ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2019 Nov 30; 7(22):3868-3873.
https://doi.org/10.3889/oamjms.2019.522
eISSN: 1857-9655
***Herbal Medicine in Pharmaceutical and Clinical Sciences***

# Antibacterial Activity of Mucoadhesive Gastroretentive Drug Delivery System of Alginate Beads Containing Turmeric Extract - PVP Solid Dispersion

Hakim Bangun[1*], Anayanti Arianto[1], Yuni Sari Bangun[1], Marline Nainggolan[2]

*[1]Department of Pharmaceutical Technology, Faculty of Pharmacy, Nanomedicine Centre of Innovation, University of Sumatera Utara, Medan, Indonesia; [2]Department of Pharmaceutical Biology, Faculty of Pharmacy, University of Sumatera Utara, Medan, Indonesia*

**Citation:** Bangun H, Arianto A, Bangun YS, Nainggolan M. Antibacterial Activity of Mucoadhesive Gastroretentive Drug Delivery System of Alginate Beads Containing Turmeric Extract - PVP Solid Dispersion. Open Access Maced J Med Sci. 2019 Nov 30; 7(22):3868-3873. https://doi.org/10.3889/oamjms.2019.522

**Keywords:** Alginate beads; Gastroretentive; Turmeric solid dispersion; Antibacterical activity

***Correspondence:** Hakim Bangun. Department of Pharmaceutical Technology, Faculty of Pharmacy, Nanomedicine Centre of Innovation, University of Sumatera Utara, Medan, Indonesia. E-mail: Hakimb17@yahoo.com

**Received:** 25-Sep-2019; **Revised:** 17-Oct-2019; **Accepted:** 18-Oct-2019; **Online first:** 14-Nov-2019



**Funding:** This research was supported by University of Sumatera Utara grant 2018 through the scheme of Talenta grant, Indonesia

**Competing Interests:** The authors have declared that no competing interests exist

**Abstract**

**BACKGROUND:** Turmeric extract is less effective because the main ingredient of curcumin has a low solubility. Therefore, it is necessary to convert turmeric extract into a solid dispersion form to increase the dissolution of curcumin.

**AIM:** To determine the antibacterial activity of mucoadhesive gastroretentive drug delivery system of alginate beads containing solid dispersion of turmeric extract.

**METHODS:** Turmeric powder was macerated with 96% ethanol for 8 days. The macerate was evaporated with a rotary evaporator at 50°C to obtain concentrated extract. Solid dispersion of turmeric extract was prepared by solvent method by using polyvinylpyrrolidone (PVP) K30 with a ratio of 1: 1 and 1: 2. The solid dispersion of turmeric extract was encapsulated with alginate gel by gelation method. The antibacterial of alginate beads containing solid dispersion of turmeric extract was tested by using hole agar plate diffusion method against *Staphylococcus aureus* and *Escherichia coli* as bacterial models.

**RESULTS:** The size of alginate beads containing turmeric extract-PVP solid dispersion was about 1.3 mm. Antibacterial activity test against *Staphylococcus aureus* and *Escherichia coli* showed that alginate beads containing turmeric extract-PVP solid dispersion gave stronger antibacterial activity than those containing turmeric extract without solid dispersion. The antibacterial activity of alginate beads turmeric extract-PVP (1: 2) solid dispersion was stronger than those containing turmeric-extract (1: 1) solid dispersion.

**CONCLUSION:** Based on the results of this study it can be concluded that alginate beads containing turmeric extract-PVP solid dispersion gives the stronger antibacterial activity than those containing turmeric extract without solid dispersion.

## Introduction

Peptikum ulcer is a disease due to disorders of the upper gastrointestinal tract caused by the by exesssive of acid and pepsin secretion [1]. Peptikum ulcers can occur due to an imbalance between aggressive factors (such as *Helicobacter pylori* infection, NSAIDS and stomach acid) and stomach defence factors (such mucin, bicarbonate and prostaglandins) resulting in damage of the gastric mucosa [2].

Turmeric (*Curcuma longa Linn* or Curcuma domestica Val.) included in the family of Zingiberaceae has long been known by the community as plant many has benefits such as antiinflamation [3], anticancer [4], antioxidants [5], antiulcer [6], and antibacterial [7].

Pharmacological effect of curcumin is limited due to its low solubility and has a fast metabolism in gastrointestinal tract [8]. A low bioavailability (1%) and the degradation in alkaline intestine pH cause very limiting its clinical application [9]. Therefore, due to the instability of curcumin in alkaline intestine pH, then it is is necessary to prepare curcumin in gastroretentive drug delivery system to prolong the residence time of

turmeric extract in the stomach.

One approaches to targeting drugs into the stomach is a mucoashesive gastroretentive drug delivery system. Alginate is a negatively-charged polysaccharide which is non-toxic, biocompatible and biodegradable, included in anionic bioadhesive polymer, forming hydrogen bond with hydroxil group in polygosaccharide chain in mucose glycoprotein and its chemical bond was noncovalent [10]. Previous study was also reported the bioadhesive properties of alginate beads [11], [12]. Alginate interacts with organic diacidic base piperazine and calcium salts [13]. Lamivudine sodium alginate beads which were prepared by ionotropic gelation method showed prolonged drug release (~12 h) and the release was controlled by diffusion from alginate beads that was slow and spreads over an extended period of time depending upon the drug polymer ratio [14]. Our previous study showed the anti-gastric activity of alginate bead containing turmeric extract [15].

As mentioned above, the low bioavailability of curcumin is due to the low solubility of curcumin. One approach to increase the dissolution of curcumin contained in turmeric extract is to convert turmeric extract into solid dispersion form. In this paper will be discussed the dissolution of curcumin and the antibacterial activity of turmeric extract-PVP solid dispersion entraped in alginate beads.

## Material and Methods

### *Materials*

The materials used in this research was turmeric rhizome obtained from Medan Central Market, Indonesia. Ethanol and Tween 80 obtained from Brataco. Polyvinylpyrrolidone (PVP) K30 was product of Nacalai Tesque. Curcumin as standard for release study was obtained from Sigma-Aldrich. Calcium chloride and hydrochloric acid were product of Merck. Sodium alginate was the product of Wako Pure Chemical Industries, Ltd., Japan. Mueller-Hinton agar (MHA), Nutrient Broth (NB), and Nutrient Agar (NA) media were the product of Difco. *Staphylococcus aureus* ATCC 6538 and *Escherichia coli* ATCC 8939 obtained from Laboratory of Microbiology, Faculty of Pharmacy, University of Sumatera Utara.

### *Preparation of turmeric extract*

Turmeric powder was macerated with ethanol 96% for 8 days. Then, the macerate was evaporated with rotary evaporator to obtaine concentrated tumeric extract.

### *Preparation of solid dispersion*

Turmeric extract-PVP solid dispersion was prepared by solvent method. The ratio of turmeric extract and PVP was 1: 1 and 1: 2. Turmeric extract and PVP were dissolved in ethanol. Then, ethanol was evaporated. The resulting turmeric extract-PVP solid dispersion were scraped and sifted using a sieve no. 12.

### *Preparation of alginate beads containing turmeric solid dispersion*

Sodium alginate solution was prepared by adding sodium alginate (1.5% w / v) in distilled water. Turmeric extract or turmeric solid-PVP solid dispersion was crushed with addition of ethanol until dissolved and it was mixed with Tween 80, then added into the alginate solution and stirred until the mixture became homogenous. The mixture was droped wise through a syringe with 21G size into 0.15 M calcium chloride solution with curing time 4-5 minutes [15]. Then, the beads formed were separated from the solution by filtration and rinsed with distilled water. Finally, the beads containing turmeric acid were dried at room temperature and stored in a desiccator. The various formula used is shown in Table 1.

**Table 1: The formula preparations alginat beads**

| Materials | FI | FII | FIII |
|---|---|---|---|
| Alginat sodium | 1.5 % | 1.5% | 1.5% |
| Turmeric extract | 15% | - | - |
| Turmeric extract solid dispersion | - | 30% | 45% |
| Twen 80 | 1.5% | 1.5% | 1.5% |
| Distilled water until | 50 ml | 50 ml | 50 ml |

FI: Beads contained turmeric extract-PVP (1: 1) solid dispersion, equivalent to 15% of turmeric extract; FII: Beads contained turmeric extract -PVP (1: 2) solid dispersion, equivalent to 15% of turmeric extract; FIII: Beads contained turmeric extract 15% (without solid dispersion).

### *Determination of calibration curve of curcumin*

Calibration curve of curcumin was determined in simulated gastric fluid of pH 1.2 at maximun wave length at 428 nm.

### *Release of curcumin from alginate beads*

The in vitro release of curcumin from alginate beads was carried out using a jacketed glass containing 100 ml of simulated gastric fluid of pH 1.2 at 37 ± 0.5°C. Two hundred milligram of beads was put into the medium. The medium was stirred using a magnetic stirrer at 50 rpm. The amount of curcumin released from alginate beads at interval of time was determined spectrophometrically at 428 nm.

### *Antibacterial activity test*

The antibacterial activity of alginate beads containing turmeric extract-PVP solid dispersion was tested by using hole agar plate diffusion method against *Staphylococcus aureus* and *Escherichia coli*

as bacterial models. Inoculum as much as 0.1 ml was inserted into the Petri dish, then added 15 ml sterile Mueller-Hinton agar (MHA) media that has been thawed and wait until the temperature reached 45°0C, homogenized and remained until solidified. After that, holes were made with a diameter of 6 mm. Each hole was filled with seven particles of alginate beads containing turmeric extract or turmeric extract-PVP solid dispersion. Then, it was incubated at 36-37°C and observed for 7 days. After incubation, the zones of inhibition (ZOI) were measured with a calliper in mm scale.

## Results

### *Beads specifications*

Determination of an alginat beads specifications was done by observing the shape, diameter and weight of the beads. The diameter and weight of beads is shown in Table 2.

**Table 2: Average diameter and weight of beads**

| Formula | Diameter average (mm) | Weight average (mg) |
|---|---|---|
| FI | 1.34 ± 0,11 | 37.33 ± 0,52 |
| FII | 1.35 ± 0,12 | 43.67 ± 0,82 |
| FIII | 1.28 ± 0,06 | 34.83 ± 1.47 |

Alginate beads containing turmeric extract or solid dispersion of turmeric extract showed a round shape as shown in Figure 1A, 1B, and 1C. Microphotograph of scanning electron microscopy (SEM) of alginate beads containing turmeric-PVP (1: 1) solid dispersion is shown in Figure 1D.

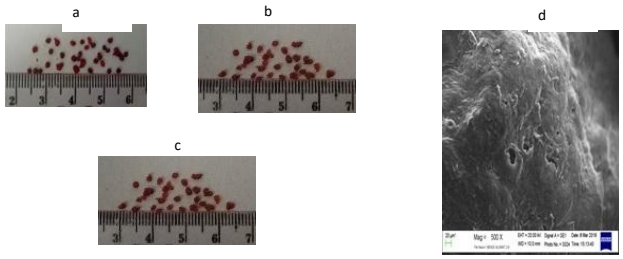


*Figure 1: Photographs of alginate beads contained turmeric extract-PVP (1: 1) solid dispersion A); Contained solid dispersion of turmeric extract-PVP K30 (1: 2) B); Contained turmeric extract only C); and microphotograph of SEM of alginate beads contained turmeric extract-PVP (1: 1) solid dispersion D)*

### *Effect of turmeric extract-PVP solid dispersion on the release of curcumin from alginate beads*

Release of curcumin from alginate beads containing turmeric extract-PVP solid dispersion in the medium of simulated gastric fluid of pH 1.2 is shown in Figure 2. This Figure shows that the amount of curcumin released from alginate beads containing turmeric extract-PVP solid dispersion is higher compared to curcumin released from alginate beads containing turmeric extract (without solid dispersion). Curcumin released was faster from alginate beads containing turmeric extract-PVP (1: 2) solid dispersion than alginate beads containing turmeric extract-PVP (1: 1) solid dispersion.

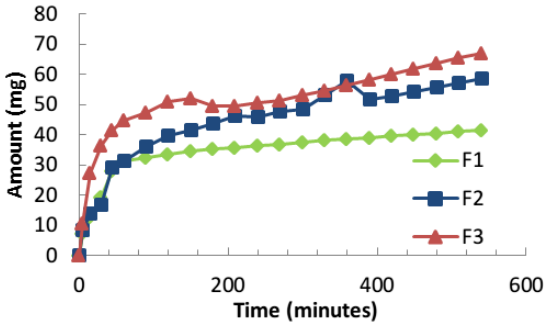


*Figure 2: Release of curcumin from alginate beads in the medium of simulated gastric fluid of pH 1.2 at 37°C; FI: Turmeric extract without solid dispersion; FII: Turmeric extract-PVP (1: 1) solid dispersion; FIII: Turmeric extrtact-PVP (1: 2) solid dispersion*

### *Effect of turmeric extract concentration on antibacterial activity of turmeric extract*

Antibacterial activity of turmeric ekstract against *Staphylococcus aureus* and *Eschericha coli* for incubation at 37°C for 24 hours is shown in Table 3.

**Table 3: Effect of turmeric extract concentration on ZOI of turmeric extract against *Staphylococcus aureus* and *Escheria coli***

| Turmeric Extract (%) | Zone of inhibition (mm) | |
|---|---|---|
| | *Staphylococcus aureus* | *Escherichia coli* |
| 6.25 | 6.45 | 6.45 |
| 12.5 | 7.35 | 7.15 |
| 25 | 9.10 | 8.15 |
| 50 | 11.65 | 10.5 |
| 75 | 12.35 | 11.55 |

The higher concentration of turmeric extracts the higher of ZOI. The photograph of zone of inhibition (ZOI) is shown in Figure 3.

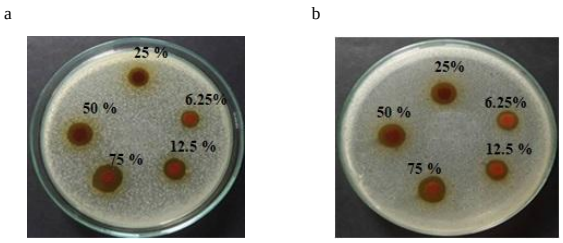


*Figure 3: Photograph of ZOI of various concentration (%) of turmeric extract against Staphylococcus aureus A) and Escheria coli B) after incubation for 24 hours*

### *Antibacterial activity of alginate beads containing turmeric extract*

The ZOI of alginate beads containing turmeric extract (without solid dispersion) against

*Staphylococcus aureus and Escherichia coli* is listed in Table 4 and the photographs of ZOI are shown in Figure 4.

**Table 4: ZOI of alginate bead containing turmeric extract and those containing solid dispersion of turmeric extract-PVP against *Staphylococcus aureus* and *Escherichia coli* after incubation for 7 days (n = 3)**

| Formula | Zone of inhibition (mm) | |
|---|---|---|
| | *Staphylococcus aureus* | *Escherichia coli* |
| FI | 11.15 ± 0.39 | 10.70 ± 1.07 |
| FII | 14.01 ± 0.47 | 13.26 ± 0.78 |
| FIII | 14.51 ± 0.67 | 13.76 ± 1.09 |

FI: Alginate beads containing turmeric extract (without solid dispersion); FII: Alginate beads containing solid solid dispersion of turmeric extract-PVP (1: 1); FIII: Alginate beads containing solid solid dispersion of turmeric extract- PVP (1: 2).

The ZOI for *Staphylococcus aureus* is 11.15 ± 0.39 mm dan for *Escherichia coli* is 10.70 ± 1.07 mm.

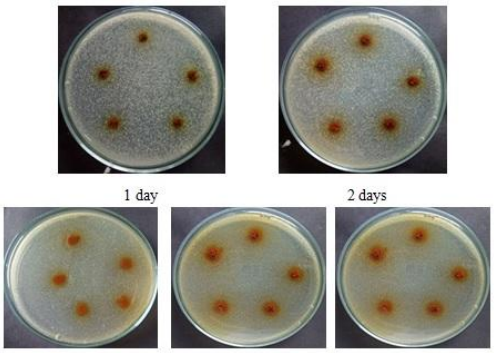


*Figure 4: ZOI of alginate beads containing turmeric extract against Staphylococcus aureus after 1 until 7 days*

### *Antibacterial activity of alginate beads containing turmeric extract-PVP solid dispersion*

The ZOI of alginate beads containing turmeric extract-PVP solid dispersion against *Staphylococcus aureus* and *Escherichia coli* is shown in Table 4 (above) and the photographs of ZOI are shown in Figure 4, 5, 6, 7, 8, and 9.

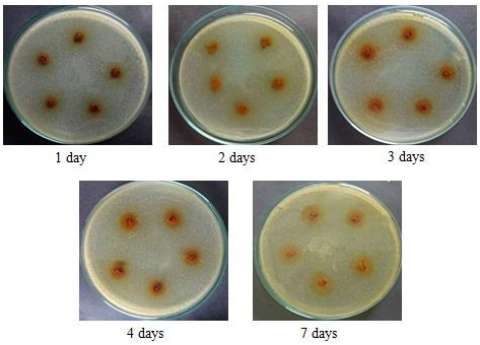


*Figure 5: Photograph of alginate beads containing turmeric extract against Escherichia coli*

Table 4 shows that the alginate beads containing solid dispersion of turmeric extract-PVP gives stronger bacterial activity which seen from the wider ZOI (FII) than alginate beads containing turmeric extract (without solid dispersion (F1).

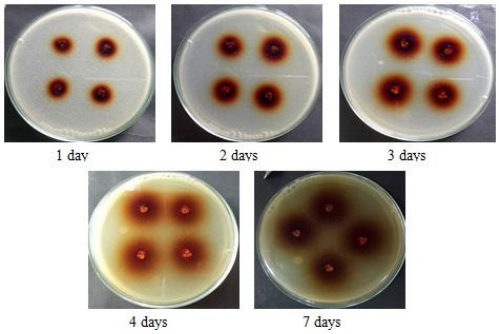


*Figure 6: Photograph of alginate beads alginat containing solid dispersion of turmeric extract-PVP (1: 1) against bacteria Staphylococcus aureus*

Zones of inhibition by alginate beads containing turmeric extract-PVP (1: 1) solid dipersion for *Staphylococcus aureus* and *Escherichia coli* were 14.01 ± 0.47 mm and 13.26 ± 0.78 mm, respectively.

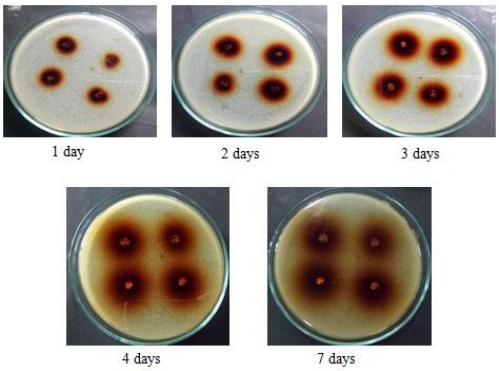


*Figure 7: Photograph of alginate beads containing solid dispersion of turmeric extract-PVP (1: 1) against Escherichia coli*

But, Zones of inhibition by alginate beads containing turmeric extract (without solid dispersion) for *Staphylococcus aureus* and *Escherichia coli* were 11.15 ± 0.39 and 10.70 ± 1.07 mm, respectively.

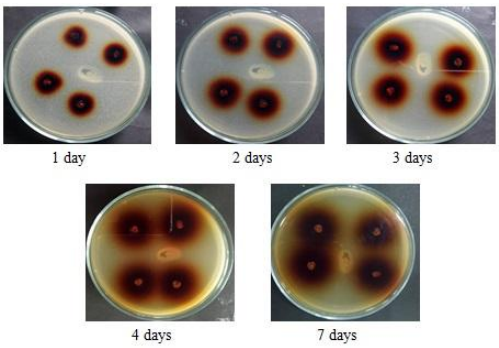


*Figure 8: Photograph of alginate beads containing solid dispersion of turmeric extract-PVP (1: 2) against Staphylococcus aureus*

The ZOI of alginate beads containing turmeric extract-PVP (1: 2) was wider than alginate beads containing turmeric extract-PVP (1: 1).

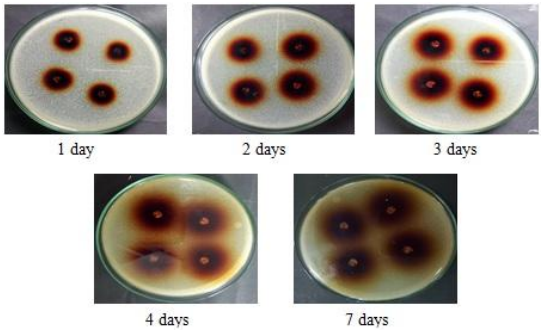


*Figure 9: Photograph of alginate beads containing solid dispersion of turmeric extract-PVP (1: 2) against Escherichia coli*

## Discussion

### *Beads specifications*

Alginate is a linear natural polysaccharide consisting of β-D-mannuronic acid and α-L-guluronic acid. Divalent cations, such as calcium ions, can bind to guluronat residues to form "egg box" structures and cause gelation to form calcium alginate gel [16], [17]. In this research, turmeric extract-PVP solid dispersion was entraped in calcium alginate gel beads. In the preparation of the beads, the alginate beads containing solid dispersion of turmeric extract-PVP (1: 1) and (1: 2) had a biger size than beads beads containing turmeric extracts (without solid dispersion) as listed in Table 2. This is due to the addition of PVP, while the amount of turmeric extract was the same for all of beads. Beads containing PVP were heavier than beads without PVP.

### *Release of curcumin from alginate beads*

Figure 4 shows that the amount of curcumin released is higher from solid dispersion form of turmeric extract-PVP than from turmeric extract without solid dispersion form in the medium of simulated gastric fluid of pH 1.2. The higher of the amount of PVP the higher amount curcumin released. In turmeric extract-PVP solid dispersion form, the dissolution rate of curcumin increases because PVP is a water-soluble polymer that enhance the wetting process of curcumin. In addition, the modification of turmeric extract to turmeric solid dispersion form reduces the particle size of curcumin so that the rate of curcumin dissolution increases, thereby the antibacterial activity increase.

The previous researchers observed that the curcumin-PVP solid dispersion increased the dissolution of curcumin [18]. Therefore, the turmeric extract-PVP solid dispersion increased the dissolution of curcumin contained in turmeric extract.

### *Antibacterial activity of turmeric extract*

ZOI increased with increasing of turmeric extract concentration (Table 3). ZOI for *Staphylococcus aureus* slightly higher than *Escherichia coli.* The bactericidal activity of curcumin is due to its bacterial membrane damaging property [19]. If we compared the bacterial activity between turmeric ectract and turmeric extract that entraped in alginate beads, the antibacterial activity of turmeric extract was faster than turmeric extract that entraped in alginate beads. In turmeric extract the ZOI reached maxium after 24 hours, while in entraped turmeric extract the ZOI reached maximum after 7 days. This result was due to in beads the turmeric extract was entraped in alginate gel matrix, so curcumin was blocked out and caused the slow release of curcumin, thereby the antibacetrial activity was slower than turmeric extract only.

### *Antibacterial activity of alginate beads containing turmeric extract-PVP solid dispersion*

The antibacterial activity of alginate beads containing turmeric extract-PVP solid dipersion was stroger than alginate beads containing turmeric extract without solid dispersion (Table 4). In turmeric extract solid dispersion form, the dissolution rate of curcumin increased because PVP is a water-soluble polymer that enhance the wetting process of curcumin. In addition, the modification of turmeric extract to turmeric extract-PVP solid dispersion form reduces the particle size of curcumin so that the rate of curcumin dissolution increased, thereby the antibacterial activity increased.

## References

1. Avunduk C. Manual of Gastroenterology: Diagnosis and Therapy. 4th Ed. USA: Lippincott Williams and Wilkins; 2008:59-60.

2. Sunil K, Amandeep K, Robin S, Ramica S. Peptic Ulcer: A Review on Etiology and Pathogenesis. International Research Journal Pharmacy. 2012; 3 (6):34-5.

3. Patil MB, Taralkar SV, Sakpal VS, Shewale SP, Sakpal RS. Extraction, Isolation and Evaluation Of Antiiflammatory Activity Of Curcuminoids from Curcuma Longa. International Journal of Chemical Sciences and Application. 2011; 2(3):172-4.

4. Naama JH, Al-Temini AA, Al-Amlery AAH. Study the anticancer activities of ethanolic curcumin extract. African Journal pf Pure and Applied Chemistry. 2011; 4(5):68-73.

5. Tanvir EM, Hossen S Md, Hossain F, Afroz R, Gan SH, Khalil, IMd, Karim N. Antioxidant Properties of Popular Turmeric (Curcuma longa) Varieties from Bangladesh. Hindawi Journal of Food Quality. Research Article. 2017; 217:1-8. https://doi.org/10.1155/2017/8471785

6. Mahattanadul S, Nakamura T, Panichayupakaranant P, Phdoongsombut N, Tungsinmunkong K, Bouking P. Comparative antiulcer effect of bisdemethoxycurcumin and curcumin in a gastric

ulcer model system. Phytomedicine. 2009; 16(4):342-351. https://doi.org/10.1016/j.phymed.2008.12.005 PMid:19188055

7. Mohammed NA, Habil NY. Evaluation of antimicrobial activity of Curcumin against two oral bacteria. 2015; 3(2):18-21. https://doi.org/10.11648/j.acis.s.2015030201.14

8. Petchsomrit A, Sermkaew N, Wiwattanapatapee R. Effect of Alginate and Surfactant on Physical Properties of Oil Entrapped Alginate Bead Formulation of Curcumin. International Journal of Medical, Pharmaceuticall Science and Engineering. 2013; 7(12):479-483.

9. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of Curcumin: Problems and Promises. Mol. Pharmaceutics. 2002; 4(6):807-818. https://doi.org/10.1021/mp700113r PMid:17999464

10. Vetter A, Schnurch AB. Bioadhesive Delivery Systems. Biodrug Delivery Systems: Fundamentals, Applications and Clinical Development. CRC Press. 2010; 220-221.

11. Arianto A, Bangun H, Harahap U, Ilyas S. The comparison of swelling, mucoadhesive, and release of ranitine from spherical matrices of alginate, chitosan, alginate-chitosan, and calcium alginate-chitosan. Journal of PharmTech Research. 2014; 6(7):2054-2063.

12. 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. Journal of PharmTech Research. 2015; 8(4):653-665.

13. Kametani F, Bangun H, Ikeda Y, Shimabayashi S. Interaction of Alginic Acid with Organic Diacidic Piperazine. Chemical Pharmaceutical Bulletin. 1990; 38(10):2623-2626. https://doi.org/10.1248/cpb.38.2623

14. Desi Reddy RB, Malleswari K, Prasad G, Prasanna D. Preparation and in vitro evaluation of lamivudine floating sodium alginate beads. International Journal of Pharmaceutical and Clinical Research. 2012; 4(4):81-88.

15. Bangun H, Aulia F, Arianto A, Nainggolan M. Preparation of mucoadhesive gastroretentive Drug Delivery System of Alginate Beads Containing Teurmeric Extract and Anti-Gastric Ulcer Activity. Asian Journal of Pharmaceutical and Clinical Research. 2019; 12(1):316-320. https://doi.org/10.22159/ajpcr.2019.v12i1.29715

16. Grant GT, Morris ER, Rees DA, Smith PJC, Thom D. Biological Interactions between Polysaccharides and Divalent Cations-Egg-box Model. Febs. Lett. 1973; 32:195-198. https://doi.org/10.1016/0014-5793(73)80770-7

17. Smidsrod O, Skjak-Brik G. Alginate as Immobilization Matrix for Cells. Trend in Biotechnol.1990; 8:71-78. https://doi.org/10.1016/0167-7799(90)90139-O

18. Kaewnopparat N, Kaewnopparat S, Jangwang A, Maneenaun D, Chuchome T, et al. Increased solubility, dissolution, and physicochemical studies of curcumin-polyvinylpyrrolidine K-30 solid dispersion. World Academic of Science, Engeneering, and Technology. 2009; (3):225-30.

16. Tyagi P, Singh M, Kumari H, Kumari A, Mukhopadhyay K. Bactericidal activity of curcumin I is associated with damaging of bacterial membrane. PloS one. 2015; 10(3):e0121313. https://doi.org/10.1371/journal.pone.0121313 PMid:25811596 PMCid:PMC4374920