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CONTENT

Formulation of Floating Tablets as Captopril Delivery System Using Direct Compression Method

Parfati N[1], Pradana AT[1*], Edrick A[2], Gunawan AA[2]
[1]Department of Pharmaceutics, College of Pharmacy, University of Surabaya, Surabaya, Indonesia
[2]Graduated student of College of Pharmacy, University of Surabaya, Surabaya, Indonesia

The corresponding author: Aditya Trias Pradana, aditya_trias@staff.ubaya.ac.id

Abstract

Captopril short elimination half-life (2-3 hours) and good stability at pH 1,2 with its major absorption in the upper part of Gastro Intestinal Tract (GIT) was the reason of this drug formulated into sustained release floating tablets. This research was conducted in order to obtain several formulations and evaluate the physical characteristics, floating lag time and dissolution rate of the floating tablets. The captopril floating tablets were produced by direct compression technique using combination of polymers (HPMC, ethyl cellulose and CMC-Na in different concentrations). The gel forming agent, gas generating agent and another polymer were used to control their floating capability and drug dissolution rate profile. The tablet floating capability was evaluated by determining lag time and floating duration. All formulas remained buoyant for more than 12 hours. The drug release evaluated for 12 hours using USP paddle-type II dissolution apparatus in a 900ml 0,1N HCl as dissolution medium. The dissolution efficiency of control tablets (Formula 1) was 90,98%. There was a significance difference compared to dissolution efficiency value of Formula 2 (2% CMC-Na), Formula 3 (4% CMC-Na), Formula 4 (6% CMC-Na), Formula 5 (10% Ethyl cellulose), Formula 6 (20% Ethyl cellulose), Formula 7 (30% Ethyl cellulose) as 86,35%, 83,88%, 80,35%, 81.25%, 75.81%, and 78.16%, respectively. The result of this research indicates that tablet formulation with different in composition of the polymers (CMC-Na and Ethyl cellulose) affects the floating capability and dissolution rate of the tablets, which is important in consider floating tablet as captopril sustained release delivery system.

Keywords: captopril, HPMC, CMC-Na, ethyl cellulose, floating tablet, sustained release

1. INTRODUCTION

The conventional tablets commonly used today have its limitations. The limitations of conventional tablets are on fluctuations in drug plasma concentrations (Brahmankar & Jaiswal, 2009). Controlled release tablets made to answer that limitations, because of the use of controlled release tablets can avoid fluctuations of drug levels in plasma. Controlled release tablets also used to improve the patient with chronic diseases compliance in taking the drug (Kumar, 2012). The use of controlled release tablet still has limitations, where the

controlled release tablet that has been designed could not survive in the absorption place during the drug release from the matrix (Prinderre *et al.,* 2011).
The way to make controlled release dosage forms can survive in the gastrointestinal tract is by using the *Gastro Retentive Drug Delivery System* (GRDDS) (Chikhalikar & Wakade, 2012). Drugs that require *GRDDS* work locally in the gut, mostly absorbed in the gastric, insoluble in an alkaline pH, and drugs that unstable at alkaline pH (Mishra & Gupta, 2012). One example of a drug that is absorbed in the stomach and degraded at an alkaline pH is captopril (Sweetman 2011; Vijayasankar *et al.,* 2011).

Floating drug delivery system is GRDDS dosage form that has smaller density than gastric fluid, so that it can float on the top of the gastric juices and is not influenced by the gastric emptying time (Narang, 2011). Materials such as HPMC in floating system are used as gelling materials and swelling agents. Swollen HPMC then locks the air inside and shows floating effect of the systems (Mishra & Gupta, 2012). In this experiment, ethyl cellulose and CMC-Na as polymers can protect the penetration of medium, lowering the floating lag time, and improve floating duration (Dhole *et al.,* 2011; Chowdary *et al.,* 2013).

The floating ability and dissolution profiles will be tested in this research based on percent dissolved, dissolution efficiency and floating duration of 7 kinds of formulas with different ethyl cellulose and CMC Na composition in each formula. It is expected that the formula can provide buoyancy and good dissolution profiles at pH 1, 2 for 12 hours.

2. MATERIALS AND METHODS

2.1 Equipments

Erweka AR 402 tablet compression machine, Monsato hardness tester, Pharmex Y cone mixer, Hanson Research SR-8 dissolution apparatus, Sartorius BP10 analytical balance, Erweka friability tester, Shimadzu spektrofotometer.

2.2 Material

Captopril p.g (Huahai), HPMC K100M p.g (Colorcon), ethyl cellulose p.g (Colorcon), spray dried lactose p.g (Foremost), $NaHCO_3$ (Inner Mongolia Ihjuchen), citric acid (Anugrah Buana), magnesium stearate p.g (Bratachem), HCl p.a (Sigma).

2.3 Method

2.3.1 Tablets Formulation

The process of producing the tablet was done by direct compression method. The powder mixture was made by mixing of captopril, HPMC K100M, ethyl cellulose, CMC Na, SDL, NaHCO3 and citric acid. Mixed mixture was screened by siever. Magnesium stearate then added and mixed to form the 240mg weight tablets.

Table 1 *Floating Tablet Formula*

Materials	Weight (mg)						
	F1 (control)	F2	F3	F4	F5	F6	F7
Captopril	25	25	25	25	25	25	25
HPMC K100M	48	48	48	48	48	48	48
CMC- Na	-	4,8	9,6	14,4	-	-	-
Etil Selulosa	-	-	-	-	24	48	72
Mg. Stearat	1,2	1,2	1,2	1,2	1,2	1,2	1,2
SDL (Spray Dried Lactose)	ad 240	ad 240	ad 240	ad 240	ad 240	ad 240	ad 240

2.3.2 Powder Mixture Evaluation

The moisture content of the powder is tested by weighing it for 5 grams and checked it in the moisture content balance. Drying will take place until it showed no change of material weight. Good moisture content value was 1-4%. Compressibility also tested with a number of material in the tap density volumenometer. The density of material before and after tapping process was determined and calculated to get the compressibility value. Powder good compressibility value was <20% (US Pharmacopoeial Convention ., 2017).

2.4 Tablet Evaluation

2.4.1 Physical Characteristics of Tablets

Tablet weight variation is measured by weighing one by one of 10 tablets with analytical balance. Weight variation data is quite good, if the acceptance value is not more than 15% (US Pharmacopoeial Convention ., 2017). Tablet hardness was measured with 10 tablets prepared. The tablet to be tested is placed on Monsanto hardness tester. The tool base rotated until the tablet breaks and the scale was read that indicates the numbers of tablet hardness. In the tablet hardness testing all tablets should be crushed by the load 4,0 to 8,0 kg (Lieberman *et al.*, 1990).

Tablet friability was measured from 20 tablets prepared, then weighed and included in the test apparatus. After rotated, the tablet is then removed and then weighed again. It said to be good if the weight loss is not more than 1% (Lieberman *et al.*, 1990).

2.4.2 Content Uniformity of Tablets

Preparation of captopril standart solution performed by weighing 50,0 mg captopril, then dissolved in 0,01N HCl until 50,0 ml. The standard solution then prepared into several working standart Maximum wavelength were observed between 200-300 nm using a UV spectrophotometer. Standard curve obtained from observations of absorption value of the standard solution at each concentration of captopril was observed at maximum wavelength. (Vijayasankar *et al.*, 2011; Mehta *et al.*, 2011).

Captopril content uniformity in tabletis measured by weighted 10 tablets are taken randomly and ground into powder. Powder weighed equal with 25 mg captopril and diluted to 100,0ml. The solution was filtered using Whatmann filter paper (0,45 µm). Dilution was observed using a UV spectrophotometer at maximum wavelength (Vijayasankar *et al.*,

2011) (Mehta *et al.*, 2011).

2.4.3 Floating Lag Time and Floating Duration

Floating lag time and floating duration time test was done with Measure Glass equipment, heater, thermometer and stop watch. 200ml 0,01N HCl solution putted into a measuring cup 250 ml in temperature of 37^{o}C, then the tablet was inserted. Floating lag time was observed. The time required for the tablet to rise up to the surface and begin to float on the medium surface is recorded as floating lag time, while the time for the tablet remains constant on the dissolution media surface is recorded as floating duration time. Floating duration time was expected to be not less than 12 hours to be able to ensure the drug is in the stomach within 12 hours (Vijasankar *et al.*, 2011).

2.4.4 Dissolution Test

The dissolution media used were 900ml 0,01N HCl solution (pH 1.2) and using a type II dissolution apparatus 50rpm. Temperature and time for dissolution test were 37 ± 0.5 ^{0} C for 12 hours. Sampling was done at 60, 120, 180, 240, 300, 360, 420, 480, 540, 600, 660, 720 minutes. Measurements performed with a UV spectrophotometer at the maximum wavelength (US Pharmacopoeial Convention., 2017) (Vijayasankar et al., 2011) (Mehta et *al.*, 2011). The drug release profile of captopril is accomplished by making the captopril released curve (% Q) per time. Dissolution profile curves calculated from AUC (Area Under the Curve) to determine the efficiency of dissolution. The results obtained were floating lag time, floating duration, percent of dissolution efficiency (%ED), percent dissolved (%Q) then analyzed using statistical methods to determine whether there were significant differences between the groups were tested.

3. RESULTS AND DISCUSSION

Materials were mixed into homogenous mixture. Before compressed into tablet, the powder mixture was tested first. The mixture showed good result in compressibility and moisture content, then it continued with compression using direct compression method.

Table 2. *Characteristics of powder mixture*

Formula	Compressibility (%)	Moisture content (%)
F1	12.00%	1.96%
F2	13,16%	2,04%
F3	12,82%	1,98%
F4	13,16%	2,08%
F5	14.29%	1.98%
F6	13.64%	1.72%
F7	14.63%	1.50%

Table 3. *Physical Characteristics of Tablets*

Evaluation	F1 (control)	F2	F3	F4	F5	F6	F7
Weight variation (mg)	244,54 ± 1,18	240,56 ± 0,59	243,80 ± 0,77	244,66 ± 0,91	243,21 ± 1,05	242,27 ± 0,94	240,87 ± 0,76
Tablet Hardness (kg)	7,00 ± 0,41	5,50 ± 0,53	5,20 ± 0,26	5,15 ± 0,24	5,05 ± 0,28	4,50 ± 0,33	4,20 ± 0,24
Tablet Friability (%)	0,16 ± 0,06	0,18 ± 0,08	0,18 ± 0,10	0,18 ± 0,06	0,12 ± 0,07	0,16 ± 0,05	0,09 ± 0,06
Floating Lag time (sec)	16,33 ± 0,57	16,67 ± 0,58	17,00 ± 1,00	17,33 ± 0,58	19,67 ± 1,00	24,67 ± 1,15	32,33 ± 2,52
Uniformity of content (%)	105,30 ± 0,67	105,01 ± 0,10	104,35 ± 0,46	104,16 ± 0,52	104,64 ± 0,72	109,55 ± 0,96	103,33 ± 0,47

Based on evaluation results, shown that all of formula had good physical characteristics. The results determined that tablets weight variation, hardness and friability of all formula met the requirements. Floating duration results showed the entire formula could float for more than 12 hours. Floating lag time of each formula was different, according to the amount of polymer. Addition of CMC-Na was not very influences the floating lag time, but it became statistically influences when ethyl cellulose added into components of formula, provided longer floating lag time. This floating resistance could be caused by the ethyl cellulose properties as a hydrophobic polymer that inhibits penetration of the medium into the tablet, so it takes longer time for HPMC K100M to expand and form a system that can make the tablet floated.

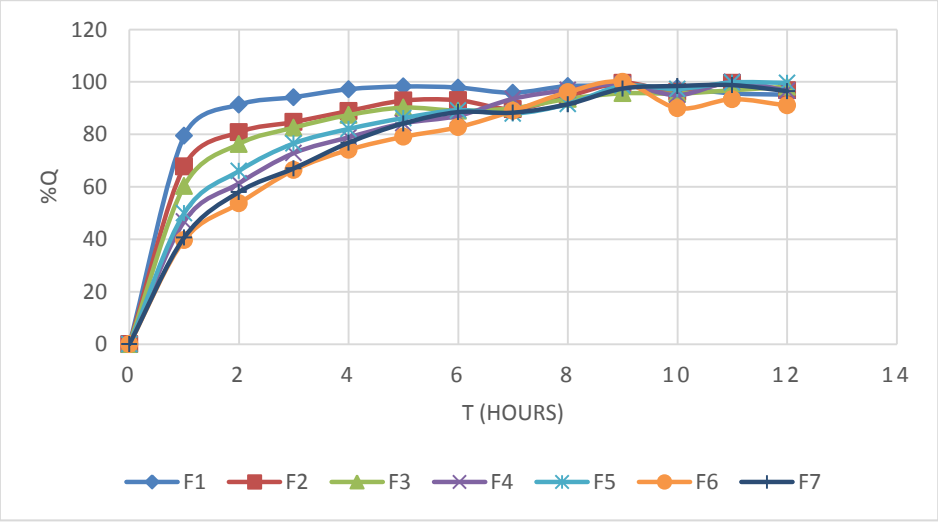

Figure 1. *Dissolution rate of Captopril*

The dissolution test results showed the release resistance on the addition of CMC-Na and ethyl cellulose in the formula. This results showed that the addition of CMC-Na and ethyl cellulose in the formula could decrease the dissolution efficiency, where the decrease in %ED indicates a decrease in the dissolution rate, but on increasing the ethyl cellulose concentration from 10% to 30% did not indicate a significant %ED change.

Table 4. *Dissolution Efficiency Results*

Formula	Dissolution Efficiency (%)
F1	90,98 ± 0,47
F2	86,35 ± 2,48
F3	83,88 ± 6,82
F4	80,35 ± 1,32
F5	81,25 ± 3,50
F6	75,81 ± 0,98
F7	78,16 ± 0,72

4. CONCLUSIONS

The ethyl cellulose and CMC-Na use as polymer showed the influence on controlled release floating tablet result. The addition of ethyl cellulose and CMC-Na reduced the dissolution rate, and showed the sustained release profile of captopril. Addition of ethyl cellulose and CMC-Na affected the floating lag time, significantly made it slower based on higher concentration of the polymer. The differences could be influenced by improvement of viscosity surrounds the tablets. Amount of ethyl cellulose and CMC-Na must be considered, also the possibility on using both of polymer as combination to get faster floating lag time, longer floating duration and sustained release effect on captopril.

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