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PREPARATION AND CHARACTERIZATION OF CO-PROCESSED EXCIPIENT CARRAGEENAN-PREGELATINIZED CASSAVA STARCH PROPIONATE AS A MATRIX IN THE GASTRORETENTIVE DOSAGE FORM

Effionora Anwar[1*)], Engkom Komariah[1], and Junaedi[2]

1. Department of Pharmacy, Faculty of Mathematic and Natural Sciences, Universitas of Indonesia, Depok 16424, Indonesia
2. Department of Pharmacy, Polytechnic of Health Jakarta II, Jakarta 10560, Indonesia

[*)]*E-mail: effionora@farmasi.ui.ac.id*

Abstract

The gastroretentive dosage form is designed to prolong the gastric residence time of the drug delivery system which also results in the development of an appropriate excipient. The purpose of this study is to develop and characterize co-processed excipient made from carrageenan (kappa-iota = 1:1) and pregelatinized cassava starch propionate (PCSP) in ratios of 1:1, 1:2, and 1:3. PCSP was prepared with propionic anhydride in an aqueous medium. The product was mixed with carrageenan (kappa-iota = 1:1), as well as characterized physicochemical and functional properties. The co-processed excipient was then used as a mucoadhesive granule and floating tablet. The USP Basket was selected to perform the dissolution test of the granules in HCl buffer (pH 1.2) and distilled water for 8 hours each. Mucoadhesive properties were evaluated using bioadhesive through a vitro test and wash-off test. As for the floating tablet, the USP Paddle was selected to perform the dissolution test of the tablets in 0.1 N HCl for 10 hours. The floating lag time and floating time were tested in 0.1 N HCl for 24 hours. The result of these studies indicated that co-processed excipient carrageenan-PCSP can retard dosage form in gastric and drug controlled release, thus making it a suitable material for the gastroretentive dosage form.

Keywords: carrageenan, co-processed excipient, gastroretentive, pregelatinized cassava starch propionate

1. Introduction

The gastroretentive dosage form is designed to prolong gastric residence time. It may be broadly classified into: high-density (sinking) systems, low-density (floating) systems, expandable systems, superporous hydrogel systems, mucoadhesive systems and magnetic systems [1]. In the formulation of the gastroretentive dosage form, polymers play an important role. The most commonly used polymers are celulosa derivatives, such as HPMC—an expensive imported material. For this reason, an appropriate excipient needs to be developed. In general, gastroretentive excipient must have sufficient bioadhesiveness, gel strength, and swelling properties.

Co-processed excipients are prepared by incorporating one excipient into the particle structure of another excipient using processes, such as co-drying. Thus, they are simple physical mixtures of two or more existing excipients mixed at the particle level [2].

Pregelatinized cassava starch propionate (PCSP) is a modified starch made from an esterification process of cassava starch using propionic anhydride and followed by pregelatinization. PCSP has been modified by combining it with cellulose derivatives and used as mucoadhesive granule matrix. The study proved a good property of mucoadhesiveness, but poor level in drug controlled release [3].

Carrageenan is a hydrocolloid consisting mainly of potassium, sodium, magnesium, calcium, and ammonium sulfate esters of galactose and 3,6-anhydrogalactose copolymers. These hexoxes alternately link α-1,3 and β-1,4 in the polymer. It differs from one another in content of 3,6-anhydro-D-galactose and the number and position of the ester sulfate groups. Three major carrageenans are *kappa-*, *lambda-*, and *iota-*carrageenans [4]. Iota and kappa-carrageenans are gell-forming carrageenans, whereas lambda-carrageenan is a

thickener/viscosity builder [5]. It has been discovered in pharmaceutical as mucoadhesive dosage forms. For example, carrageenan combined with eudagrit RLPO has been used in mucoadhesive tablets which could control the release of drugs [6]. In addition, carrageenans have also been used in mucoadhesive michrosphere for mucocitis oral [7].

The co-processing method is used in mixing PCSP and carrageenan to create new gastroretentive excipients. Application of this new co-processed excipient as a matrix in the gastroretentive dosage form is in the form of mucoadhesive granules and floating tablets. Amoxicillin is used as a drug model for granules and famotidin is used as drug model for floating tablets. Each product is evaluated in accordance with Indonesian Pharmacopoeia or other pharmaceutical references. The result of this study showed that co-processed excipient from carrageenan and PCSP could be used as a matrix in gastroretentive dosage form to prolonged gastric residence time and drug controlled release.

2. Methods

Preparation of co-processed excipient. Pregelatinized cassava starch propionate was prepared with propionic anhydride following the method of Billmers [8]. Fifty percent of the starch suspension (w/w of water) was adjusted to a pH of 8.0-9 by adding 1 N sodium hydroxide and lowering the temperature to 10–15 ºC. Acid anhydride served as the esterifying agent. 50% w/w of dried starch was then slowly added to the suspension, with continuous stirring and pH controlling at 8.0-9.0. The reaction was complete when all the anhydride had been added and the pH stabilized. The suspension was then neutralized to pH 7.0 by 0.5 N chlorida acid. The starch was filtered and any residual material removed by washing the filter cake three times and drying it using a double drum dryer (R. Simon Dryers). The product was mixed with a slurry of carragenan (kappa-iota = 1:1) in ratios of 1:1, 2:1 and 3:1 using a EH 2010 homogenizer (CKL Machinery, Malaysia), then dried using a double drum drum dryer (R. Simon Dryers). Afterwards, the particle size of the co-processed excipients were reduced by a discmill, before the product was finally shifted. The physicochemical properties of the co-processed excipients were characterized before applied to the dosage forms.

Preparation of gastroretentive dosage forms. The co-processed excipients were applied in preparation of the gastroretentive dosage forms, such as mucoadhesive granules and floating tablet. Granules were prepared through wet granulation. Then the product was evaluated, including in terms of moisture content by moisture balance (Adam AMB 50, USA), particle size distribution using micromeritic test (Retsch Technology, German), and flowability by flowmeter GDT (Erweka, Germany). The dissolution test was carried out using the Electrolab TDT-08L dissolution apparatus (Merck, Germany) in HCl buffer (pH 1.2) and in distilled water for 8 hours. The concentration of drug released was analyzed using spectrophotometer UV-Vis (JASCO V-530, Japan) (Indonesia Pharmacopeae Ed. IV, 1995). Mucoadhesive properties were evaluated using bioadhesive in vitro test and wash off test using disintegration tester ZT3 (Erweka, Germany).

Tablets were processed using a tablet compression machine AR 400 (Erweka, Germany). The tablets' characteristics, such as hardness and friability, were evaluated using the TBH 28 hardness tester and TAR friability tester, respectively. The dissolution test was carried out using the Electrolab TDT-08L dissolution apparatus (Merck, Germany) in 0.1 N HCl for 10 hours. The concentration of drug released was analyzed using the UV-Vis spectrophotometer (JASCO V-530, Japan) (Indonesia Pharmacopeae Ed. IV, 1995). The floating lag time and floating time were evaluated in 0.1 HCl for 24 hours.

3. Results and Discussion

Preparation of co-processed excipient. Co-processed excipient consists of carragenan (kappa-iota = 1:1) and PCSP in ratios of 1:1, 1:2 and 1:3. For more details, see Table 1.

The obtained co-processed excipient carrageenan-PCSP was light brown powder with a varied degree of subtitution (DS) depending on the amount of PCSP in the co-processed excipient. All of the co-processed excipients were produced through the drum-drying method yielding in production of 6.16 to 90.00% and moisture content of 8.81 to 10.62% (Table 2).

The scanning electron microscope (SEM) images are shown in Figure 1. This indicates that the PCSP and co-processed excipients prepared through the drum-drying method are almost irregular and take the form of flakes. The excipient produced from the mixture of kappa and iota-carrageenan, on the other hand, occured as gravels due to the machine production of industrial scale.

Figures 2, 3, and 4 show the FTIR spectra of normal starch and PCSP, *kappa*- and *iota*-carrageenan and co-processed excipient, respectively. Observations reveal a

Table 1. The Ratio of Material Using in Co-processed Excipient

Material	Co-processed excipient		
	A	B	C
PCSP	1	2	3
Carrageenan kappa-iota (1:1)	1	1	1

Table 2. Yield, Moisture Content and Degree of Subtitution of PCSP and Co-processed Excipient

Excipient	Pecentage yield (w/w)	Moisture content (%)	DS
PCSP	84.40	10.15	0.20 ± 0.006
Co-processed excipient A	66.16	10.62	0.02 ± 0.00
Co-processed excipient B	74.16	9.67	0.08 ± 0.01
Co-processed excipient C	90.00	8.81	0.12 ± 0.00

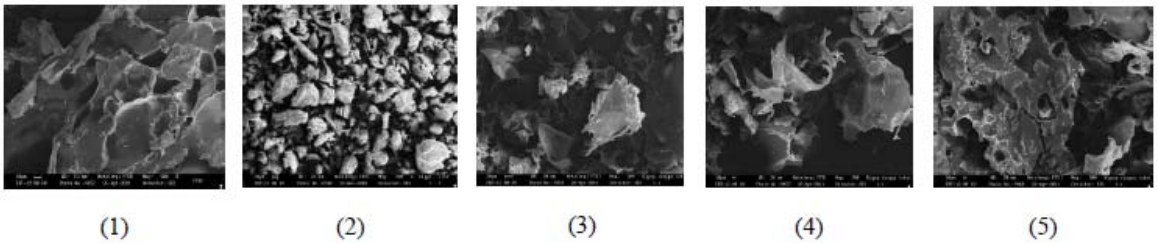

Figure 1. SEM Images of PCSP (1), Kappa- and Iota-carrageenan Mixed (2), Co-processed Excipient A (3), Co-processed Excipient B (4), Co-processed Excipient C (5)

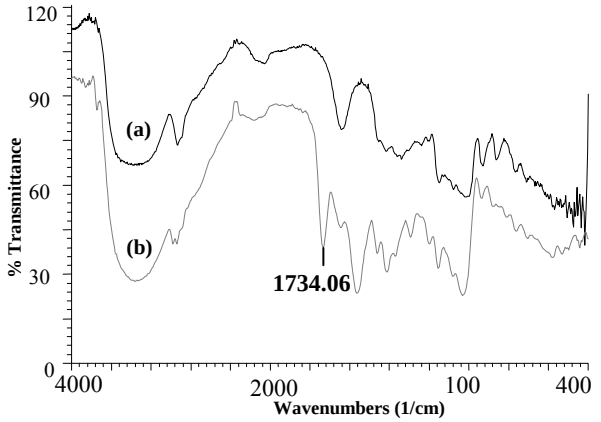

Figure 2. FTIR Spectrum of Cassava Starch (a), and PCSP (b)

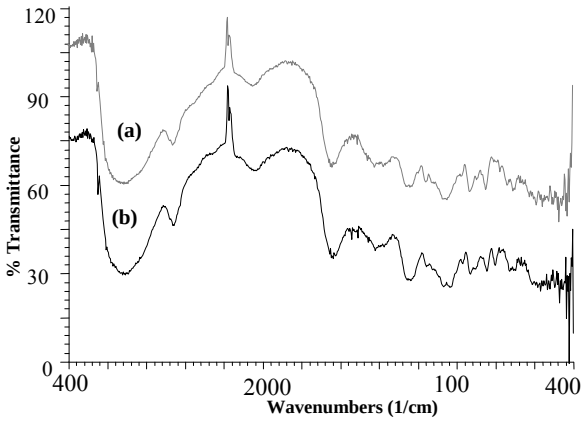

Figure 3. FTIR Spectrum of *Kappa*- (a), and *Iota*-Carrageenan (b)

new peak at 1734.06 cm^{-1}. A C=O absorption specifically for ester was also created after the esterification, which suggested that the starch ester propionat was produced. The frequency for esters are within the range of 1750–1725 cm^{-1} [9]. Another esterification with propionic anhydride and pyridine as chatalist is showed in the C=O absorption at 1740 cm^{-1} [10]. Figure 3 has shown that the peak of 1734.06 cm^{-1} still remains in the FTIR spectrum of co-processed excipients. This indicates that the co-processing methode has created the product through physical modification without altering the chemical structure.

The co-processed excipient is then characterized regarding its functional properties, including gel strength and bioadhesive properties. The results are summarized in Table 3. The gel strengtheness of co-processed excipients depend on the amount of the ratio of carrageenan. Gel strength from co-processed excipient A showed the highest value.

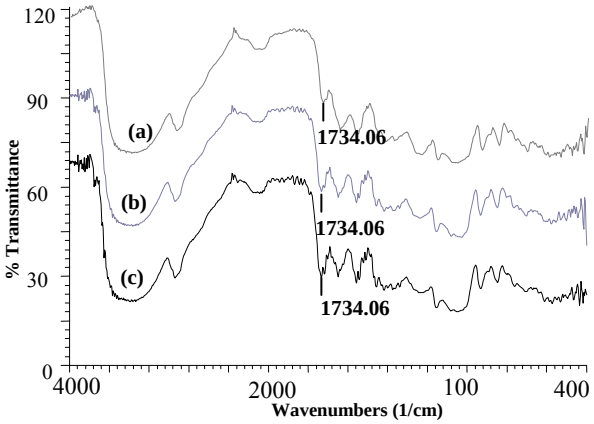

Figure 4. FTIR Spectrum of Co-processed Excipient A (a), Co-processed Excipient B (b), and Co-processed Excipient C (c)

Table 3. Gel Strength, Bioadhesive Properties, Swelling Index of Co-Processed Excipient

Coprocessed Excipient	Gel Strength in 10% w/w (gF)	Bioadhesive properties (gF)		Swelling index (%)	
		stomach	intestine	pH 1.2	pH 7.2
A	730.23	7.50±0.95	7.2±0.77	90	110
B	390.07	8.325±0.99	7.325±0.53	100	90
C	296.67	10.125±1.28	7.3±0.80	120	100

Bioadhesive properties of the produced co-processed excipients within the stomach and intestine of rats were studied using a texture analyzer. Mucoadhesion strength is the mean maximum forces required to breaking the adhesive bond between the microspheres and the rat gastric or intestine mucosa in the presence of different mediums. The results showed that the co-processed excipients have good mucoadhesive properties and could adequately adhere on stomach and intestine mucosa.

The co-processed excipients showed better adhesion at a medium of pH 1.2 than that of a pH of 7.2, since hydroxyl groups and ester of PCSP might be in a protonated form with a small degree in ionization. Adhesion may occur through hydrogen bonding of the unionized forms [11]. Increase in the pH of the medium produces a suitable degree of ionization and may cause excessive hydration. This occurrence could reduce the strength of the polymer-mucosa bound due to the formation of a slippery mucilage. There is a double effect of the water excess in mucoadhesive properties. Firstly, the gel consistency is reduced; secondly, water competes against functional groups of sugars (oligosaccharides from mucus) present in the mucosa surface for the formation of hydrogen bonds with the hydroxyl groups of the polymers [12]. As a consequence, co-processed excipient C which contains the highest content of PCSP has a stronger adhesion property when there is a low amount of ionized forms.

Preparation of gastroretentive dosage forms. Mucoadhesive granules were prepared through wet granulation using amoxicillin trihydrate, an antibiotic which is widely used in Indonesia. Amoxicillin trihydrate is obtainable, but known to be instable at a pH below 4. Thus, studies on the development of the formulation of amoxicillin is very interesting. Amoxicillin tryhidrate is used in a drug-polymer ratio of 1:1 (Table 4). The granules obtained have the highest particle size distribution at 710–1180 μm (Figure 5), and were then used in another test.

In this study, the production yield of the granules show relatively high values (76.05–97.21%) and amoxicillin trihydrate, as a model drug, was entrapped in the granules of 104.01–109.92%. Moisture content of granules varied in a range of 5.13–6.80. The index of swelling from granules are in a range of 3.89–4.64 (Table 5).

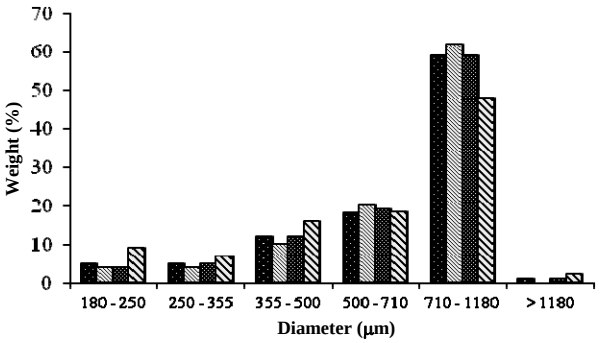

Figure 5. Particle Size Distribution of Mucoadhesive Granules, F1 (■), F2 (▨), F3 (▩), F4 (▨)

Table 4. Ratio of Material Using in Formula of Mucoadhesive Granules

Material (g)	Formula of Granules			
	F1	F2	F3	F4
Amoxicillin trihydrate	1	1	1	1
Co-processed excipient A	1		1	
Co-processed excipient B		1		
Co-processed excipient C			1	
HPMC				1

Mucoadhesion properties of the produced granules to stomach of rabbit were studied using bioadhesion in vitro test and wash off test. The results showed that the granules have good mucoadhesive properties and could adequately adhere to the stomach in bioadhesion in a vitro test. However, in a wash-off test granules started to rupture in the stomach at the 90th minute, except for F4 granules, they did not countable after 60th minutes because they become slippery mucilago. Both of test are showed that granules from coprocessed excipients (F1, F2, and F3) have better mucoadhesive properties to tomach than the granules control from HPMC (F4). For detailed information, see Table 6 and Table 7.

In vitro release study of the amoxicillin granules was performed in a medium of HCl buffer with a pH of 1.2 and in a medium of distilled water using the dissolution apparatus type basket. As shown in Figure 6 and 7, the amoxicillin release in distilled water medium is higher than in a medium of pH 1.2. Two mediums are used in this study as amoxicillin is known to degrade in a pH

Table 5. Yield, Entrapment Efficiency, Moisture Content and Swelling Index of Formula Granules

Formula	Percentage yield (w/w)	Entrapment Efficiency (%)	Moisture content (%)	Swelling index
F1	97.21	109.92	6.8	4.64
F2	96.90	106.89	6.69	4.54
F3	96.75	104.01	6.52	4.48
F4	76.05	108.55	5.13	3.89

Table 6. Wash-Off

Formula	Granules still adhere in the stomach (%)			
	30'	60'	90'	120'
F1	100.00 ± 0.00	90.00 ± 5.00	10.00 ± 1.00	0
F2	100.00 ± 0.00	94.67 ± 2.52	14.67 ± 2.52	6.00 ± 3.00
F3	100.00 ± 0.00	96.67 ± 1.53	14.67 ± 3.06	4.67 ± 0.58
F4	100.00 ± 0.00	0	0	0

Table 7. Bioadhesion in Vitro Test

Formula Granules	Granules still adhere to stomach (%)	
	5'	10'
F1	100.00 ± 0.00	100.00 ± 0.00
F2	100.00 ± 0.00	100.00 ± 0.00
F3	100.00 ± 0.00	100.00 ± 0.00
F4	100.00 ± 0.00	100.00 ± 0.00

lower than 4 [13]. The excessive amount of amoxicillin release in distilled water and HCl buffer pH 1.2 was presented as the amount of amoxicillin degraded (Table 8). This study indicated that F3 granules have better protection amoxicillin from acid condition. This could be due to the co-processed excipient that C F3 granules are made from which has a ratio carrageenan-PCSP of 1:3. The more carrageenan in the formula of a granul, the greater the degradation. This is because carrageenan in the matrix would be hydrolized after forming the gel [4], and amoxicillin is more easily released from the matrix and degraded due to longer contact with the acid medium.

The Zero Order Kinetic model could explain the release mechanisms involved in the drug release from granules in distilled water medium. Based on the Zero Order Kinetic model, drug released from the matrix was at constant rate and is expected to be in a controlled drug release system [14]. The R value for each formula of granule is 0.9978; 0.9995; 0.9997; and 0.9991, respectively. Whereas according to the Banakar equation [15], for F1 and F2 in distilled water medium at 8th hours meet $Q_{0.5}$ = 46–75% so it can be used as controlled release matrix for 16 hours and for F3 in distilled water medium at 8th hours meet $Q_{0.25}$ = 20–45% so it can be used as controlled release matrix for 32 hours.

Floating tablets were prepared by wet granulation then compresed with tabletting machine to form tablet with

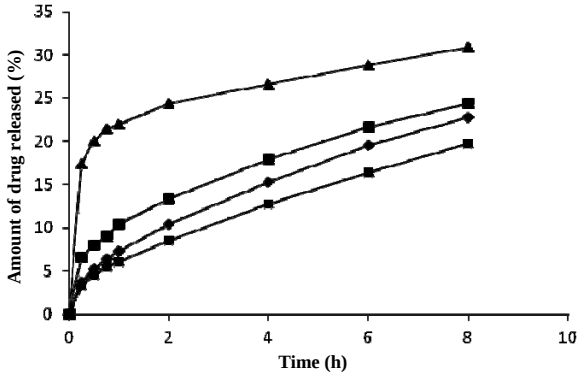

Figure 6. Amoxicillin Trihydrate Release from Granules in the Medium of HCl Buffer pH 1.2, F1 (♦), F2 (■), F3 (▲), F4 (■)

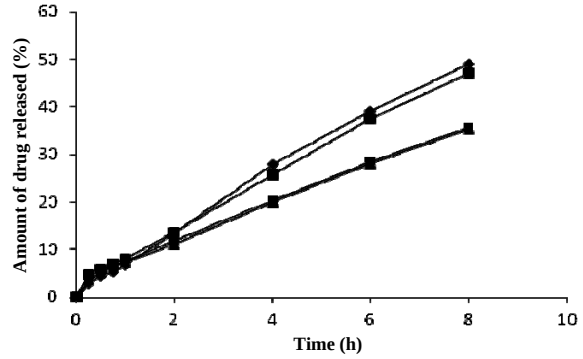

Figure 7. Amoxicillin Trihydrate Release from Granules in the Medium of Distilled Water, F1 (♦), F2 (■), F3 (▲), F4 (■)

300 mg in weight. Pre-eliminary study have been conducted and based on that study, formulation of floating tablet using co-processed excipient C and then combined with HPMC (Table 9).

Table 8. Degradation of Amoxicillin

Formula	Amount of amoxicillin released in distilled water at the 480th minute (%)	Amount of amoxicillin released in HCl buffer pH 1.2 at the 480th minute (%)	Amount of degradation of amoxicillin (%)
F1	49.6	23.19	26.41
F2	47.63	24.81	22.82
F3	35.72	31.61	4.11
F4	36.19	20.05	16.14

Table 9. Ratio of Material Using in Formula of Floating Tablets

Bahan	Formula (mg)			
	I	II	III	IV
Famotidin	40	40	40	40
Co-processed excipient C	129	144	154	0
HPMC	65	50	40	194
Mg Stearat (1%)	3	3	3	3
Talk (2%)	6	6	6	6
PVP (4%)	12	12	12	12
NaHCO3	45	45	45	45
Total	300	300	300	300

Table 10. Characteristic of Floating Tablets

Parameters	FI	FII	FIII	FIV
Compresibility index	12.82	14.63	12.19	12.19
Flow rate (g/s)	1.85	1.6	1.98	1.65
Angel of repose	25.2	27.07	27.05	27.09
Hardness (Kp)	5.55 ±0.39	5.9 ±0.28	5.56	5.64±0.37
Friability (%)	0.879±0.00	0.359±0.00	0.528±0.00	0.372±0.00
Efficiency of entrapment (%)	98.06±0.802	95±0.918	98.46±0.569	98.53±0.58
Floating lag time (s)	243.2±3.044	480.4±0.62	179.37±0.85	10.8 ±0.65
Floating time (h)	<12 h	24 h	<12 h	24 h

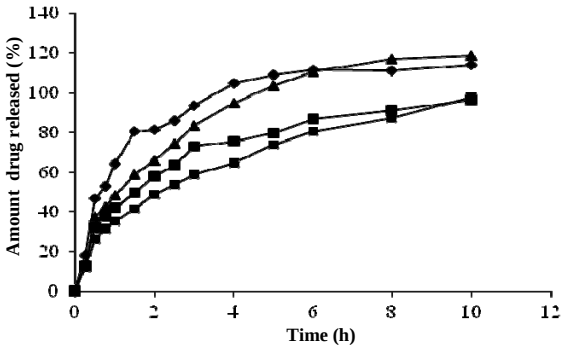

Figure 8. Famotidine Release from Floating Tablet in the Medium of HCl 0,1 N, FI (◆), FII (■), FIII (▲), FIV (●)

The massa of granules for tablet and floating tablets have been evaluated including compresibility index, flow rate, hardness, friability, efficiency of entrapment, floating lag time and floating time (Table 10). Floating time evaluated through buoyancy test is an important evaluation of floating dosage forms. A floating dosage form had to float immediately as it was immersed into a HCl medium and remained afloat for a prolonged time [16].

Floating lag time and floating time are critical parameters for floating tablets. The FII has floating time same as FIV (formula control) are 24 hours, the best result compared with the other. But, the best floating lag time is still owned by FIV.

In vitro release study of the famotidine floating tablets was performed in a medium of HCl 0.1 N using the dissolution apparatus type paddle. As shown in Figure 8, the amoxicillin release at the 10th hour for FI, FII, FIII, FIV are 114.15; 96.30; 118.65; and 97.86, respectively. This study indicated that FII has a release mechanism that is similar to FIV (control). The FII has the most suitable formula for the floating tablet matrix

which could remain afloat in HCl 0.1 N for 24 hours—though it only can be used as controlled release matrix for 10 hours.

4. Conclusion

Co-processed excipients combination of carrageenan and PCSP are suitable for matrix in gastroretentive dosage form, i.e. on mucoadhesive granules and floating tablets. In mucoadhesive granules with a formula ratio of drug:polymer 1:1, co-processed excipient C is the most suitable excipient which has a good bioadhesive properties and can be used as controlled release matrix for 32 hours. Whereas in floating tablets, co-processed excipient C combined with HPMC in formula II is suitable for matriks floating tablet which has a 24-hour floating time in HCl 0.1 N. However, it can only be used as a controlled release matrix for 10 hours.

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