

FORMULATION OF METFORMIN HYDROCHLORIDE FLOATING TABLET WITH HPMC K4M CR AND SODIUM BICARBONATE

By Agus Siswanto

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Abstract: Metformin HCl is an anti-hyperglycemic agent used in the treatment of non-insulin dependent diabetes mellitus. It has been reported that oral bioavailability of metformin HCl is 50-60 % due to its selective absorption from upper part of gastrointestinal tract. It has biological half-life of 1.7 hours, hence the development of floating drug delivery system is recommended in order to enhance the bioavailability. The aim of this study was to determine the optimum formula of metformin HCl floating tablet. The tablets were prepared by wet granulation technique, using HPMC K4M CR as hydrophilic polymer and sodium bicarbonate as a gas-generating agent. A 2² factorial design was applied to optimize the formula of metformin HCl floating tablet. The amounts of HPMC K4M CR (X₁) and sodium bicarbonate (X₂) were selected as independent variables. The optimum formula was determined based on numeric method with floating lag time, total floating time, and the drug dissolution for 1, 3, 10 hours as independent variables. The optimum formula was shown by the greatest desirability value (0.672) with the compositions of 179.38 mg HPMC K4M CR and 37.5 mg sodium bicarbonate.

Keywords: floating tablet of metformin HCl, HPMC K4M CR, sodium bicarbonate

INTRODUCTION

Floating drug delivery system is a technology which is developed to solve physiological problems such as unpredictable gastric emptying time and short gastric residence time. Metformin HCl is one of biguanides which is a widely used antihyperglycemic drug. Usually, metformin has a half-life of about 2 hours, and taken in three divided doses with meals per day. The characteristics of pharmacokinetics of metformin makes fluctuation of its plasma concentration very large and the compliance of patients for administration is poor. It has been reported that oral bioavailability of metformin HCl is 50-60 % due to its selective absorption from upper part of gastrointestinal tract. It has biological half-life of 1.7 hours, hence the development of floating drug delivery system is recommended in order to enhance the bioavailability.

Metformin HCl were formulated as floating tablet dosage form using effervescent system (sodium bicarbonate) in combination with hydrophilic matrix (HPMC K4M CR). HPMC has low density and, thus, floating in water medium. Meanwhile, sodium bicarbonate produce carbon dioxide (CO₂) when it reacts with acidic medium.

The aim of this study was to obtain the optimized floating tablet formulation of metformin in combination with Methocel K4M CR and sodium bicarbonate, and Ethocel. A factorial design was adopted to optimize the formulation variables.

MATERIALS AND METHODS

Materials

Metformin HCl was obtained from PT Zenith Indonesia, sodium bicarbonate was obtained from Tosoh Corporation (Tokyo, Japan), and HPMC K4M CR was obtained from Colorcon Asia Pvt. Ltd. Hydrochloric acid and sodium chloride (analytical grade) were purchased from Merck (Darmstadt, Germany). All other chemicals were used of pharmaceutical grade.

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Methods

9. Factorial design

In this design, 2 factors were evaluated, each at 2 levels; experimental trials were performed at all 4 runs (table 1). The percentage of HPMC K4M CR (X_1) and sodium bicarbonate (X_2) were selected as independent variables. The flow rate of tablet mass, floating lag time ($F_{lag\ time}$), total floating time, and the drug dissolution for 1, 3, 10 hours were selected as independent variables. The resulting data were fitted into Design Expert 7.1.5 software.

15. Preparation of metformin HCl floating tablet

Tablets were prepared by wet granulation method. The drug was mixed with all the ingredients except magnesium stearate and sodium bicarbonate. Required quantity of ethanolic PVP K30 was added as a granulating agent to make a coherent mass. The coherent mass was passed through sieve no 12 mesh and the granules were then dried in an oven at a temperature of 50°C for 90 minutes. The dried granules were passed through sieve no 14 mesh, mixed with sodium bicarbonate and magnesium stearate in a cube mixer at 50 rpm for 2 minutes. The tablet compression process used single punch tablet machine.

In-vitro buoyancy studies

Tablet immersed in beaker containing 100 mL of simulated gastric fluid without pepsin (SGF, pH 1.2).

8. In-vitro dissolution studies

Aliquots of 5 ml were taken out at intervals of 15, 30, 45, 60, 120, 180, 240, 360, 480, and 600 minutes. Exactly 5 ml of fresh SGF was added to the dissolution vessel after each withdrawal to maintain a constant volume. The samples were analyzed by UV-Vis spectrophotometer at 232 nm.

RESULTS AND DISCUSSION

In-vitro buoyancy studies

Based on the equation (1), sodium bicarbonate (X_1) effect of reducing the floating lag time. At the time of contact with the dissolution medium, effervescent reaction occurs between the sodium bicarbonate with the HCl in the simulated gastric fluid generate CO_2 . The greater the number of sodium bicarbonate, the CO_2 gas produced will also be more and more so the lower the specific gravity of the tablet and the tablet will more quickly lead float in the medium. Meanwhile, total floating time varies according to the composition of the tablet excipients in a tablet. Tablets with HPMC K4M CR in high levels has a total floating time > 12 hours. Equation (2) shows that the factor of HPMC K4M CR (X_2) has positive effect increasing the total floating time. HPMC K4M CR is a hydrophilic matrix with a good gelling agent. At the time of contact with the dissolution medium, HPMC K4M CR swells to form a thick gel layer. This gel layer serves to maintain the integrity of the dosage form. Figure 1 shows that the greater the amount of HPMC K4M CR, the greater the total floating time.

In-vitro dissolution studies

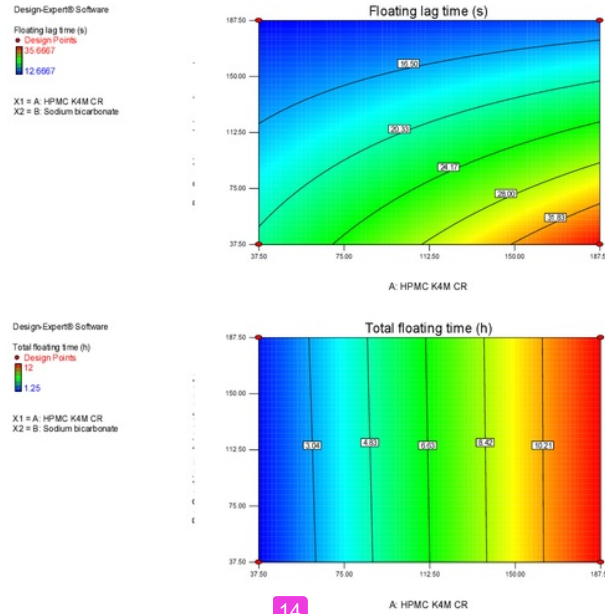
The dissolution profiles of metformin HCl floating tablet presented in Figure 2. The tablet of runs 1 and 3 which contain high levels of HPMC K4M CR showed a slow dissolution profile. Meanwhile, the tablet of runs 2 and 4 show the drug release soon because of the high sodium bicarbonate in the dosage form. Equation (3), (4) and (5) showed that sodium bicarbonate has dominant influence in increasing the release of metformin HCl. The coefficient of sodium bicarbonate in the equation indicates a negative value which is smaller than the coefficient of HPMC K4M CR. Sodium bicarbonate interaction with simulated gastric fluid medium (acidic) will generate CO_2 gas trapped in the tablet matrix and have a tendency to come out so as to form pores in the tablet. Metformin HCl dissolution can occur through the pores in the tablet. Therefore, the greater the

amount of sodium bicarbonate in tablet then CO₂ gas and pore formed in the tablet the more so that the amount of dissolved metformin HCl were also greater (figure 3).

$$C_{60} (\%) = 47.79 - 26.84 X_1 - 3.25 X_2 + 0.23 X_1 X_2 \quad (3)$$

$$C_{180} (\%) = 57.53 - 22.46 X_1 - 5.33 X_2 - 2.42 X_1 X_2 \quad (4)$$

$$C_{600} (\%) = 81.23 - 0.59 X_1 - 2.64 X_2 + 0.34 X_1 X_2 \quad (5)$$



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Figure 1. Contour plot for floating lag time and total floating time

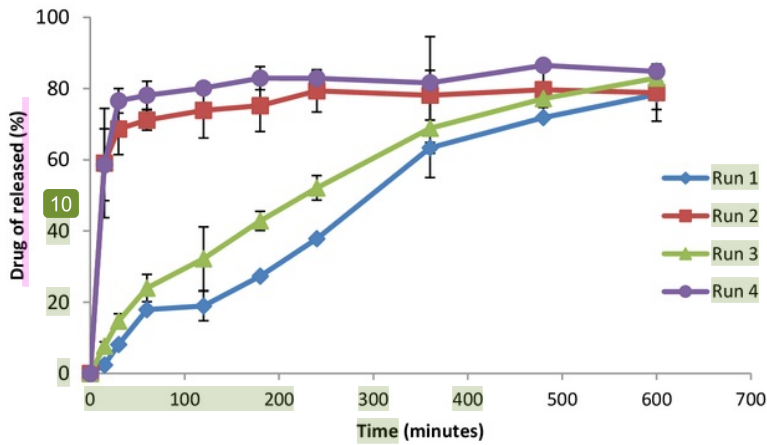


Figure 2. Dissolution profil of metformin HCl floating tablet (n=3)

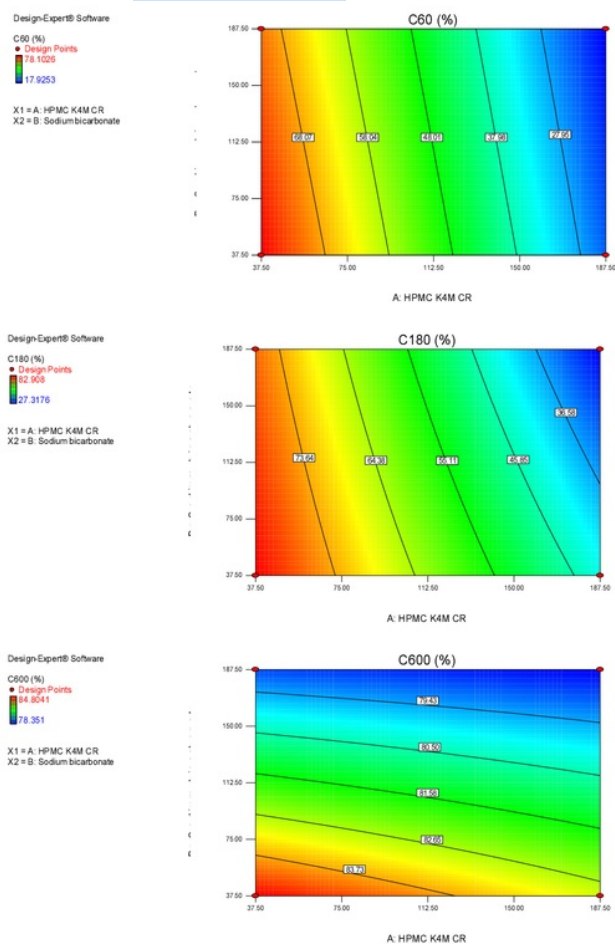


Figure 3. Contour plot for C_{60} , C_{180} , and C_{600}

Determination of the optimum formula of floating tablet

A 2^2 factorial design was constructed to study the effects of the amount of HPMC K4M CR and sodium bicarbonate on the characteristics of metformin HCl floating tablets. The optimum formula was determined based on floating lag time < 180 s, total floating time > 10 jam, C_{60} = 20-40 %, C_{180} = 45-65 %, dan C_{600} > 80 %. Based on SLD optimization using numerical method in Design Expert 7.1.5 version, the optimum formula of metformin floating tablet was obtained with the composition of HPMC K4M CR and sodium bicarbonate. The optimum formula was shown by the greatest desirability value (0.621) in figure 4 with the compositions of 179.38 mg HPMC K4M CR and 37.5 mg sodium bicarbonate.

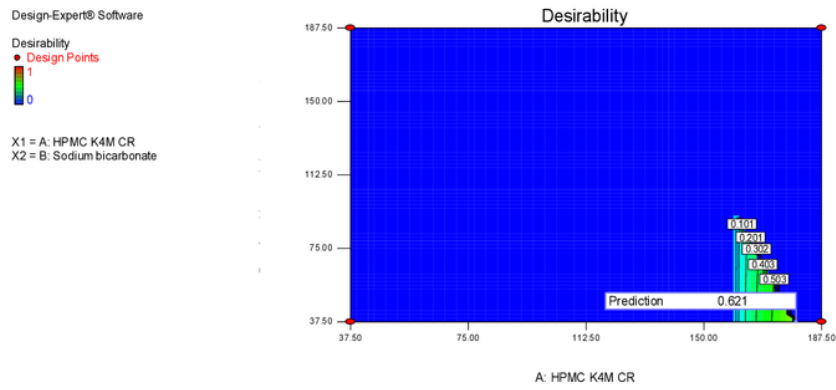


Figure 4. Superimposed of contour plot for optimum formula with the highest desirability of 0.621

CONCLUSION

The result of the equation from $F_{lag\ time}$, total floating time, C_{60} , C_{180} , and C_{600} analysis using Design Expert 7.1.5 program showed that the optimum formula of metformin HCl floating tablet was 179.38 mg HPMC K4M CR and 37.50 mg sodium bicarbonate.

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