentage of drug release is probably because the layer was not thick enough.

As the tablet travels from the stomach to the intestine (pH 7.2), the Eudagrit® layer will dissolve. Therefore, we added pectin with a degree of esterification of 71% as an inner layer for extra protection. Pectin with a high degree of esterification is less soluble in basic medium and was thus expected to retain the drug release in the intestine. The dissolution test for all the formulas in the phosphate buffer medium pH 7.2 for 3 hours showed around a 30% increase in cumulative drug release since exposure to pH 1.2 (Figure 3). This means around 60% of drugs had been released since 0h.

Pectin is a polysaccharide that can be degraded by pectinase, an enzyme available in the colon. Therefore, we expected that the pectin layer would be degraded in the colon, allowing the tablet to disintegrate and release the rest of the drugs. We also added probiotics in the tablet formulas to assist the disintegration process. When the dissolution test was continued to phosphate buffer pH 6.8, which represents the pH of the colon, the total cumulative drug release after 7 hours was 98.81 ± 3.37%, 102.83 ± 1.56%, and 105.08 ± 1.70% for F1, F2, and F3 respectively. These results suggest that increased probiotic concentration in the tablet could slightly increase the cumulative drug release.

CONCLUSION

We successfully prepared a double layer-coated dexamethasone tablet containing probiotics. Although the drug release in the pH 1.2 and pH 7.2 medium was high, all the formulae could be promising candidates for developing colon-targeted drug delivery. Further optimisation of the coating layer and probiotic concentration are essential to obtain the best drug release profile.

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CONFLICT OF INTEREST

The authors declared no conflict of interest

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