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Novel Excipient for Matrix of Floating Tablet Containing Nile Tilapia Gelatin, Chitosan and Cellulose Derivatives

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Floating system has a density lower than the density of the gastric juice. Thus, gastric residence time and hence the bioavailability of drugs that are absorbed in the upper part of the gastrointestinal tract will be improved. Intragastric floating dosage forms are useful for administration of drugs that have a specific absorption site, area insoluble in the intestinal fluid. The aim of this study was to use combination of nile tilapia gelatin, chitosan and ethyl cellulose, methyl cellulose and carboxymethyl cellulose sodium in floating system tablet and to evaluate physical properties and drug release profile of the tablets dosage form. In this study, tablet was formulated by wet granulation method and using diltiazem hydrochloride as a drug model. The swelling and buoyancy of the floating tablets were evaluated. Furthermore, the drug releases from the floating tablets were analyzed using several kinetic models. The result showed that formula containing nile tilapia gelatine and ethyl cellulose at ratio of 1:18 was the best formula which had swelling ratio 16,4% and floating lag time 61 minutes. This formula also revealed a profile of controlled drug release and approached to Higuchi kinetics model and Fickian diffusion mechanism.

Key words: Floating tablet, nile tilapia gelatin, chitosan, cellulose derivatives, diltiazem hydrochloride

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INTRODUCTION

Marine based polysaccharides are widely used in pharmaceutical industry because of their biocompatibility and low toxicity. Some of these polisaccharides are polyelectrolites and show great potencial to interact with another material like fish gelatin and chitosan. Both of them are marine-source hydrophyllic polymers recently developed for pharmaceutical application due to its biodegradability and biocompatibility. Nile tilapia fish (*Oreochromis niloticus*) is one kind of fish which its skin could be processed into gelatin. Simanjuntak (2006) reported that nile tilapia gelatin showed suitable to be used as tablet binder and matrices-forming.

The Gastroretentive Drug Delivery System (GRDDS) is kind of dosage form to retain in stomach and assist in improving the oral sustained delivery of drug that have an absorption window in particular region of gastrointestinal tract. Therefore, the dosage form can improves the oral absorption and bioavailability of the drugs that are having site specific absorption from stomach or upper part of the small intestine. The problems of conventional oral dosage forms which are affected by several factors such as pH environment, limited absorption window in specific site of Gastrointestinal Tract (GIT), drug stability and drug retention time in GIT (Jain *et al*., 2005; Davis, 2005). This dosage form release the drug in contant rate and prolong time in absorption site without affected by gastric emptying rate. The controlled gastric retention dosage forms could be achieved by density modification (flotation and sedimentation) that delay gastric emptying (Arora *et al*., 2005; Bardonnet *et al*., 2006).

In this study, three cellulose derivatives were combined with nile tilapia gelatin and chitosan to improve retain effect of matrix. They are Methyl Cellulose (MC), carboxy methyl cellulose sodium (CMC-Na) and Ethyl Cellulose (EC) and Diltiazem hydrochloride as drug model. Diltiazem hydrochloride is a calcium channel blocker belonging to the benzothiazepine family. It is widely prescribe of hypertension and angina. Nevertheless, it has poor bioavailability (40-50%) and narrow absorption window in upper part of GI tract. It also has short biological half-life (3-4 h) with single dose of 30-60 mg (Lacy *et al*., 1997). Therefore, it was proposed to develop a FDDS to enhance the absorption of the drug, intended to increase its bioavailability.

MATERIALS AND METHODS

Materials: Diltiazem hydrochloride (Nicholas, India), nile tilapia gelatin (Indonesian Research Bureau of Marine), chitosan (Fuji Spiunning, Japan), sodium carboxy methyl cellulose (CMC-Na) (Daiichi, Japan), methyl cellulose and ethyl cellulose (ShinEtsu, Japan), sodium bicarbonate (Penrice Soda, Australia), stearic acid and citric acid (WuXi Ltd, China).

Preparing of diltiazem hydrochloride floating tablet: Composition of Diltiazem Hydrochloride Floating Tablet was described in Table 1. All of these floating tablets were prepared by wet granulation method using 5% of cellulose mucilage as binding solution. Active pharmaceutical ingredient (diltiazem hydrochloride) and gas generating agent (sodium bicarbonate and stearic-citric acid mixture) were separately granulated. Three-fourth of gas generating agents was granulated and one-fourth was gently mixed before lubrication step. Granules was then lubricated by 2% talc and 1% magnesium stearate and compressed into 700 mg weight of tablets.

Physical properties of tablets: The amount of tablets from each formulation was evaluated include weight uniformity, friability, hardness and thickens of tablets as were determined by procedure stated in the US Pharmacopoeia (Anonim, 2006).

Swelling test: This test was performed by calculate the percentage of tablet weight gain after tablet was immersed into 100 mL hydrochloric acid solution 0.1 N for 1 h. The measurement was carried out in triplicate. Percentage of swelling was calculated using the following equation:

$$\%\ \text{swelling} = \frac{\text{Weight of swollen tablets (w2)-Initial weight of tablet (w1)}}{\text{Initial weight of tablet (w1)}} \times 100\%$$

Buoyancy test: Buoyancy characteristic of tablets were determined in a USP dissolution apparatus type 2 (paddle type) with agitation speed of 50 rpm in 900 mL hydrochloric acid 0.1 N at temperature 37±0.5°C. This test was performed to define buoyancy lag time and total floating time of tablets from each formula after immersed into dissolution test apparatus (Mahesh *et al*., 2006).

Table 1: Formulation of diltiazem hydrochloride floating tablet

	Formula (mg)						
Item	1	2	3	4	5	6	7
Ingredient							
Diltiazem HCl	180	180	180	180	180	180	180
Chitosan	83.3	83.3	83.3	-	83.3	-	-
Nile Gelatin	16.7	16.7	16.7	-	-	16.7	100
CMC-Na	300	-	-	-	-	-	-
Ethylcellulose	-	300	-	300	300	300	300
Methylcellulose	-	-	300	-	-	-	-
Gas generating							
Stearic acid	6.6	6.6	6.6	6.6	6.6	6.6	6.6
Citric acid	26.7	26.7	26.7	26.7	26.7	26.7	26.7
$NaHCO_3$	66.7	66.7	66.7	66.7	66.7	66.7	66.7
Lactose	-	-	-	100	16.7	83.3	-

Drug release profile: Drug release profile and buoyancy test of tablets was investigated in triplicate. Drug release study was performed using a USP type 2 dissolution test apparatus (paddle type) with agitation speed of 50 rpm in 900 mL hydrochloric acid 0.1 N at temperature 37±0.5°C. At the appropriate intervals 15, 30, 60, 120, 180, 240, 300, 360 and 480 min, 5 mL of samples was withdrawn and an equal volume of medium was added to maintain the volume constant. Samples were analyzed spectrophotometrically at 235.8 nm (Anonim, 2006). Different kinetic models (zero-order, first-order and Higuchi) were applied to interpret the release from matrices and Korsmeyer-Peppas kinetics model was used to describe the release mechanism were calculated according to the equations below:

$$\text{Zero order} = Q_t/Q_o = k_o\, t$$

$$\text{First order} = \ln Q_t/Q_o = k_1\, t$$

$$\text{Higuchi} = Q_t/Q_o = k_H t^{1/2}$$

$$\text{Korsmeyer-peppas} = Q_t/Q_o = k\, t^n$$

RESULTS AND DISCUSSION

The floating tablet of Diltiazem HCl were prepared by using gas generating agents. Gastric juice diffused into tablets and then interacted with gas generating agents and form carbon dioxide gas. This gas was entrapped in gel matrices, causing decrease of tablet density and cause tablet float.

The physical properties of the floating tablet (Table 2) shows that the weight of tablet varied between 698.1-705.1 mg which was accordance with Pharmacopoeial specifications ±5%, indicated each formula produced tablets with good weight uniformity. Tablets from all formula were compressed with the same compression force. Tablets hardness was also affected by its matrix-forming polymer. Table 2 shows, Formula 5 containing chitosan and ethyl cellulose was hardest than Formula 6. This data indicate that addition of chitosan can increase tablet's friability and gelatin increase its compatibility. In small amount, nile tilapia gelatin increase tablet's hardness and compatibility due to its role as tablet binder. Ethyl cellulose could influence increasing tablet's hardness (Wade and Weller, 1994), there is evidence in Formula 4 which only containing ethyl cellulose. In general physical properties of the floating tablets were accordance with Pharmacopoeial specification.

Buoyancy and swelling test: Several specific tests need to be performed on this floating dosage forms, include buoyancy test, swelling test and drug release test (Arora *et al*., 2005). Buoyancy test is an important evaluation of floating dosage forms. A floating dosage form had to float immediately as it was immersed into HCl medium and remain float for prolonged time (Dave *et al*., 2004). Effervescent system was applied to produce floating tablets in this study. Effervescent system utilized two main components: matrices prepared with swellable polymer and gas forming (gas generating agents) contained of basic (sodium bicarbonate) and acid components (citric acid, tartaric acid, stearic acid). Buoyancy mechanism of tablets due to forming of carbon dioxide gas from interaction of HCL medium and gas generating agents which gets entrapped in between the gelatinous layer of polymer and cause floatation of dosage forms (Singh and Kim, 2000; Arora *et al*., 2005; Bardonnet *et al*., 2006). Buoyancy lag time of FDDS is influenced by swelling capacity of polymer in formula. Swelling ratio of polymer indicate polymer's ability to absorbs medium and allow medium entering the tablet and contact with gas generating agents. Swelling ability of polymer determine buoyancy lag time of FDDS, while its ability to retain carbon dioxide gas within tablets determine total floating time. The higher swelling index, the faster buoyancy lag time of dosage forms.

In this study, the fastest buoyancy lag time was achieved by Formula 3 tablet, containing methyl cellulose, chitosan and Nile tilapia gelatin but it only remain buoyant for 1 h. The slowest buoyancy lag time was achieved by Formula 4 which containing of ethyl cellulose as single tablet matrix. Another formula showed buoyancy lag time of 40-60 min and total floating time up to 8 h (Table 3).

Table 3 showed the lowest swelling capacity was possessed by Formula 4 tablet and the highest swelling capacity was Formula 3. Based on the data in

Table 2: Physical properties of floating tablets

Formula	Friability (%)	Hardness (kP)	Weight (mg)	Thickness (mm)
1	0.73	7.16±0.32	699.3±5.59	5.39±0.058
2	0.75	7.87±0.10	701.0±3.23	5.27±0.056
3	0.46	7.15±0.34	699.3±5.71	5.52±0.074
4	0.51	10.08±0.42	700.4±6.34	5.16±0.087
5	1.41	6.29±0.43	698.1±4.84	5.49±0.069
6	0.23	8.92±0.43	705.1±4.75	5.50±0.089
7	0.96	5.94±0.26	698.9±6.64	5.71±0.102

Table 3: Results of swelling and buoyancy test

Formula	Buoyancy lag time (min)	Total floating time (min)	Swelling index (%)
1	43.7±0.47	431.0±2.49	125.0±3.20
2	47.0±0.82	453.3±3.09	60.1±2.33
3	20.7±0.94	67.3±1.70	1344.1±2.60
4	275.7±4.50	521.0±3.56	9.0±6.33
5	48.7±0.94	289.3±2.05	48.9±3.88
6	61.7±1.25	465.0±3.27	16.4±8.53
7	51.0±2.16	464.3±2.05	528.4±0.341

Table 4: Kinetic model on drug release profile of diltiazem HCl floating tablet

	Zero order		First order		Higuchi		Korsmeyer-peppas		
Formula	r	k	r	k	r	k	r	k	n
F1	0.9403	0.0022	0.8641	0.0052	0.9734	0.0558	0.9958	0.0074	0.8510
F2	0.9423	0.0019	0.8844	0.0037	0.9878	0.0486	0.9916	0.0331	0.5650
F3	0.7010	0.0016	0.6443	0.0016	0. 8591	0.0445	0.9744	0.0776	0.5612
F4	0.9194	0.0013	0.8887	0.0027	0.9905	0.0330	0.9969	0.0631	0.4039
F5	0.8755	0.0020	0.8417	0.0028	0.9685	0.0494	0.9931	0.0611	0.4982
F6	0.9317	0.0016	0.9078	0.0028	0.9941	0.0382	0.9989	0.0698	0.4077
F7	0.9306	0.0016	0.9120	0.0027	0.9938	0.0389	0.9991	0.0761	0.3970

Table 4, that swelling capacity is equivalent to floating time. The higher swelling capacity, the faster buoyancy lag time. Nevertheless, Formula 7 showed an exception. Swelling capacity of Formula 7 tablet was not influenced by swelling property of polymer (Nile tilapia gelatin) but by uncompact structure of the tablet that cause easier penetration of HCl medium into tablet. Buoyancy lag time of the hydrophilic polymer because of HCl from stomach penetrate easier into tablet form hydrocolloid gel layer and entrap the CO_2 which allow tablet to float. Tablets containing ethyl cellulose showed slowest buoyancy lag time due to its hydrophobic property which cause difficulties of HCl medium to penetrate tablets. Formula 4 containing only ethyl cellulose as matrix showed the slowest buoyancy lag time. Addition of nile tilapia gelatin (Formula 6) and chitosan (Formula 5) cause buoyancy lag time of tablet faster due to swelling property of those materials.

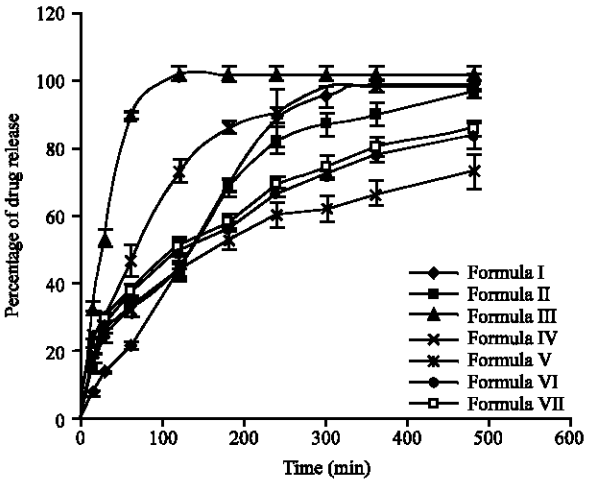

Fig. 1: Drug release profile of diltiazem HCl floating tablet

Drug release study: Figure 1 showed that Formula 3 have the fastest drug release rate than the other formula, on the other hand Formula 4 was release the drug (73.22%) in 8 h.

In fact combination of ethyl cellulose with nile tilapia gelatin could improve buoyancy lag time of tablets and increase drug release rate (Formula 6 and 7). The higher amount of nile tilapia gelatin in formula, the faster release rate of the drug. This phenomena was caused by swelling property of nile tilapia gelatin which allow easier diffusion of HCl medium into tablets. Addition chitosan as combination with ethyl cellulose also increase release rate of drug from tablet which based on dissolution mechanism of chitosan in HCl medium (Formula 5).

Drug release profile of all formulas were analyzed and fit with several kinetic models: zero order, first order, Higuchi and Korsmeyer-Peppas equation. The "r" value obtained from different kinetic model (Table 4) suggest that the release from the formulations may follow one of these models. Drug release of the dosage form is stated as zero order if the release rate is constant and unaffected by time. The first order release profile is depended on remaining concentration of the drug within dosage forms (Koester *et al*., 2004). Higuchi equation describe time-dependent release profile and Korsmeyer-Peppas equation indicate Fickian diffusion release mechanism. When Peppas release exponent ("n" value) is less than 0.45, it indicate Fickian diffusion mechanism of drug release. But if "n" value is between 0.45 and 0.89, it indicate non-Fickian release mechanism (Peppas, 1985).

Monolithic (matrix) system controlled-release dosage form generally possess dissolution profile which fit with Higuchi equation. The floating tablet were produced in matrix system and all of those tablets follow Higuchi equation more than zero order or first order kinetic model. Among those tablets, formula 6 was the most suitable with Higuchi equation, based on linearity ("r" value) of its drug release to Higuchi equation (Table 4). Formula 4, 6 and 7 showed diffusion Fickian release model (based on its "n" value <0.45). Drug release from tablet was based on diffusion mechanism: HCl medium diffuse into tablet and dissolve-out the active drug. Formula 1,2,3 and 5 showed "n" value between 0.45-0.89 which indicate non-Fickian releasing pattern. Drug release from those tablets follows diffusion-dissolution mechanism. This phenomena is reasonable since those formulas contain of chitosan which could be dissolved in HCl medium. Drug release was affected by both diffusion of HCl medium through matrix pores of cellulose derivatives and

dissolution of matrix which formed by chitosan. This double mechanism will facilitate dissolving and releasing diltiazem HCl from tablets.

Based on statistical calculation (ANOVA and student t-test), it was concluded both of the formulas showed significant differences of drug release pattern ($\alpha<0.05$), except Formula 6 and 7. It describe that each polymer give different characteristic on tablet matrix which have impact on differences release pattern of each formula. There are no significant differences on release pattern of Formula 6 and 7, its indicate that increasing of nile tilapia gelatin on formula give no affect on drug release rate. Nevertheless, amount of nile tilapia gelatin influence significantly on physical properties, swelling index and buoyancy lag time of tablet. Based on evaluation result of all parameters, it can be concluded that Formula 6 was the best formula among those seven formulas. Formula 6 showed good physical properties of tablet, prolonged release profile (83.73% drug release in 8 h) and buoyancy lag time less than 2 h in acid solution (gastric medium). Drug release profile from Formula 6 was the best fit to Higuchi equation and performs Fickian diffusion mechanism.

Although Formula 6 tablet showed prolonged drug release profile, this formula only comply specification for dosage forms to be administered twice a day, instead of once a day (Anonim, 2006). Therefore, it still needs improvement on formula to obtain dosage form which can be orally administered once a day.

CONCLUSION

This study conclude formula 6 that containing nile tilapia gelatine and ethyl cellulose at ratio 1: 18 was the best tablet floating tablet which showed good physical properties of the tablet, prolonged release profile (83.73% drug release in 8 h) and complied buoyancy lag time (61 min) and linearity to Higuchi equation and Fickian diffusion mechanism.

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