



Formulation of Metformin HCl Floating Tablet using HPC, HPMC K100M, and the Combinations

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ABSTRACT: Diabetes Floating tablet is one of the most suitable dosage forms that used for delivering long term drug release. The objective of this study was to evaluate Hydroxypropyl cellulose (HPC), Hydroxypropyl Methyl Cellulose (HPMC) K100M, and the combination as matrix in manufacturing floating tablets. Metformin HCl, an anti-diabetic, was used as a drug model. Metformin HCl floating tablet was manufactured by wet granulation method in three formulas using variation of matrix, which were 40% of HPC (F1), 40% of HPMC K100M (F2), combination of 20% HPC and 20% HPMC K100M (F3). Prior to tablet compaction, evaluation for granules were done which included moisture content, angle of repose using, bulk and tapped density, Hausner ratio, and compressibility. The evaluations of floating tablet were physical properties, floating ability, and in vitro drug release. The average of floating lag time for F1, F2, F3, were 7 minutes 13 seconds; 5 minutes 27 seconds; and 14 minutes 5 seconds, respectively. In addition, the floating time for F1 was 3 hours 16 minutes whereas F2, F3 were more than 48 hours. F2 showed the best floating ability to retain the drug release, which was 84.68% over 8 hours, while F1 and F3 were completely dissolved less than 6 hours.

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INTRODUCTION

Floating tablet is one drug delivery systems which designed to retain in stomach for a long time and release the active ingredient during that period [1]. Floating system is controlled by the low density, which is able to float and remain in the stomach without being influenced by the rate of gastric emptying for a long period of time [2]. The system is prepared by adding one or more high-concentration gel (20-75% b / b) gel-forming hydrocarbons in formulations such as sodium carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and hydroxypropyl methyl cellulose [3]. The mechanism of the floating drug delivery system occurs because the bulk density of the preparation is lower than that of the stomach fluid density [4]. This system causes the preparation to float in the stomach for a certain time, without being affected by the time of gastric emptying. The drug is released continuously from the expanding hydrophilic matrix [5,6].

Previous studies have been made on the form of floating tablet preparations, including the manufacture of floating tablet propranolol HCl using HPMC K4M, HPMC E15LV, HPC, carbopol, and xanthan gum as polymers,

by direct forging method. As a result, the floating tablet formulated using HPMC K4M gave the best detention effect of release of the drug about 92% for 18 hours, in which tablets formulated with HPMC E15LV, HPC, and carbopol could not form a matrix. Tablets formulated with xanthan gum show the ability to withstand drug release, but have poor floating capabilities [7]. In addition, Sungthongjeen, et al [8] has formulated a theophylline floating tablet with several HPMC types, HPMC K100LV, HPMC K4M, and HPMC K100M by the method of wet granulation, in which tablets formulated with HPMC K100M demonstrated the ability to withstand the best release of drugs.

Based on the results of the above research, a floating tablet metformin HCl was made using HPC, HPMC K100M, and combination of HPC and HPMC. Bioavailability of metformin HCl when administered orally is about 50-60%. The biological half-life of metformin HCl ranges from 1.5 to 1.6 hours, and its absorption occurs in the proximal portion of the small intestine [9]. Floating tablets of metformin HCl are expected to float for a long time in the stomach fluid and the drug is in a soluble form where the drug is absorbed. This will

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increase the bioavailability of metformin HCl. Therefore, this dosage form is more advantageous when compared with conventional dosage forms.

MATERIALS AND METHODS

Materials

Metformin HCl was kindly donated from PT. Phapros, Indonesia. HPMC K100M, HPC and PVP K-30 were gift from PT. Kimia Farma, Indonesia. Talc, magnesium stearate, lactose and methanol were purchased from Bratachem, Indonesia. All the materials were used as received.

Formulation of tablet

Tablets was manufactured by wet granulation method by varying composition, HPC HPMC, and chitosan in each formula as can be seen in [Table 1](#). Granules were prepared by mixing Metformin HCl, HPC, HPMC, lactose homogenously. Then, PVP K-30 in ethanol was added as the binder. The wet mass mixture was dried in an oven at 50°C for 8 hours. The dried granules were sieved on a 12 and 14 mesh sieve. Talc and magnesium stearate were added to the dried granules in a tubular mixer for 5 and 2 minutes, consecutively. The mass then was compacted and compressed to manufacture the tablets.

Table 1. Formulation of metformin HCl floating tablet.

Composition	F1	F2	F3
Metformin HCl (mg)	500	500	500
HPC (mg)	400	-	200
HPMC K100M (mg)	-	400	200
PVP K-30 (%)	5	5	5
Talc (mg)	10	10	10
Mg Stearate (mg)	10	10	10
Lactose (mg)	Qs	Qs	Qs

Evaluation of granules

Prior to tablet compaction, granules were evaluated include moisture content using a digital Infrared Moisture Balance, angle of repose using a funnel, bulk and tapped density using a tapped density tester, Hausner ratio, and compressibility.

Evaluation of tablet

Tablets were evaluated the variety of size and weight, hardness test using a Monsanto hardness tester, friability

test using a friability tester.

Determination of metformin HCl in tablet

An amount of metformin HCl tablet that equivalent to 100 mg metformin HCl was diluted in methanol. The solution was sonicated and filtered using a Whatmann filter paper. The absorbance of solution was measured using spectrophotometry UV at wavelength 237.40 nm. The concentration of sample was calculated using a regression equation which was determined prior to the measurement.

Determination floating lag time and floating time

Tablet was placed in a beaker glass containing 250 mL of 0.1N HCl pH 1.2. The floating lag time is determined by the time in which the tablet arise to the surface and float. The duration of the tablet floats is known as floating time.

Drug release study

Drug release test was performed using a dissolution tester using type 2 (Hanson research SR08, USA) with a speed of 100 rpm in 900 mL of 0.1N HCl (pH 1.2) as the medium. The temperature was maintained at 37±0.5 °C. Sample was pipetted in 5, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480, minutes. Samples were analyzed using spectrophotometry UV as described previously in determination of metformin HCl. Each formula tablet was done in triplicate (n = 3).

RESULTS AND DISCUSSION

Granules formed from each formula were tested in accordance with general granule testing. The evaluations performed for granules were moisture content, angle of repose, bulk and tapped density, Hausner ratio, and compressibility. The results are shown in [Table 2](#). These results were compared to the requirements in the literature. The moisture content, angle of repose, Hausner

Table 2. Evaluation of granules.

Parameters	F1	F2	F3
Moisture content (%)	4.51 ± 0.23	3.81 ± 0.13	4.35 ± 0.05
Angle of repose (°)	22.43 ± 0.76	29.36 ± 0.39	23.76 ± 0.63
Bulk density (g/mL)	0.42 ± 0.01	0.25 ± 0.01	0.36 ± 0.02
Tapped density (g/mL)	0.49 ± 0.01	0.28 ± 0.01	0.41 ± 0.01
Hausner ratio	1.16 ± 0.01	1.13 ± 0.01	1.15 ± 0.02
Compressibility (%)	16.49 ± 0.31	12.66 ± 1.17	15.06 ± 2.24

Table 3. Tablet evaluations

Evaluations	Formula		
	F1	F2	F3
Average weight (mg)	502.7 ± 2.02	498.1 ± 1.91	498.7 ± 1.17
Average diameter (mm)	13 ± 00	13 ± 00	13 ± 00
Hardness (kg/cm ²)	18.4 ± 0.52	4.4 ± 0.52	16.1 ± 0.57
Friability (%)	0.03	0.32	0.06
Drug content (%)	96.86	96.51	98.92

ratio and compressibility in all granules formula met the requirement.

The granules were then mixed with talc and magnesium stearate to be compacted into tablets. Furthermore the tablets were evaluated the quality which include weight uniformity, size uniformity, hardness test, friability test, and drug assay. The result of tablet evaluations can be seen in [Table 3](#). The result of average weight, size and diameter met the requirement of Indonesia Pharmacopeia III [\[10\]](#). In general, the criteria for good tablet hardness was 4-8 kg/cm². From the results of hardness test can be seen that tablets using HPC as a polymer in the formula had the value above the criteria of a good tablet hardness. It can be caused by the nature of HPC. The friability of tablet also met the requirement which is less than 0.8%. Moreover, the metformin HCl assay in tablets met the requirement, which the drug content is in a range 90 – 110 %.

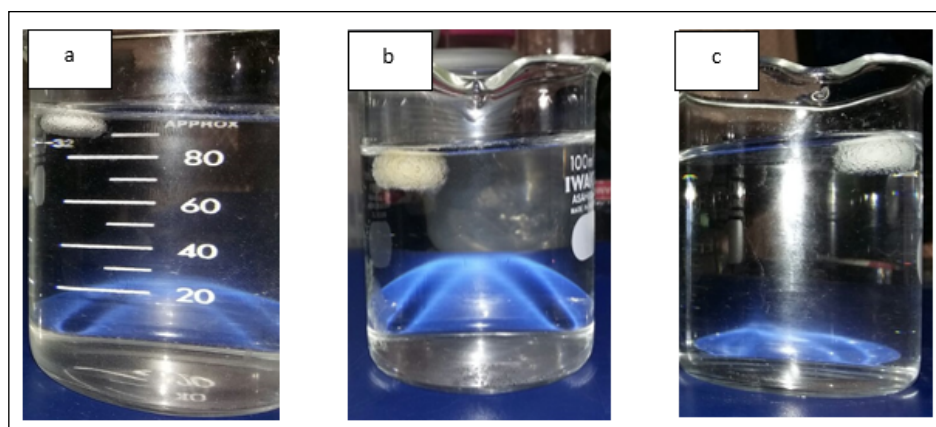
The floating tablet of metformin HCl is shown in [Figure 1](#) and result of floating lag time and floating time of each formula can be seen in [Table 4](#). The main requirement for preparation can float is the system must continue to have a specific gravity lower than the overall specific gravity of the specific contents of the stomach [\[11\]](#). When

Table 4. Floating lag time and floating time.

Formula	Floating lag time (minutes)	Floating time (hours)
F1	07.13	03.16
F2	05.27	>48
F3	14.05	>48

the density of tablets was less than 1, the tablet becomes floating [\[7\]](#). Differences floating lag time can be influenced by the molecular weight of each polymer. The smaller the value of the molecular weight of a polymer, the faster the tablet floats to the surface of the medium. Floating time is also affected by the solubility of the polymer used as a matrix. The longer the matrix is dissolved in the medium, the longer the matrix floats on the surface of the medium [\[12\]](#).

The result of dissolution test of metformin HCl tablet can be seen in [Figure 2](#). From these results it can be seen that the only formula 2, which uses a single K100M HPMC as the polymer, which can withstand the release of the drug, while the other formulas, the drug has been off entirely before 480 minutes. This happens because the HPMC K100M forming a barrier gel with high viscosity, which is more resistant to the diffusion process, so that the drug release from the matrix tablets to be slow [\[8\]](#). Tablets are formulated with HPC cannot resist the drug release. HPC is easily soluble in water temperatures below 38 °C, in hot water, insoluble and precipitates form a precipitate which expands at a temperature between 40-45 °C. HPC probably could not resist the drug release in dissolution conditions used [\[7\]](#). The polymers used in the formulation of a floating tablet dosage form should be able to form a barrier gel that is cohesive and should dissolve slowly, as an appropriate drug reservoir [\[13\]](#). F3, which used a

**Figure 1.** Floating tablet of Metformin HCl (a) F1, (b) F2 and (c) F3

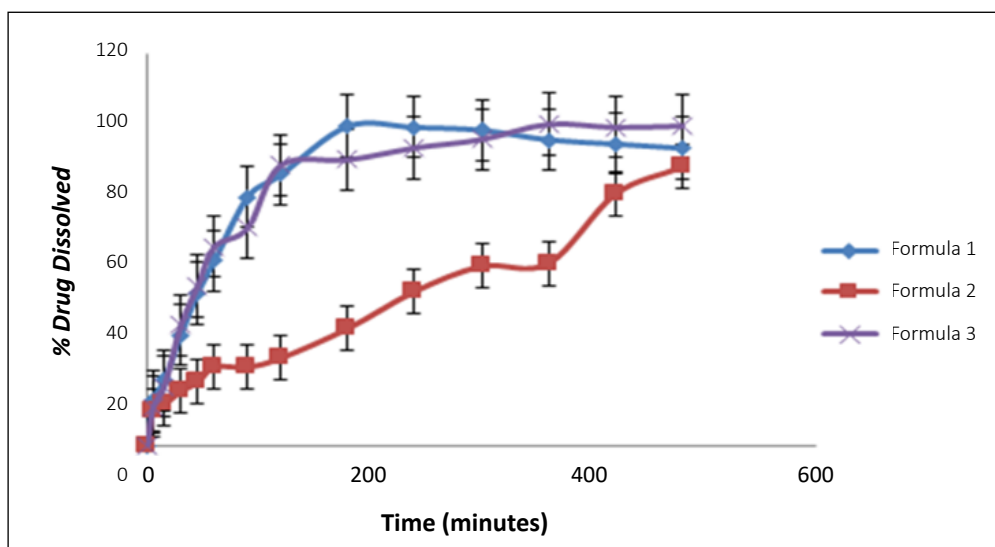


Figure 2. Dissolution profile of metformin HCl floating tablets.

combination of HPC and HPMC K100M as polymers, dissolved completely in 365 minutes. This can be caused by barrier gel that forms a lower viscosity when compared with formula 2, which used HPMC as the polymer. The decrease viscosity gel barrier due to reduced concentration of HPMC K100M were used, while the HPC does not form a gel barrier due to the acidic pH, HPC undergo hydrolysis which results in HPC solution viscosity [13,14]. This will cause erosion and dilution of the matrix tablet [15].

CONCLUSION

Based on the data in the research, it can be concluded that metformin HCl floating tablet used HPMC (F2) was the best formula, as the matrix can withstand drug release up to 8 hours.

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