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Research Article

IN VITRO AND *IN VIVO* EVALUATION OF FLOATING GASTRORETENTIVE DRUG DELIVERY SYSTEM OF CIMETIDINE USING HARD ALGINATE CAPSULES

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ABSTRACT

Objective: The objective of this study was to evaluate *in vitro* and *in vivo* of gastroretentive drug delivery system of cimetidine using hard alginate capsules.

Methods: Drug release study was tested to various hard alginate capsules containing 200 mg cimetidine with paddle method dissolution apparatus in artificial gastric fluid pH 1.2. Concentrations of cimetidine were measured using ultraviolet spectrophotometer at 218.4 nm wavelength. The product that fulfilled the sustained release profile was evaluated for bioavailability using male rabbits at dose 9.3 mg/kg orally, and the antiulcer studies were evaluated by HCl-induced ulcer method at cimetidine dose 18 mg/kg once a day orally. Gastric lesions were evaluated by macroscopic and microscopic observations.

Results: The results of drug release test showed that hard alginate capsule made from sodium alginate 500–600 cP gave sustained release profile of cimetidine for 12 h. *In vivo* bioavailability studies showed that cimetidine given with hard alginate capsules gave higher of Cmax, Tmax, and area under the curve of cimetidine compared to cimetidine that given with conventional hard gelatin capsules. The antiulcer studies showed that the healing effect of cimetidine that given with hard alginate capsules was faster than cimetidine given in suspension form. Cimetidine that given with hard alginate capsules macroscopically showed no gastric lesion and histopathologically also showed normal gastric mucosa of rats after 4 days treatment. However, cimetidine given in suspension form showed of 0.036±0.024 ulcer index and microscopically there was still erosion of gastric mucosa of rats after 4 days treatment.

Conclusion: Floating gastroretentive of cimetidine using hard alginate capsules give a sustained release of cimetidine with better bioavailability and antiulcer effect of cimetidine.

Keywords: Hard alginate capsules, Gastroretentive, Cimetidine, Release, Bioavailability, Antiulcer effect.

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INTRODUCTION

Peptic ulcer is erosion at anywhere on mucosal lining in the gastrointestinal tract, usually in the stomach or duodenum. The two main causes of ulcers are too little mucus production or excessive acid production in the stomach [1]. Oral drug delivery routes are the most convenient and most commonly used as route of administration [2]. However, this route has several physiological problems including gastric retention time and unexpected levels of gastric emptying. This situation drastically reduces the drug absorption time, which is followed by reduced bioavailability [3]. These limitations have prompted to design gastroretentive drug delivery systems that can retain in the stomach for extended time and also increase the bioavailability of the drug by increasing gastric retention time.

Several approaches of dosage formulations with gastroretentive system have been developed to achieve controlled release of cimetidine to stay longer in the stomach [4-6]. One of the gastroretentive systems is floating system [7]. Recently, it was reported that the formulation floating tablets of nizatidine using hydroxypropyl methylcellulose (HPMC K4M) [8], design and optimization of multiparticulate gastroretentive delivery system of ranitidine hydrochloride [9], and formulation and evaluation of ranitidine hydrochloride as floating *in situ* gel [10].

Sodium alginate is a polysaccharide that is derived from seaweed (brown algae) and non-toxic [11]. Alginate can be used for the preparation of periodental drug delivery system and gastroretentive drug delivery system of ranitidine HCl and antacids [12-16].

Alginate interacts with organic diacidic base piperazine [17] and calcium salts. It is well known that interaction of alginate with calcium salts solution form gel immediately. Based on the interaction properties of alginate and calcium ion, Bangun *et al*. reported the preparation and characterization of hard alginate capsules shell and it is found that hard alginate capsules shell is resistant or do not disintegrate in simulated gastric fluid pH 1.2, but it swells and disintegrates in simulated intestinal fluid [18]. Previously, it was studied the floating gastroretentive of amoxicillin using hard alginate capsules and its antibacterial activities of amoxicillin [19].

Cimetidine is a class of H_2 receptor antagonists used to treat gastric ulcers and duodenal ulcers, gastroesophageal reflux disease, and gastric ulcers due to NSAIDs. Cimetidine has a half-life of 2 h. It is poorly absorbed from the lower gastrointestinal tract, and the bioavailability of cimetidine is <70% [20]. Therefore, it is necessary to raise the bioavailability and enhances the antiulcer effect of cimetidine.

In this paper, it will be discussed the application of hard alginate capsules as floating drug delivery system of cimetidine. The lag time, floating time, drug release, bioavailability, and antiulcer effect will be discussed.

MATERIALS AND METHODS

Materials

Cimetidine was obtained from Jiangsu Baosheng Longcheng Pharmaceutical Co., Ltd., China. Hydrochloric acid, acetonitrile,

perchloric acid, formaldehyde, ethanol, xylene, hematoxylin, and eosin, all were the products of Merck. Sodium alginate 80–120 cP, sodium alginate 300–400 cP, and sodium alginate 500–600 cP were purchased from Wako Pure Chemical Industries, Ltd., Japan. Hard alginate capsules (size 1 used for *in vitro* study and capsules with length 0.9 mm and diameter 0.2 mm used for *vivo* study) were obtained from Laboratory of Physical Pharmacy, Faculty of Pharmacy, University of Sumatera Utara. Hard gelatin capsules obtained from A to H Pharmacy, Medan. The photo of capsules is shown in Fig. 1.

Animals

Healthy male rabbits with weight 1.8–2 kg for bioavailability studies were used. Rattus norvegicus rats used weighing 180–200 g for antiulcer studies were maintained in standard animal house, given standard pellet diets and tap water *ad libitum*. The rabbits and rats were fasted from all medications at least 2 weeks before the tests were done. All the rats and rabbits were adhered to the standard operating procedures and approved by the Animal Research Ethics Committee in Faculty of Mathematics and Natural Sciences University of Sumatera Utara, before the beginning of the project work.

Methods

Floating lag time and floating time

Hard alginate capsules made from sodium alginate 500–600 cP were placed in simulated gastric fluid pH 1.2 at 500 ml flask, and both the time needed to float on the surface of the fluid and the floating time were determined as conducted in previous experiment [19].

In vitro drug release studies

The drug release from hard alginate capsules made from sodium alginate 500–600 cP was performed using paddle method with 100 rpm speed in simulated gastric fluid (pH 1.2) at 37± 0.5°C. The capsules contained 200 mg cimetidine. Drug released amount was determined using ultraviolet (UV) spectrophotometer at wavelength 218.4 nm (n=3).

In vivo studies

Bioavailability studies

The test was done by cross-over design method using six rabbits which washout period was 2 weeks [21]. Cross-over design of cimetidine administration into rabbits can be shown in Table 1.

In bioavailability studies, the dose of cimetidine given was determined from the conversion of human dose (cimetidine 200 mg) to rabbit dose. The cimetidine dose used for rabbits was 9.3 mg/kg. Water was given *ad libitum* during fasting and 2 ml every 1 h throughout the experiment. Determination of absorption curve, calibration curve, and drug concentrations following the method reported by Mastiholimath [22,23], as follows.

Determination of absorption curve

The absorption curve was prepared by preparing a solution of cimetidine in acetonitrile at concentration of 6 µg/ml. 1 mm of the solution was added to 5 ml using acetonitrile, added 1 ml of rabbit blood plasma containing no drug, centrifuged at 2500 rpm for 15 min. 4 ml of the supernatant was piped out to a flask which contained 0.2 ml of 1.47 M perchloric acid. The absorption was measured at 200–400 nm wavelength. The blank was prepared using plasma of undosed rat as conducted in the plasma of dosed rat.

Determination of calibration curve

The calibration curve preparation of cimetidine as follows. Cimetidine solutions in acetonitrile were prepared at concentrations of 2, 4, 6, 8, and 10 µg/ml. 1 ml of this solution was made up to 5 ml acetonitrile. To each of these solutions, 1 ml of undosed rabbit blood was added and the contents centrifuged at 2500 rpm for 15 min. 4 ml of supernatant was piped out and into flask which contained 0.2 ml of 1.47 M perchloric acid, and the absorbance was measured at wavelength 265.60 nm. The blank was prepared using plasma from the undosed animal.

Determination of drug concentrations

Blood samples, each 2 ml, were collected from the marginal ear vein of the rabbits and transferred into heparinized centrifuge tubes just before dosing (undosed sample), then rabbits are given cimetidine according to cross-over design method that has been explained above, and the intervals of blood sampling were 15, 30, 60, 90, 120, 180, 240, 360, 400, 440, 480, 600, and 720 min. Blood samples were centrifuged at 1500 rpm for 15 min and the plasma was separated. One undosed plasma sample was prepared as blank. 5 mms of acetonitrile was added into each 1ml of other plasma samples. The tubes were centrifuged at 2500 rpm for 15 min, 4 ml of the supernatant was piped out and put into flask which contained 0.2 ml of 1.47 M perchloric acid, and the drug concentrations were determined by UV spectrophotometer at 265.60 nm wavelength.

Antiulcer studies

Antiulcer studies were conducted in healthy white male rats with weight 150–200 g. For antiulcer activity experiment, the dose of drugs given was determined from the conversion of human dose (cimetidine 200 mg) to rat dose. The cimetidine dose used for rats was 18 mg/kg.

The antiulcer activity was studied following the method previously reported [23]. 42 rats were fasted for 36 h before the test, then all of rats were orally induced with 1 ml of 0.6 N HCl solution to produce gastric lesions. After 1 h, six rats were sacrificed by chloroform inhalation and the stomachs were observed to determine the condition of gastric lesions. This condition was thought as initial condition of gastric lesion. The remaining rats (36 rats) were divided into three groups and each group divided two subgroups, each subgroup consisted of six rats.

Group I (negative control): Given with 1 ml distilled water orally once a day for 4 days. Six rats were sacrificed after 2 days treatment and another six rats were sacrificed after 4 days treatment.

Table 1: Cross-over design of cimetidine administration into rabbits

Rabbits	Dosage form	Washout for 2 weeks	Rabbits	Dosage form
1	A		1	B
2	A		2	B
3	A		3	B
4	B		4	A
5	B		5	A
6	B		6	A

A: Gelatin capsules containing cimetidine (9.3 mg/kg), B: Hard alginate capsule made from sodium alginate 500–600 cP containing cimetidine (9.3 mg/kg)

Fig. 1: Hard alginate capsules used for *in vitro* studies (a) and for *in vivo* studies (b)

Group II (positive control): Given with 1 ml cimetidine suspension (18 mg/kg) once a day for 4 days. Six rats were sacrificed after 2 days treatment and another six rats were sacrificed after 4 days treatment.

Group III (test group): Given with one hard alginate capsule made from sodium alginate 500–600 cP containing cimetidine orally (18 mg/kg) once a day for 4 days. The rats were given 2 ml distilled water every 1 h [24]. Six rats were sacrificed after 2 days treatment and another six rats were sacrificed after 4 days treatment.

For macroscopic observation, the number of gastric lesion and the area of lesion were determined. The lesion index was counted by area of mucosal damage (mm^2) divided by area of gastric mucosa (mm^2) [25,26]. The length and width of each lesion in mm were measured with a micrometer. For microscopic observation, the stomachs were washed with 0.9% NaCl solution and immersed in 10% formalin solution, then processed for histological staining with hematoxylin-eosin.

RESULTS AND DISCUSSION

Floating capability

Floating lag time of all hard alginate capsules containing cimetidine was 0 min, it means that when capsule was immersed in simulated gastric fluid pH 1.2, it floated immediately as found in the previous experiment [19]. The capsule floated during drug release experiment for 12 h as shown in Fig. 2. Capsule floated was due to the air was entrapped inside of the capsule shell and the density of alginate capsule shell was lower than the density of simulated gastric fluid.

In vitro drug release studies

Hard alginate capsules which were placed in artificial gastric fluid (pH 1.2) remained in intact condition during drug release. This is caused by the content of alginate capsules 47.5% is calcium guluronate that is insoluble in simulated gastric fluid (pH 1.2) [27]. Therefore, hard alginate capsules can be used as floating gastroretentive drug delivery system. Hard alginate capsules disintegrate in the small intestine.

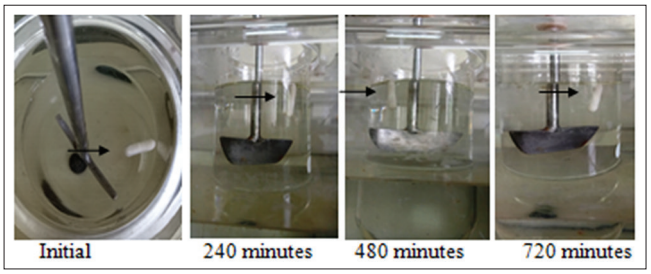

Fig. 2: Floating of hard alginate capsule containing cimetidine during drug release experiment in artificial gastric fluid at 37°C. Arrow shows the floating capsule

The difference of cimetidine release from hard gelatin capsules and various types of alginate capsules is shown in Fig. 3. The release of cimetidine from hard gelatin capsule is an immediate release which drug released 81.6% at 5 min, while the release of cimetidine from hard alginate capsule is a non-immediate release. The release of cimetidine from hard alginate capsules is slower with higher viscosity of sodium alginate used to prepare the hard alginate capsules. This is due to differences in the characteristics of the three types of alginate capsule, especially in terms of thickness. The hard alginate capsule made from sodium alginate 500–600 cP is thicker than the hard alginate capsule made from sodium alginate 80–120 cP and 300–400 cP, so the release of cimetidine from hard alginate capsule is slower. As a sustained release product, the release of cimetidine from hard alginate capsules made from sodium alginate 80–120 cP and 300–400 cP is too fast and does not meet the general requirement of sustained release product, while the cimetidine release from alginate hard alginate made from sodium alginate 500–600 cP is slower as shown in Fig. 3.

The cimetidine release from alginate capsules made from sodium alginate 500–600 cP at 180 min was 49.80%, at 360 min was 61.31% and at 720 min is 80.03%. This release profile meets the general sustained release requirements [28], as shown in Table 2. Therefore, hard alginate capsules made from sodium alginate 500–600 cP provide optimal drug release as a gastroretentive floating drug delivery system in an artificial gastric medium of pH 1.2. In previous study, about floating gastroretentive of amoxicillin using hard alginate capsules, to obtain the sustained release profile of amoxicillin from hard alginate capsules, the amoxicillin should be the solid dispersion form [19]. However, in this study, to obtain the sustain release profile of cimetidine using hard alginate capsules does not need to change the cimetidine to solid dispersion form of cimetidine. To obtain the sustained release of cimetidine simply to select the alginate capsules type, i.e., alginate capsules made from sodium alginate 500–600 cP.

In vivo studies

Bioavailability studies

The plasma of cimetidine levels obtained in this study is shown in Fig. 4. The mean pharmacokinetic parameters of drug from hard gelatin capsule and hard alginate capsules made from sodium alginate 500–600 cP are listed in Table 3.

The pharmacokinetics parameters for bioavailability are Cmax, Tmax, and area under the curve (AUC). Cmax representing the maximum plasma drug concentration obtained after oral administration of drug [21]. The difference in Cmax values can be seen in Fig. 4 and Table 4. The Cmax values obtained on using hard gelatin capsules and hard alginate capsules were 4.429±1.512 and 6.674±2.629 µg/ml, respectively. It is shown that the Cmax is higher in using hard alginate capsules than hard gelatin capsules, but it is not different statistically significant ($p>0.05$).

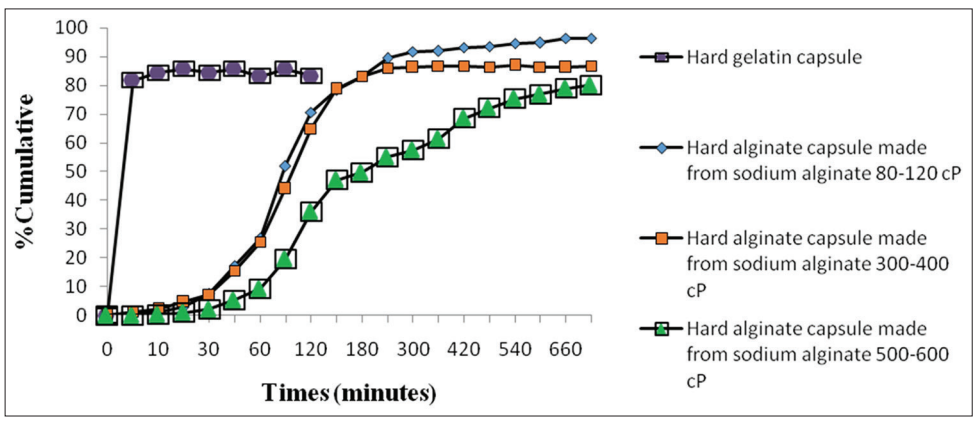

Fig. 3: Graph of cimetidine release from hard alginate capsules and gelatin capsules in artificial gastric fluid pH 1.2 at 37°C

Tmax representing the time required to reach maximum drug concentration after oral administration of drug [21]. The Tmax values obtained on using hard gelatin capsules and hard alginate capsules were 15 and 180 min, respectively. It is shown that the Tmax is longer in using hard alginate capsules and this value is significant difference. It is caused by drug release from hard alginate, capsules are a sustained release, while from hard gelatin capsules are immediate release.

AUC representing the total amount of active drug that reaches the systemic circulation [21]. The difference in AUC values can be seen in Table 3. The AUC values obtained on using hard gelatin capsules and hard alginate capsules were 2290.315±475.162 and 3141.055 ±835.113 min. µg/ml, respectively. It shows that the AUC is larger in using hard alginate capsules than using hard gelatin capsules, but it is not different statistically significant ($p>0.05$).

Furthermore, the correlation of drug dissolved *in vitro* with drug absorbed *in vivo* is shown in Fig. 5. The correlation (R^2) of *in vitro* cimetidine released in simulated gastric fluid pH 1.2 with *in vivo* cimetidine absorbed is 0.957. It shows that it is a good correlation between *in vitro* and *in vivo* results.

Antiulcer studies

Macroscopically and microscopically of normal rats gastric mucosa

The stomach wall comprises four concentric layers: Mucosa, submucosa, muscularis externa, and serosa. The mucosa of the fundic stomach is composed of the usual three components: (1) An epithelium lining the lumen; (2) an underlying lining connective tissue, the lamina propria; and (3) the smooth muscle layers forming the muscularis mucosa [29]. Fig. 6 shows rat normal gastric mucosa (a), and microscopic of gastric mucosa (b) that was observed in this experiment.

Macroscopic and microscopic of gastric mucosa after induction with 0.6 N HCl solution

After orally induction with 1 ml 0.6 N HCl solution, all rats (Group I) showed gastric lesions as shown in Fig. 7. The lesions were on the surface of the gastric mucosa. The lesion of gastric mucosa was due to gastric mucosa was exposed directly with 0.6 N HCl solution. Hydrochloric acid is an acid that can cause the mucosal blood flow to be damaged in large quantities. The lesion index was 0.44±0.08 and the number of gastric lesion was 8.16±2.22 as shown in Table 3. Fig. 7

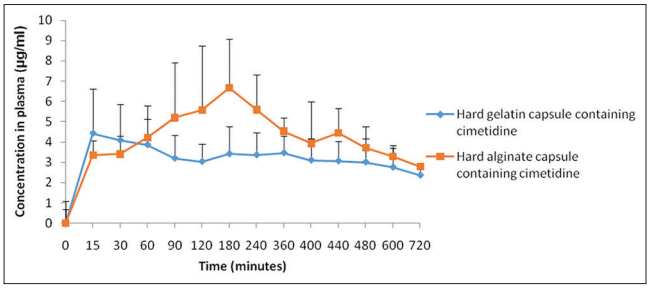

Fig. 4: Plasma cimetidine concentrations in rabbits blood plasma (n=6)

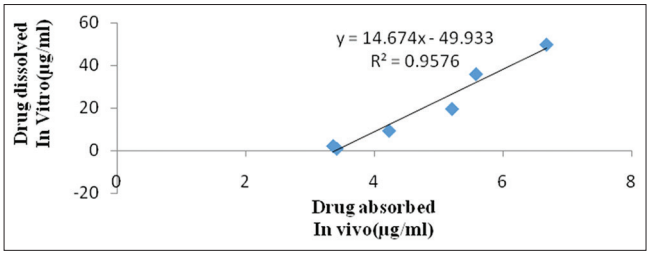

Fig. 5: The correlation of *in vitro* cimetidine released with *in vivo* cimetidine absorbed using hard alginate capsules

shows there were lesions in the stomach rats induced by HCl 0.6 N 1 h before surgery. Fig. 8 shows microscopic of stomach tissue after HCl 0.6 N administration. It shows many lesions in stomach of all rats.

Without treatment

Two days: The condition of rats' gastric mucosa of Group II (without treatment) is shown in Fig. 9. After 2 days, there were still many lesions in gastric mucosa. The lesion index was 0.18±0.16 and the number of lesion was 5.8±2.92. If we compared with initial condition, after 2 days, the lesion index and number of lesion are reduced but it is not different significantly. Fig. 10 shows the microscopic of gastric mucosa of rats after 2 days treatment. It shows there are many erosions in the stomach of all rats tested.

Four days: Fig. 11 shows the gastric mucosa of rats after 4 days without treatment. It shows that there are still many of lesions of stomach. After 4 days, the lesion index was 0.09±0.05 and the number of lesion was 5±3.52. If we compared with the condition at 2 days, after 4 days, the lesion index and number of lesion were also decreased, but statistically, it is not different significantly. The microscopic stomach tissue of rats after 4 days (without treatment) is shown in Fig. 12. It shows there is still erosion of all rats mucosa.

Treatment with cimetidine suspension

Two days: Groups of rats given cimetidine suspension show the gastric mucosa in Fig. 13. It shows that there are still many lesions in stomach.

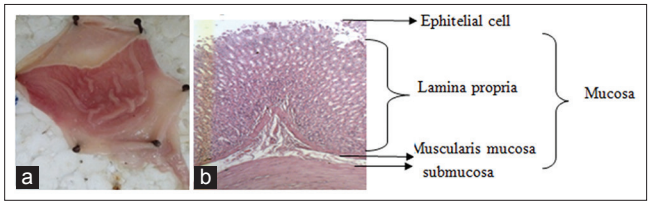

Fig. 6: (a-c) Normal stomach of rat. (a) Macroscopic of gastric mucosa, (b) microscopic of gastric mucosa

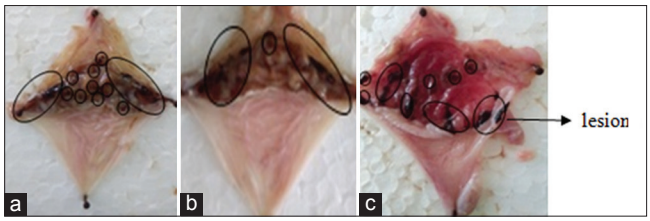

Fig. 7: (a-c) Macroscopic of rats gastric mucosa after induction with HCl 0.6 N solution

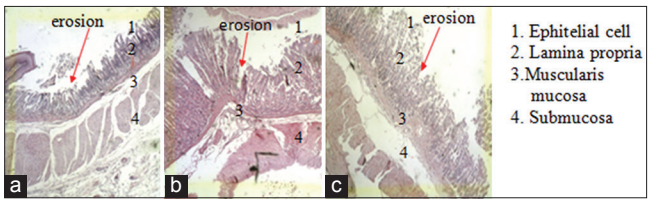

Fig. 8: (a-c) Microscopic of rats gastric mucosa after induction with HCl 0.6 N solution

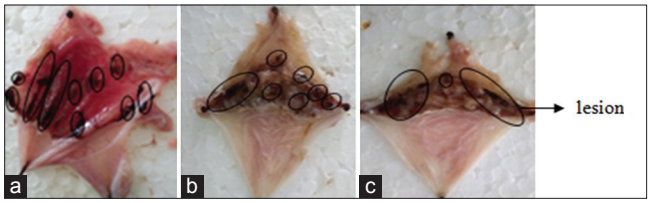

Fig. 9: (a-c) Macroscopic of rats gastric mucosa after 2 days (without treatment)

After 2 days, the lesion index was 0.12±0.10 and the number of lesion was 2.5±1.76. If we compared with initial condition, after 2 days, the lesion index and number of lesion are reduced but it is not different significantly. Fig. 14 shows the microscopic gastric mucosa of rats after 2 days. It shows many erosions in the stomach of all rats.

Four days: Fig. 15 shows the gastric mucosa of rats after 4 days for cimetidine suspension. It shows that there are still many of lesions of stomach. After 4 days, the lesion index is 0.036±0.024 and the number of lesion is 2.4±1.14. If we compared with the condition at 2 days, after 4 days, the lesion index and number of lesion are also decreased, but statistically, it is not different significantly. The microscopic stomach tissue of rats after 4 days (cimetidine suspension) is shown in Fig. 16. It shows there is still erosion of all rats mucosa.

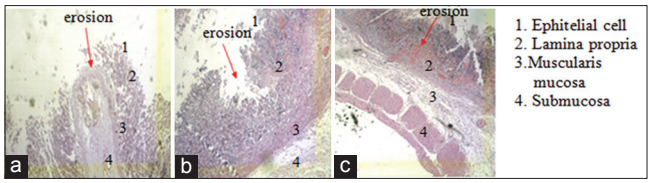

Fig. 10: (a-c) Microscopic of rats gastric mucosa after 2 days (without treatment)

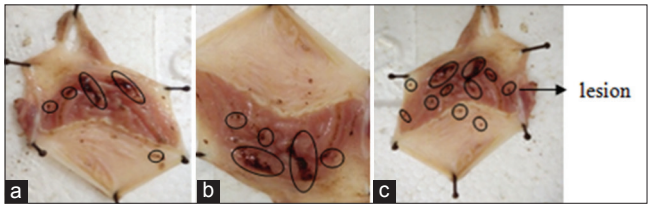

Fig. 11: (a-c) Macroscopic of rats gastric mucosa after days (without treatment)

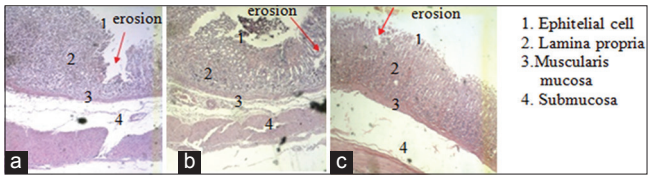

Fig. 12: (a-c) Microscopic of rats gastric mucosa after 4 days (without treatment)

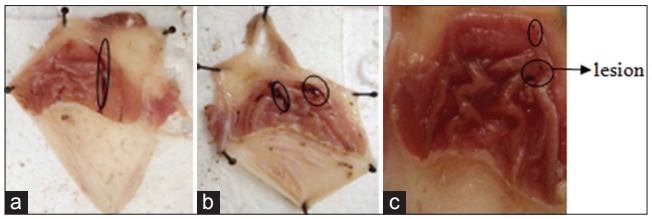

Fig. 13: (a-c) Macroscopic of rats gastric mucosa after 2 days treatment with cimetidine suspension

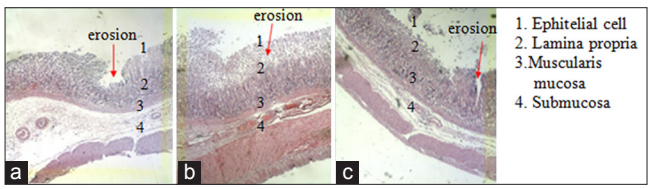

Fig. 14: (a-c) Microscopic of rats gastric mucosa after 2 days treatment with cimetidine suspension

Treatment with hard alginate capsule containing cimetidine

Two days: Groups of rats given hard alginate capsules show the gastric mucosa in Fig. 17. It shows that there are still lesions of the stomach in 1 of 6 rats. After 2 days, the lesion index was 0.007±0.01 and the number of lesion was 1.16±1.60. If we compared with initial condition, after 2 days, the lesion index and number of lesion are reduced and it is different significantly. Fig. 18 shows the microscopic of gastric mucosa of rats after 2 days. It shows there is still erosion in the stomach in 1 of 6 rats.

Four days: Groups of rats given hard alginate capsules show the gastric mucosa in Fig. 19. It shows no lesion in the stomach. After 4 days, the lesion index was 0.00±0.00 and the number of lesion was 0.00±0.00. If we compared with 2 days treatment, after 4 days, the lesion index and number of lesion are reduced and it is not different significantly. Fig. 20 shows the microscopic of gastric mucosa of rats after 4 days. It shows that there is no erosion like normal gastric mucosa.

CONCLUSION

The most suitable alginate capsules formulation for the floating preparation of gastric cimetidine is hard alginate capsules made from sodium alginate 500–600 cP. The release of cimetidine from hard alginate capsules as a floating dosage form is a sustained release.

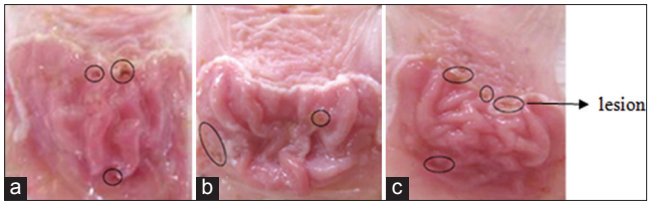

Fig. 15: (a-c) Macroscopic of rats gastric mucosa after 4 days treatment with cimetidine suspension

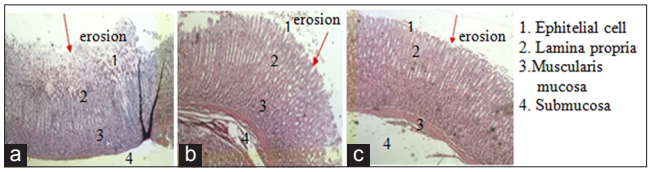

Fig. 16: (a-c) Microscopic of rats gastric mucosa after 4 days treatment with cimetidine suspension

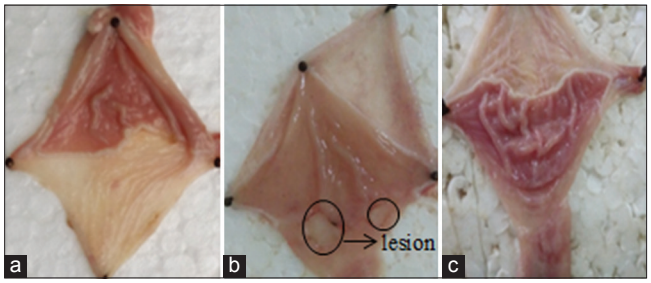

Fig. 17: (a-c) Macroscopic of rats gastric mucosa after 2 days treatment with hard alginate capsules containing cimetidine

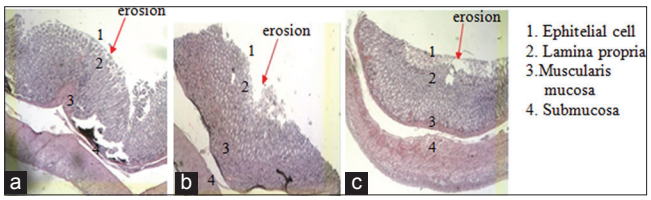

Fig. 18: (a-c) Microscopic of rats gastric mucosa after 2 days treatment with hard alginate capsules containing cimetidine

Table 2: Cimetidine release from hard alginate capsules that prepared from various viscosity of sodium alginate in artificial gastric fluid pH 1.2

Administration interval	Time (h)	Amount released (%)			General requirements of SR[26] (%)
		80–120 cP	300–400 cP	500–600 cP	
0.25 D	3 h	83.03	83.23	49.80	20–50
0.5 D	6 h	91.89	86.64	61.31	45–75
1 D	12 h	96.27	86.69	80.03	≥75

D: Dose interval (12 h)

Table 3: Average lesion index and the number of lesion in each group (n=6) during the treatment

Days	Lesion index (n=6) (X±SD)			Number of gastric lesion (n=6) (X±SD)		
	Distilled water (without treatment)	Treatment with cimetidine suspension	Treatment with hard alginate capsules containing cimetidine	Distilled water (without treatment)	Treatment with cimetidine suspension	Treatment with hard alginate capsules containing cimetidine
0	0.44±0.08	0.44±0.08	0.44±0.08	8.16±2.22	8.16±2.22	8.16±2.22
2	0.18±0.16	0.12±0.10	0.007±0.01	5.8±2.92	2.5±1.76	1.16±1.60
4	0.09±0.05	0.036±0.024	0.00±0.00	5±3.52	2.4±1.14	0.00±0.00

SD: Standard deviation

Table 4: Pharmacokinetics parameter of cimetidine using hard gelatin capsules and hard alginate capsules after oral administration in rabbits (n=6)

Samples	Cmax (µg/ml)	Tmax (min)	$AUC^{0-\infty}$ (min. µg/ml)
Hard gelatin capsules	4.429±1.512	15±14.747	2290.315±475.162
Hard alginate capsules	6.674±2.629	180±70.142	3141.055±835.113

AUC: Area under the curve

The hard alginate capsules which contain cimetidine have higher bioavailability than cimetidine in hard gelatin capsules. The hard alginate capsules containing cimetidine are more effective as antiulcer effect compared to cimetidine given in suspension form.

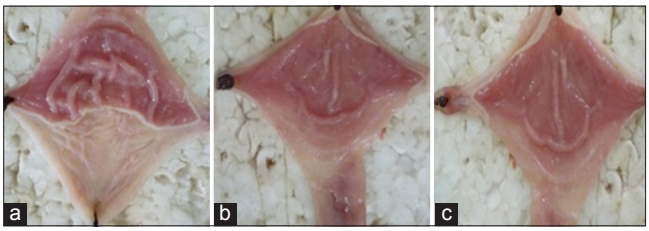

Fig. 19: (a-c) Macroscopic of rats gastric mucosa after 4 days treatment with hard alginate capsules containing cimetidine

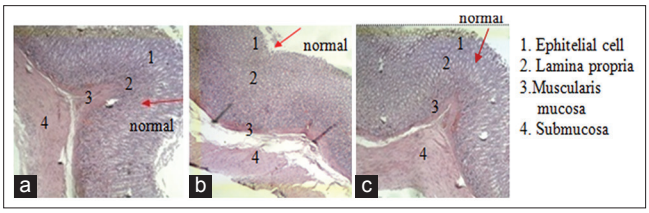

Fig. 20: (a-c) Microscopic of rats gastric mucosa after 4 days treatment with hard alginate capsules containing cimetidine

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AUTHOR'S CONTRIBUTIONS

Ririyen Dessy N Siahaan conducted the study, Hakim Bangun planned and designed the study, and Sumaiyah supported the conduction of study.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1. Corwin EJ. Handbook of Pathophysiology. 3rd ed. Philadelphia, PA: Pennsylvania State University, University Park; 2008. p. 603.
2. Dhiman S, Singh TG, Rehni AK, Sood S, Arora S. Gastroretentive: A controlled release drug delivery system. Asian J Pharm Clin Res 2011;4:5-13.
3. Shasank C, Prabha K, Sunil S, Kumar AV. Approaches to increase the gastric residence time: Floating drug delivery systems-a review. Asian J Pharm Clin Res 2013;6:1-9.
4. Vinod M, Jitendra N, Priyenka S, Navin S. Formulation and *in vitro* evaluation of cimetidine microsphere as gastro retentive floating drug delivery system. Int J Chem Environ Biol Sci 2013;1:701-6.
5. Srivastava AK, Ridhurkar DN, Wadhwa S. Floating microspheres of cimetidine: Formulation, characterization and *in vitro* evaluation. Acta Pharm 2005;55:277-85.
6. Begum A, Raju B. *In vitro* and *in vivo* evaluation of cimetidine loaded mucoadhesive microspheres. Int J Drug Deliv 2016;8:60-5.
7. Nasa P, Mahant S, Sharma D. Floating systems: A novel approach towards gastroretentive drug delivery systems. Int J Pharm Pharm Sci 2010;2:2-7.
8. Balata G. Design and evaluation of gastroretentive floating tablet of nizatidine: A trial to improve its efficacy. Int J Pharm Pharm Sci 2014;6:423-9.
9. Marabathuni VJ, Deveswaran R, Bharath S, Basavaraj BV, Madhavan V. Design and optimization of multiparticulate gastroretentive delivery system of ranitidine hydrochloride. Int J Pharm Pharm Sci 2012;4:597- 603.
10. Hasan MJ, Kamal BA. Formulation and evaluation of ranitidine hydrochlorideas floating *in situ* gel. Int J Pharm Pharm Sci 2014;6:401- 5.
11. Draget KI, Smidsrod O, Gudmund S. Alginate from Algae. Weinheim: Wiley Vch Verlag GmbH and Co; 2005.
12. Aryana, Sinurat D, Ervina I, Bangun H. Formulation of alginate based metronidazole periodontal gel. Asian J Pharm Clin Res 2014;7:224-7.
13. Mariadi, Bangun H, Karsono. Formulation and *in vitro* evaluation of gastroretentive drug delivery system of antacids using alginate-chitosan films. Int J Pharmtech Res 2015;8:1-12.
14. Adliani N, Bangun H, Karsono. Preparation and evaluation of floating-

mucoadhesive alginate beads as gastroretentive drug delivery system of antacids. Int J Pharmtech Res 2016;9:212-22.
15. Arianto A, Bangun H, Harahap U, Ilyas S. The comparison of swelling, mucoadhesive, and release of ranitidine from spherical matrices of alginate, chitosan, alginate-chitosan, and calcium alginate-chitosan. J Pharmtech Res 2014;6:2054-63.
16. Arianto A, Bangun H, Harahap U, Ilyas S. Effect of alginate chitosan ratio on the swelling, mucoadhesive, and release of ranitidine from spherical matrices of alginate-chitosan. J Pharmtech Res 2015;8:653- 65.
17. Kametani F, Bangun H, Ikeda Y, Shimabayashi S. Interaction of alginic acid with organic diacidic piperazine. Chem Pharm Bull 1990;38:2623- 6.
18. Bangun H, Simanjuntak MT, Tarigan P, Ismanelly T. Preparation and characterization of gastric resistant alginate capsules. Media Farm 2005;13:70-9.
19. Arianto A, Bangun H, Yohana A, Silalahi J. Floating gastroretentive of amoxicillin using hard alginate capsules and its antibacterial activities. Asian J Pharm Clin Res 2017;10:413-9.
20. Katzung BG. Basic and Clinical Pharmacology. United States of America: McGrawHill Companies Inc; 2007. p. 1013-5.
21. Shargel L, Yu A. Applied Biopharmaceutics and Pharmacokinetics. 5th ed. Boston: McGraw Hill; 1999. p. 253, 263.
22. Mastiholimath VS, Dandagi PM, Gadad AP, Mathews R, Kulkarni AR. *In vitro* and *in vivo* evaluation of ranitidine hydrochloride ethyl cellulose floating microparticles. J Microencapsul 2008;25:307-14.
23. Arianto A. Antiulcer effect of gastroretentive spherical matrices of alginate-chitosan containing ranitidine HCl. Int J Pharmtech Res 2016;9:342-52.
24. Saritha D, Satish D, Rao M. Formulation and evaluation of gastroretentive floating tablets of domperidone maleate. J Appl Pharm Sci 2012;2:68-73.
25. Sabiu S, Garuba T, Sunmonu T, Ajani E, Sulyman A, Nurain I, *et al*. Indomethacin-induced gastric ulceration in rats: Protectiveroles of spondiasmombin and ficus exasperate saheed. Toxicol Reports 2015;2:261-7.
26. Arianto A, Bangun H. Healing effect of alginate liquid against HCl-induced gastric mucosallesion in rats. Int J Pharmtech 2016;9:287-96.
27. Bangun H. Preparation, Physical Properties, and Application of Hard Alginate Capsules. Proceeding of International Seminar on Individualized Pharmaceutics for Optimized Drug Delivery, College of Pharmacy, Seoul National University; 2012.
28. Murthy KS, Ghebre-Sellassie I. Current perspectives on the dissolution stability of solid oral dosage forms. J Pharm Sci 1993;82:113-26.
29. Eroschenko VP. Difiore's Atlas of Histology with Functional Correlation. 12th ed. USA: Lippincolts Williams & Wilkins/Wolter Kluwer Health Inc; 2013. p. 324-31.