ORIGINAL ARTICLE

Formulation and Evaluation of Low Floating Lag Time Metformin Hydrochloride 500 mg Sustained Release Floating Tablet

Thao Nguyen Ngoc Nha[1], Toan Pham Duy[2], Mai Thi Ngoc[1]

[1]Department of Pharmaceutics, Faculty of Pharmacy, Can Tho University of Medicine and Pharmacy, Can Tho 92000, Vietnam, [2]Department of Pharmaceutical Technology, Faculty of Pharmacy, Can Tho University of Medicine and Pharmacy, Can Tho 92000, Vietnam

Abstract

Introduction: Diabetes mellitus (DM) is a worldwide disease with high mortality rate. Metformin hydrochloride has been used as the first-line drug for the treatment of DM Type 2. However, the high water solubility and short half-life lessen the potential effectiveness of using conventional metformin tablet. Floating tablet is an attractive pharmaceutical formula which can make the drugs staying with an adequate time in the absorption part of the gastrointestinal tract (i.e., the stomach), and as a consequence, increase the oral bioavailability of drugs. **Aim:** To develop and evaluate novel metformin sustained release floating systems using combinations of polymers for the prolong release and absorption purposes. **Materials and Methods:** All of the ingredients used were qualified as pharmaceutical ingredients based on USP 36. The wet granulation and tableting method were used to formulate the systems. Quantitation method was developed and validated using ultraviolet (UV)-visible spectrophotometry method at the wavelength of 232.8 nm. Dissolution profile and *in vitro* equivalence test was done using paddle apparatus, 100 rpm/min, in 900 ml of phosphate buffer pH 1.2, at 37°C ± 0.5°C. Floating test was observed in simulated gastric condition. Physical tests (hardness, friability), weight uniformity, qualification, and quantification were performed followed USP 34 and BP 2013. Products' kinetics profiles were also determined. **Results and Discussion:** We found that the combination of HPMC K15 and HPMC K100 with the ratio of 90:260 w/w, and the amount of $NaHCO_3$ and citric acid at 65 mg and 13 mg, respectively, in the formulation could significantly lower the floating lag time to 1 min, and enhance the similarity value f_2 to 79.78 compared to the reference drug Glucophage XR®. The systems' kinetics followed the Higuchi model. Furthermore, the systems passed all analytical tests such as hardness, friability, weight uniformity, infrared qualification, and UV quantification. **Conclusion:** The combination of HPMC K15 and HPMC K100 can benefit the floating sustained release tablet formulation. These studies suggest that metformin may contribute for delivery system in the future.

Key words: Floating lag time, floating tablet, HPMC, metformin hydrochloride, sustained release

INTRODUCTION

Diabetes mellitus (DM), long considered a disease of minor significance to world health, is now taking its place as one of the main threats to human health in the 21st century.[1,2] Diabetes is now one of the most common non-communicable diseases globally.[3] It is the fourth or fifth leading cause of death in most high-income countries, and there is substantial evidence that it is epidemic in many low- and middle-income countries. Complications from diabetes such as coronary artery and peripheral vascular disease, stroke, diabetic neuropathy, amputations, renal failure and blindness are resulting in increasing disability, reduced life expectancy and enormous health costs for virtually every society. DM is a heterogeneous group of disorders characterized by high blood glucose levels.[4] Although the pancreatic b cell and its

Address for correspondence:
Toan Pham Duy, Department of Pharmaceutical Technology, Faculty of Pharmacy, Can Tho University of Medicine and Pharmacy, Can Tho 92000, Vietnam.
E-mail: pdtoan@ctump.edu.vn

Received: 31-07-2016
Revised: 08-10-2016
Accepted: 17-10-2016

secretory product insulin are central in the pathophysiology of diabetes, the pathogenic mechanisms by which hyperglycemia arises differ widely. Several distinct forms of diabetes exist which are caused by a complex interaction of genetics, environmental factors, and lifestyle choices. Some forms are characterized by absolute insulin deficiency or a genetic defect leading to defective insulin secretion, while other forms share insulin resistance as their underlying etiology. Although insulin replacement is the only treatment for diabetes Type 1, Type 2 diabetes can be monitored using oral medications. Among them, metformin hydrochloride (MH, brand-name Glucophage®, marketed by Merck) is considered the first-line drug for the treatment of Type 2 diabetes, especially for obese patients, based on its safety and beneficial effects on weight and cardiovascular mortality.[5,6] This highly water-soluble biguanide drug has a low oral bioavailability of 50-60% in fasting state and short half-life of about 6.2 h.[7] Because of that, MH has been developed in the form of extended-release drug (i.e., Glucophage XR®, Merck; Glumetza XR®, Depomed; Gluformin XL®, Abbott). Recently, many efforts have been made to overcome the disadvantages of MH. One approach is using sustained release floating tablet to prolong the residing time in the stomach of MH, thus making it more absorbable into the bloodstream.[8] Some authors have already published their works about this.[9-13] Nevertheless, no best formulation was reported so far. One concern should be noted for this kind of formulation is the optimization ratio between the floating lag time (FLT) (i.e. the time needed for the tablet to emerge on the surface of the medium, FLT), the total floating time (TFT), and the dissolution rate. A low FLT usually correlates with fast dissolution rate.[14] The FLT value of most studies was higher than 2 min, which is not an optimal condition for floating formulation [Table 1].[15] Hence, further researches are in need.

In this work, we aim to develop a sustained release floating tablet of MH 500 mg with low FLT; optimize the formulations; evaluate the product by hardness, friability, dissolution test, qualification, and quantification; determine the *in vitro* equivalence with Glucophage XR®.

MATERIALS AND METHODS

Materials

MH was imported from Norway; MH reference was purchased at Institute of Drug Quality Control, Ho Chi Minh City, Vietnam, with purity of 99.54%. Glucophage XR® 500 mg tablets, batch number T0147143, were acquired from Kim Loi drugstore, Can Tho, Vietnam. Sustained release excipients included HPMC K100, HPMC K15, NaCMC, and xanthan gum were bought from the USA. Gas generating excipients such as sodium bicarbonate ($NaHCO_3$) and citric acid were obtained from China. Binder PVP K30, diluent Flocel®, lubricant and glidant magnesium stearate, aerosil, were imported from India. De-ionized water and absolute ethanol were bought from Vietnam. All of the ingredients used were qualified as pharmaceutical ingredients based on USP 36.

Tablet formulation

Nineteen formulas with different amounts of sustained release excipients and gas generating excipients were manufactured using wet granulation method [Table 2] at the Department of Pharmaceutical Technology, Faculty of Pharmacy, Can Tho University of Medicine and Pharmacy, Can Tho, Vietnam. Briefly, MH, diluent, sustained release excipients, and gas generating excipients were mixed and blended with the binder solution. Granulation took place after that with Erweka AR-402 (Germany) machine, and wet granules were dried and mixed with lubricant and glidant. Then, the mixture was tableted with Rimek Mini Press-I (India) to get 995 mg tablets.

Quantification method validation

MH concentration in tablet and dissolution test was determined by ultraviolet-visible (UV-Vis) spectrophotometry method at the wavelength of 232.8 nm, using Hitachi U-2000 Spectrophotometer (Japan). The method was developed and validated according to International Council for Harmonization guidelines[16,17] with the parameters, namely specificity, linearity, accuracy, and precision.

Dissolution profile and *in vitro* equivalence test

Glucophage XR® tablet and manufactured formulas were tested dissolution profiles with Pharmatest PT-DT8S Tester (Germany) using paddle apparatus, 100 rpm/min, in 900 ml of phosphate buffer pH 1.2, at 37°C ± 0.5°C. 5 ml of each sample was withdrawn at each time interval of 1, 2, 6, and 10 h, filtered with 0.45 µm membranes, diluted

Table 1: Summary of some MH sustained release floating tablet studies

Sustained release excipient	Gas generating excipient	Best FLT (min)	References
Carbopol 934P	Sodium bicarbonate	2.5	[9]
HPMC K100, gellan gum	Sodium bicarbonate	5.0	[10]
HPMC K4M, ethyl cellulose	Sodium bicarbonate	9.6	[11]
HPMC K100M, eudragit RL100	Sodium bicarbonate	5.2	[12]

MH: Metformin hydrochloride

Table 2: Formulas of MH sustained release floating tablet

S.No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
MH (mg)	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500
HPMC K15 (mg)	270	270	270	270	270	270	350				50	70	90	260	280	300	90	90	90
HPMC K100 (mg)	30	30	30	30	30	30		350			300	280	260	90	70	50	260	260	260
Xanthan gum (mg)									350										
NaCMC (mg)										350									
Flocel (mg)	118	106	94	82	70	130	20	20	20	20	20	20	20	20	20	20	14	8	2
$NaHCO_3$ (mg)	10	20	30	40	50	0	50	50	50	50	50	50	50	50	50	50	55	60	65
Citric acid (mg)	2	4	6	8	10	0	10	10	10	10	10	10	10	10	10	10	11	12	13
PVP K30 (mg)	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Magnesium stearate (mg)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Aerosil (mg)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Total (mg)	995	995	995	995	995	995	995	995	995	995	995	995	995	995	995	995	995	995	995

MH: Metformin hydrochloride

10 times, and determined the drug concentration based on validated method. All tests were done in triplicate. *In vitro* equivalence test was done with the average value from 12 tablets' dissolution profiles with Glucophage XR®. The similarity factor f_2 was used to justify the equivalence with an acceptable value of more than 50. The formula to calculate f_2 is as follow:

$$f_2 = 50 \times log\{[1 + (1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2]^{(-0.5)} \times 100\}$$

Where: n is the number of time point (4 in this case); R_t, T_t are the average dissolved percentages of the reference and the test tablets, respectively, at each time point.

Floating test

FLT and TFT were determined based on observation. Manufactured tablets were immersed in simulated gastric condition at pH 1.2 with the temperature kept constant at 37°C ± 0.5°C. The time needed for the tablet to float at the surface of the medium and to completely deform are FLT and TFT, respectively.[18] Each experiment was performed in triplicate.

Physical test

About 20 tablet's hardness and friability were measured by Erweka hardness tester and Erweka friability tester (Germany), respectively. The hardness was determined by calculating the average crushing forces after three independent tests. For the friability, the speed of 25 rpm/min for 4 min was run, and the value was calculated as follow:

$$F = (m - m')/m \times 100\%$$

Where: m, m' are the total weight of 20 tablets before and after experiments, respectively.

Weight uniformity test

The test was done according to USP 34 instruction.[19] Briefly, 20 units were weighed independently, and the average value was calculated. The weight range limit was ±5% of the average content. To satisfy the test, there should be no more than two units that have the weight outside of the range, and no unit has the weight outside of the range of ±10% of the average value.

Qualification

The tablets were qualified by infrared (IR) method based on BP 2013.[20] Crushed tablet powder equivalent to 20 mg MH was weighed, extracted with 20 ml ethanol, evaporated the solvent, and mixed with KBr. The mixture was then pressed into a pellet and measured IR under fourier transform infrared Bruker Alpha T spectrophotometer – Bruker (USA).

Quantification

Twenty tablets were crushed and weighed an amount equivalent to approximately 0.1 g of MH. The powder was extracted with 70 mL de-ionized water in 15 min, filtered and diluted 100 times with de-ionized water. This solution was measured UV absorption at the wavelength of 232.8 nm. The amount of MH in the tablet was calculated based on the can libration curve of the validated quantification method and expressed in percentage.

Kinetics of drug release

Three kinetic models for *in vitro* drug release included zero order, first order, and Higuchi, were used to identify the characteristics of formulas. The equations are as follow:[21]

Zero order: $C = k_0 t$

First order: $\ln C = (-k)_1 t + \ln (C_0)$

Higuchi: $C = k_H t^{(1/2)}$

Where C, C_0 is the drug concentration at time t and 0, respectively, and k_0, k_1, k_H are rate constants.

Statistical analysis

Analysis of variance (ANOVA) in Microsoft Excel 2007 was used to analyze the data. Any difference was confirmed with the P value of less than 0.01.

RESULTS AND DISCUSSION

Quantification method validation

The UV-Vis spectrophotometry method has been used for quantification, and dissolution studies were developed and validated. The linearity with a concentration range of 0.6-12.0 µg/ml was confirmed via calibration curve [Figure 1]. Using ANOVA test (data not shown), the correlation between absorbance value (y) and MH concentration (x) follows equation y = 0.0783x with coefficient of determination R^2 at 0.9998, which is suitable for use. The specificity of the method was validated at the wavelength of 232.8 nm without any interference of excipients (data not shown). The standard method was repeatable with relative standard deviation percentage value of 0.69% (<2%). The accuracy was tested by adding a standard solution of MH at concentrations of 80%, 100%, and 120% compared to the estimated amount of MH in manufactured tablets into the test samples. The average recovery rate of the samples was 99.96%, which was within the acceptable range of 95-105%. Overall, the quantification method was validated for further use.

Tablet formulation

MH is freely soluble in water,[22,23] hence, to prolong the release time, excipients with high viscosity parameter as well as fast swelling time should be utilized. We have investigated 4 of such materials such as HPMC K15, HPMC K100, xanthan gum, and NaCMC. In addition, we aim to make low FLT floating tablet, so gas generating excipients such as $NaHCO_3$ and citric acid were used. The polymer matrix may help in increasing the TFT by entrapping the gas inside the systems.

Among many available tableting methods such as direct compression, dry granulation, and wet granulation, the wet granulation method was chosen. The reasons were to avoid the low compressibility, low flowability, and high percentage in formulas (>50%) of MH.[24]

The nineteen formulas were determined the dissolution profiles, FLT, TFT, and f_2 value compared to Glucophage XR®. The results are shown in Table 3. The six formulas from 1 to 6 were made to investigated the effects of gas generating agents (i.e., $NaHCO_3$ and citric acid) on the FLT, TFT, and dissolution profile. We found that the higher amount of these agents, the lower the FLT and the faster the dissolution time. These results are similar to that of Bhoi *et al*.,[25] and Salve,[26] and may be explained by the fast hydration of sustained matrix by pore increment due to the gas generating agents. For formula 6, the tablet could not float because of the absence of gas generating agents; this phenomenon proves

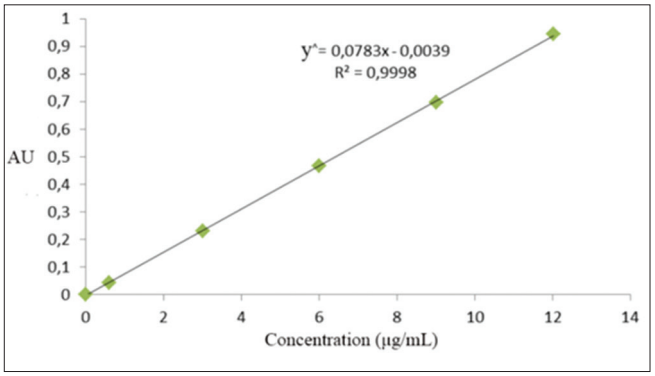

Figure 1: Calibration curve for metformin hydrochloride quantification method. AU: Absorbance unit

Table 3: Dissolution profiles, FLT, TFT, and f_2 value compared to Glucophage XR® of MH sustained release floating tablets

Dissolution percentage (%)				FLT (min)	TFT (h)	f_2
1 h	2 h	6 h	10 h			
29.74	45.07	76.74	90.23	35	>10	58.04
34.93	44.94	76.84	92.75	30	>10	53.74
36.41	50.96	83.13	93.80	23	>10	45.26
37.80	52.86	84.65	98.79	8	>10	41.81
40.45	56.87	85.83	100.60	6	>10	38.55
25.21	41.29	62.56	81.07	N/A*	N/A*	69.77
26.84	37.49	74.67	88.43	8	>10	67.89
23.34	36.35	71.55	81.12	6	>10	68.48
34.02	49.06	90.18	99.47	16	>10	40.92
27.27	45.31	95.43	100.76	11	>10	39.04
24.12	34.52	62.37	84.32	5	>10	74.83
23.56	33.56	68.34	89.53	2	>10	75.63
26.48	33.35	69.02	88.74	4	>10	76.21
28.93	36.77	59.34	83.73	6	>10	68.06
27.34	35.22	58.67	89.23	6	>10	67.71
29.89	39.58	57.23	90.05	7	>10	63.29
27.73	35.53	69.45	84.32	3	>10	77.87
28.45	36.89	69.23	83.89	2	>10	77.85
28.23	37.56	69.99	85.69	1	>10	79.78

FLT: Floating lag time, TFT: Total floating time; N/A*: Not available (un-floatable tablets), MH: Metformin hydrochloride

that these agents are necessary in floating tablets. The next step with four formulas from 7 to 10 was done to determine the effect of different kinds of polymer on the FLT and drug dissolution profiles. From the results, we may conclude that the prolong release effects decrease from HPMC K100, HPMC K15, xanthan gum, to NaCMC. This may be due to the rapid swelling time of HPMC[27,28] and the high viscosity of HPMC K100, which helps in the sustained release of drugs. Furthermore, polymers such as xanthan gum and NaCMC could be significantly augmented the FLT of the products (i.e., from 2 min to more than 10 min). Since HPMC K15 and HPMC K100 formulas (no. 7 and 8) had high f_2 values at 67.89 and 68.48, respectively, they were selected to be further modified. The purpose of making six formulas from 11 to 16 was to inspect the outcome of HPMC K100 and HPMC K15 combination. The highest f_2 value at 76.21 was observed in formula 13, which had the amount of HPMC K100 and HPMC K15 at 260 mg and 90 mg, accordingly. The previous studies have also demonstrated that the combination of HPMC K100 and HPMC K15 may control the drug release in a satisfying manner.[29,30] The last three formulas from 17 to 19 were manufactured to further reduce the FLT to the acceptable value (i.e., <2 min). The best formula (no. 19) was found with the amount of $NaHCO_3$ and citric acid of 65 mg and 13 mg, respectively. Formula 19 had highest f_2 value at 79.78, lowest FLT at 1 min, and TFT at >10 h, so it passed all parameters. To the best of our knowledge, the FLT of 1 min is considered the best compared to previous studies.[9-12] Therefore, formula 19 was used for further studies.

Tablet characteristics

The manufactured tablet was white, oval biconvex shape with the size of 9.5 mm × 19.5 mm [Figure 2]. Tablet's characteristics such as hardness, friability, weight uniformity, qualification, and quantification are summarized in Table 4 and pass the requirements.

Kinetics of drug release

After preliminary studies (data not shown), the drug release profile of Glucophage XR® was found to be followed the Higuchi model [Figure 3]. Thus, Higuchi model was applied for the determination of formulas' kinetics. The coefficient of determination R^2 of 19 formulas is shown in Table 5. From the results, we can conclude that all formulas' kinetics profiles reflect the Higuchi model.

In vitro equivalence test

The equivalence test [Figure 4] confirms the similarity in dissolution profile between our manufactured tablets (formula 19) and the marketed Glucophage XR® with acceptable f_2 value of 79.78 (i.e., more than 50).

CONCLUSION

In this study, we presented the novel formulation of MH 500 mg sustained release floating tablet with not only high *in vitro* dissolution equivalence compared to marketed Glucophage XR® (f_2 = 79.78) but also low FLT (1 min) and high TFT (>10 h). Furthermore, we also developed

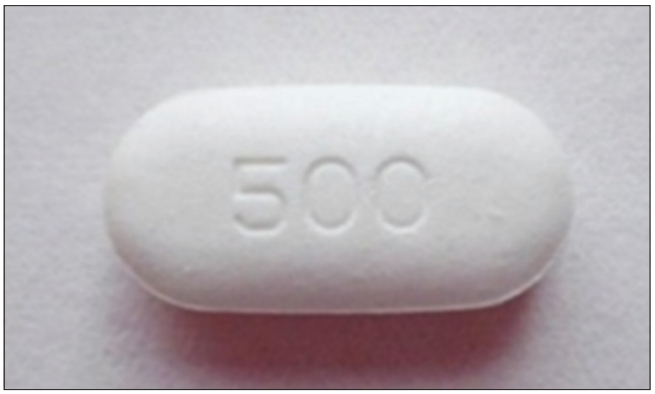

Figure 2: Manufactured metformin hydrochloride sustained release floating tablet

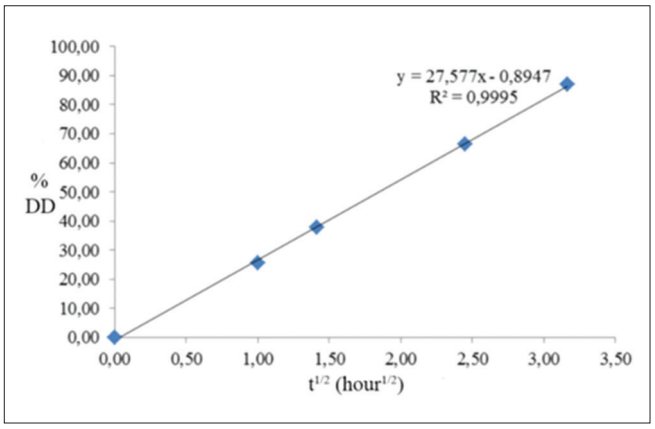

Figure 3: Higuchi model of Glucophage XR® dissolution profile. DD: Drug dissolved

Table 4: MH sustained release floating tablet's characteristics

Parameter	Requirement range	Results	Conclusion
Hardness	40-50 N	48.95 N	Pass
Friability (%)	<1.5	0.76	Pass
Weight uniformity	946.68-1046.33 mg	All weights were within the range	Pass
Qualification (%)	>95 similarity in IR	98 similarity	Pass
Quantification (%)	95-105	99.78	Pass

MH: Metformin hydrochloride; IR: Infrared

Table 5: Coefficient of determination (R^2) of manufactured formulas' drug dissolution followed Higuchi model

S. No.	R^2
1	0.9930
2	0.9713
3	0.9856
4	0.9949
5	0.9798
6	0.9946
7	0.9980
8	0.9996
9	0.9843
10	0.9704
11	0.9981
12	0.9977
13	0.9968
14	0.9956
15	0.9994
16	0.9983
17	0.9983
18	0.9986
19	0.9974
Glucophage XR®	0.9995

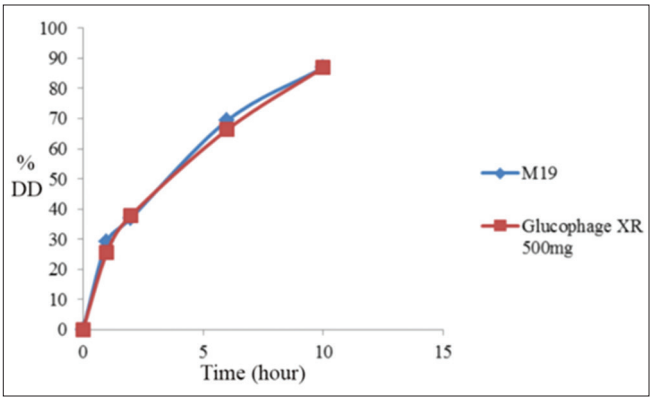

Figure 4: *In vitro* equivalence test of formula 19 (M19) and Glucophage XR® with an f_2 value of 79.78. DD: Drug dissolved

and validated the quantification method for MH, as well as investigated the relationship between excipients and tablet's properties. Finally, it may be concluded that using combination of HPMC K15 and HPMC K100 can benefit the floating sustained release tablet formulation of MH in the treatment of DM. Explore the possibility of collaborative with pharmaceutical industries and develop a new therapeutic molecular mechanism of MH in improving diabetic.

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Source of Support: Nil. **Conflict of Interest:** None declared.