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Formulation of Extended-Release Gliclazide Tablet Using a Mathematical Model for Estimation of Hypromellose

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***Abstract*—**Formulation of gliclazide in the form of extended-release tablet in 30 and 60 mg dosage forms was performed using hypromellose (HPMC K4M) as a retarding agent. Drug-release profiles were investigated in comparison with references Diamicron MR 30 and 60 mg tablets. The effect of size of powder particles, the amount of hypromellose in formulation, hardness of tablets, and also the effect of halving the tablets were investigated on drug release profile. A mathematical model which describes hypromellose behavior in initial times of drug release was proposed for the estimation of hypromellose content in modified-release gliclazide 60 mg tablet. This model is based on erosion of hypromellose in dissolution media. The model is applicable to describe release profiles of insoluble drugs. Therefore, by using dissolved amount of drug in initial times of dissolution and the model, the amount of hypromellose in formulation can be predictable. The model was used to predict the HPMC K4M content in modified-release gliclazide 30 mg and extended-release quetiapine 200 mg tablets.

***Keywords*—**Hypromellose, gliclazide, drug release, modified-release tablet, mathematical model.

I. Introduction

THE reduction of frequency and/or increasing the effectiveness of the drug is the main goal of controlled delivery systems [1]. In these systems, drug release from the dosage form is controlled mainly by the properties of polymer and drug used in the preparations [2].

The commonly used polymers for controlled release are hydroxypropylmethylcellulose or hypromellose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), ethylcellulose (EC), methylcellulose (MC), carboxymethylcellulose (CMC), polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG). These polymers, which swell in aqueous medium, are often used for the preparation of controlled release dosage forms. These are highlighted with the presence of a solvent front, the potential for unlimited swelling, and the combined controlling mechanism of diffusion and erosion as being the distinguishing feature of HM devices [1].

Cellulose ethers are found to accommodate a large percentage of drugs and are easy to use in tablets. They are also very stable over a wide range of conditions. In the presence of strong acid, water, and heat, a cellulose ether polymer will be degraded by chain scission causing a loss of average molecular weight or viscosity. HPMC is often used to prepare matrix of sustain release (SR) tablets because the polymer is non-toxic and easy-to-handle and it does not require any special manufacturing technology [3]-[6]. It was evident that HPMC 2208 (methocel K4M premium) and carboxy vinyl polymers can release drugs for longer time by quickly forming a gel layer [1].

Tahara et al. described overall mechanism behind matrix SR tablets prepared with hydroxypropyl methylcellulose 2910 [7]. Many factors affecting the release of drugs from cellulose matrices have been investigated [8]. The particle size of polymer is a key parameter because it affects hydration rate and thus the rate of gel formation and drug release. Another important factor is viscosity of the polymers, which is higher as the molecular weight increases. If the viscosity of the polymer increases, the gel layer viscosity also increases, so that the gel layer becomes resistant to dilution and erosion [1]. The drug release rate is then slower. Like viscosity of the polymer, the concentration of polymer can also affect the strength of the gel. The increase in polymer concentration can result in stronger diffusion layer that is resistant to diffusion or erosion. Ultimately, this will slow drug release [1].

Size and shape (e.g. tablet or capsule) of matrix are the other factors. For instance, smaller tablets will generally require higher polymer content. An increase in tablet size can result in slower drug release due to a smaller surface to volume ratio and a smaller amount of initial gel formation [1].

In this work, we investigate whether making smaller particles of ready-to-press powder of modified-release gliclazide tablets can have an impact on drug release profile; the effect of hardness was investigated on drug release, also the drug release profile of half of a tablet of modified-release gliclazide 60 mg was investigated and compared with modified-release gliclazide 30 mg tablet and Diamicron MR 60 mg tablet as a reference tablet. The mathematical model was developed to investigate the behavior of HPMC in initial times of drug release profile of modified-release gliclazide 60 mg tablet. Estimation of HPMC amount in formulation will be feasible through the data of dissolved amount of drug in initial times and the proposed model. This model will give us a good estimation of HMPC amount in formulation and will reduce the experiments to optimize the content of HPMC in modified-release gliclazide tablets. Also, this model can be used in other formulations to predict HPMC amount. It was used to predict HPMC amount in extended-release quetiapine tablets and good estimation was achieved by the model.

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II. Experimental

A. Materials

KH_2PO_4, NaOH, and citric acid were purchased from Merck. Gliclazide from Shandong Keyuan Pharmaceutical Co. Ltd., Mannitol from Microlex, Anhydrous dibasic calcium phosphate from Tabriz petrochemical Co., HPMC (Benecel K100 LV Pharm) and HPMC (Benecel K4M Pharm) from Ashland (Belgium), trisodiumcitrate dihydrate from Behansar Co., colloidal anhydrous silica (Aerosil 200) from Evonik industries (Germany) and magnesium stearate from Behansar Co. were provided. Diamicron MR 30 mg and Diamicron MR 60 mg (Servier Company (France)) were provided and used as reference tablets. Mylan MR 30 mg (Mylan Company) was provided as a reference tablet. Lactose monohydrate from DFE Pharma and quetiapine fumarate was provided from Hetero Labs Limited. Extended-release Seroquel 200 mg (AstraZeneca) was purchased as a reference tablet.

B. Preparation of Matrix Tablets

1. Tablet Preparation

The ready-to-press powder of tablets was prepared by wet granulation method. The drug substance is kneaded with the internal phase (that contains the total amount of mannitol and anhydrous dibasic calcium phosphate and some of HPMC K4M) after passing through 40-mesh screen for 15 minutes. This first mixture is kneaded with binder solution (prepared by dissolving of HPMC K100 in purified water) and sodium citrate solution (prepared by dissolving of sodium citrate in purified water). The wet mass is dried in hot-air chamber at 50 °C, protected from light. The next step is passing the dried produced mass through oscillating granulator with 16- and 24-mesh screens. In the following step, the dry granular mass is mixed with the excipients of the external phase (the remaining of HPMC K100 and HPMC K4M, colloidal anhydrous silica) after passing through 40-mesh screen for 20 minutes. Then, magnesium stearate after passing through 80-mesh screen is added and mixed for an additional 5 minutes. After that, powder was compressed using a mini rotary press machine (Kambert Machinery Co. PVT. LTD. India) with 7 mm diameter concave punch for modified-release gliclazide 30 mg tablets and 9 mm diameter concave punch for modified-release gliclazide 60 mg tablets. Extended-release quetiapine 200 mg tablet was manufactured by the same method and using oblong punches with 16 mm length and 7 mm width.

2. Determination of Tablet Hardness and Thickness

The hardness of tablets was determined using hardness tester (Pharma Test PTB-311F, D-63512 Hainburg, Germany). The mean of the tablet hardness was calculated for ten tablets. The thickness of tablets was determined using a digital caliper (CE ISO 9001, Guanglu Electrical Co., LTD. China), and the results were expressed as mean values of ten determinations.

3. In vitro Drug Release Studies

An in-vitro release of gliclazide and quetiapine from tablets was studied using USP dissolution apparatus II and I (Pharma Test, PTW S600, Germany), respectively. 900 ml of phosphate buffer (pH 7.4), as the dissolution medium, was placed in the glass vessel, the apparatus assembled, and the dissolution medium equilibrated to 37±0.5 ºC. The rotation speed of paddle was 100 rpm. At predetermined time intervals, the dissolution medium was removed for determining the drug concentration, and fresh medium was replaced. The amount of drug released in the dissolution medium was measured using a double beam UV-Vis spectrophotometer (Cecil 9000 series, USA) by obtaining absorbance difference at the wavelengths of 226 nm and 290 nm and using calibration curve. The studies were carried out in six vessels. The cumulative percentage of drug release was calculated and plotted against time. Dissolution medium for quetiapine tablets was considered as 5 hours in citric acid buffer (pH 4.8) and 19 hours in phosphate buffer (pH 6.6). HPLC (Alliance, Waters) with C18 column (4.6 mm×15 cm, 5 µm particle size) was used to measure the drug release for extended-release quetiapine tablet.

III. Results

A. Investigation of Manufacturing of Modified-Release Gliclazide 30 mg Tablet

After making of modified-release gliclazide 30 mg granule (internal phase), the dried granule was passed through the oscillating granulator with 16-mesh screen and mixed with the remaining of excipients (external phase). Then, the compression was completed (HPMC content was considered 20% in formulation). The six modified-release tablets with an average hardness of 7.1 kp (kilopond) were selected for in vitro test study. Six tablets of Diamicron MR 30 were used as reference tablets. The dissolved amount of gliclazide tablet in dissolution medium was obtained at time intervals of 1h, 2h, 4h, 8h, 12h, and 16h using an appropriate calibration curve for gliclazide. Dissolution profiles of gliclazide and Diamicron tablets were compared using a similarity factor equation ($f2$) and difference factor equation ($f1$).

$$f2 = 50 \times \log\{\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n}(Rt - Tt)^2\right]^{-0.5} \times 100\}$$

$$f1 = \sum(|Rt - Tt|)/(\sum Rt) \times 100$$

Two dissolution profiles are considered similar when the f2 value is ≥50.

Difference factor (f1) should be equal to/or less than 15 between two similar dissolution profiles.

f2 and f1 were obtained as 40.06 and 21.94, respectively, which indicates that the two tablets are not similar and produced tablet is different from the reference one significantly. Dissolution profiles of two kinds of tablets are shown in Fig. 1.

Comparison of dissolution profiles of the produced tablet with the reference tablet from Mylan (Mylan MR 30) showed that two tablets are similar (f2 and f1 were obtained as 58.72 and 10.13, respectively). Dissolution profiles of two kinds of tablets are shown in Fig. 2.

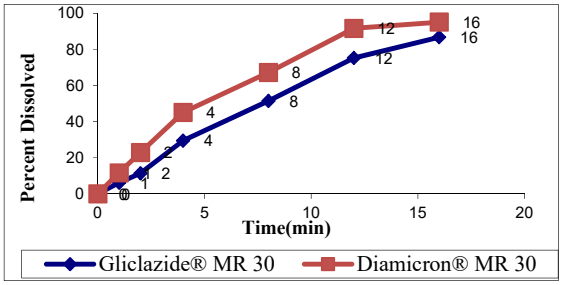

Fig. 1 Dissolution profiles of modified release gliclazide 30 mg tablet after passing of the granule through oscillating granulator with 16-mesh screen and Diamicron MR 30 tablets

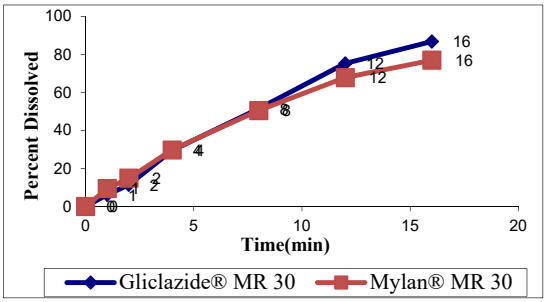

Fig. 2 Dissolution profiles of modified release Gliclazide 30 mg tablet after passing of the granule through oscillating granulator with 16 mesh screen and Mylan MR 30 tablets

In another experiment, the dried granule of gliclazide 30 mg was passed through the oscillating granulator with 24 mesh screens and mixed with the remaining of excipients. The dissolution profile of the produced tablet was compared with Diamicrom MR 30. The tablets were similar (f2 and f1 were obtained as 64.41 and 5.94, respectively). Dissolution profiles of two kinds of tablets are shown in Fig. 3. By making finer particles of ready to press powder using mesh screen 24, the surface area to volume ratio of tablet particles increases, therefore drug release increases [1].

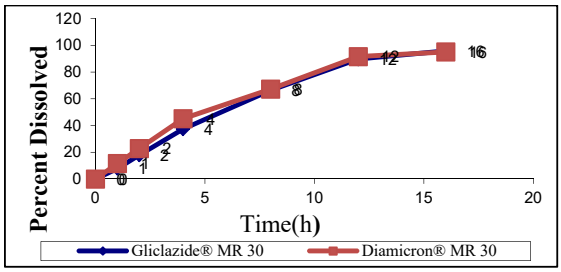

Fig. 3 Dissolution profiles of modified release gliclazide 30 mg tablet after passing of the granule through oscillating granulator with 24-mesh screen and Diamicron MR 30 tablets

B. Modified Release Gliclazide 60 mg Tablet

The ready to press powder of modified-release gliclazide 60 mg tablet was manufactured as like as modified release Gliclazide30 mg tablet with passing the dried granule through oscillating granulator with mesh screen 24. The tablets were produced with 9 mm concave punch with the average hardness of 5.42 kp (HPMC content was considered 20% in formulation). Diamicron MR 60 was used as a reference tablet. After performing in vitro study, f2 and f1 were obtained as 34.30 and 24.21, respectively. Dissolution profiles of two kinds of tablets are shown in Fig. 4.

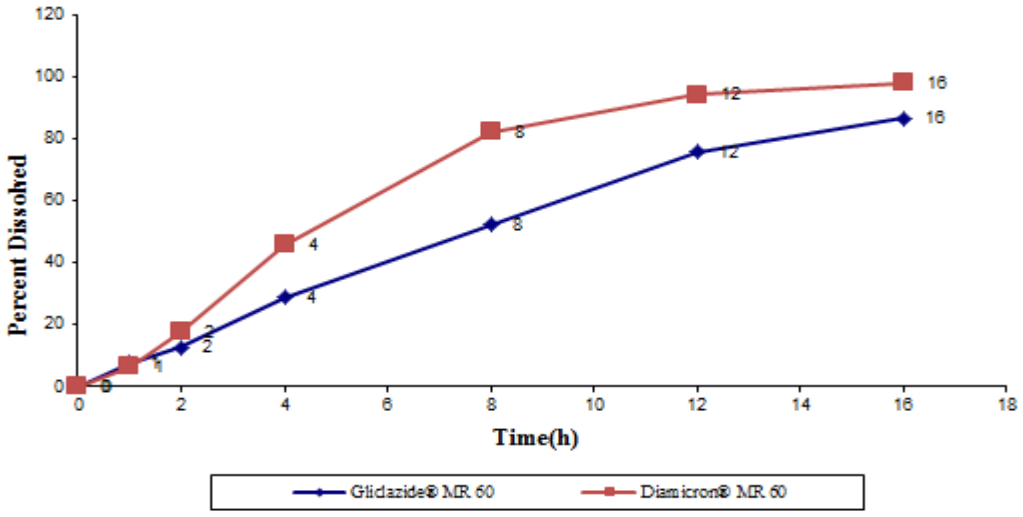

Fig. 4 Dissolution profiles of modified release gliclazide 60 mg tablet after passing of the granule through oscillating granulator with 24-mesh screen with average hardness of 5.42 kp and Diamicron MR 60 tablets

Although we used small mesh screen (mesh screen 24) like modified-release gliclazide 30 mg tablet, the similarity factor between the tablet and the reference one was not good. It indicates that, by increasing the diameter of the tablet, the surface area to volume ratio decreases, therefore drug release decreases [9]. It seems that reduction of surface area to

volume ratio does not compensate by fining of the granule particles (mesh screen 24). For a round biconvex tablet, surface area to volume ratio was calculated using SolidWorks software. This ratio was estimated as 1.2699 and 1.0134 for modified-release gliclazide 30 mg and 60 mg tablets, respectively. Therefore, for increasing the rate of drug release in modified release gliclazide 60 mg tablet, we had to decrease the content of HPMC K4M in formulation.

1. Effect of Hardness

By increasing the hardness of the tablet and reduction of thickness, surface area to volume ratio increases, and therefore, drug release increases. Modified-release gliclazide 60 mg tablet was produced like above with average hardness of 6.4 kp. After performing in vitro study, f2 and f1 were obtained as 39.43 and 18.18, respectively. Dissolution profiles of two kinds of tablets are shown in Fig. 5. As it is seen, by increasing the hardness, similarity and difference factor become better.

2. Effect of Halving of Tablet

In another experiment, we used half of a modified-release Gliclazide tablet 60 mg and investigated the in vitro study. f2 and f1 were obtained as 42.12 and 16.61 respectively. Dissolution profiles of two kinds of tablets are shown in Fig. 6. As seen, dissolution profile of half of a Gliclazide tablet 60 mg is more similar to the reference tablet in comparison with the whole tablet.

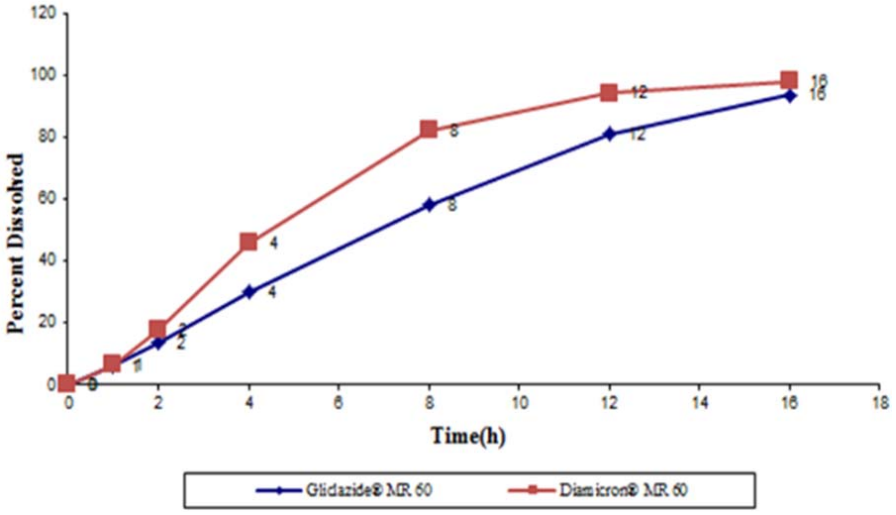

Fig. 5 Dissolution profiles of modified release gliclazide 60 mg tablet after passing of the granule through oscillating granulator with 24-mesh screen with average hardness of 6.4 kp and Diamicron MR 60 tablets

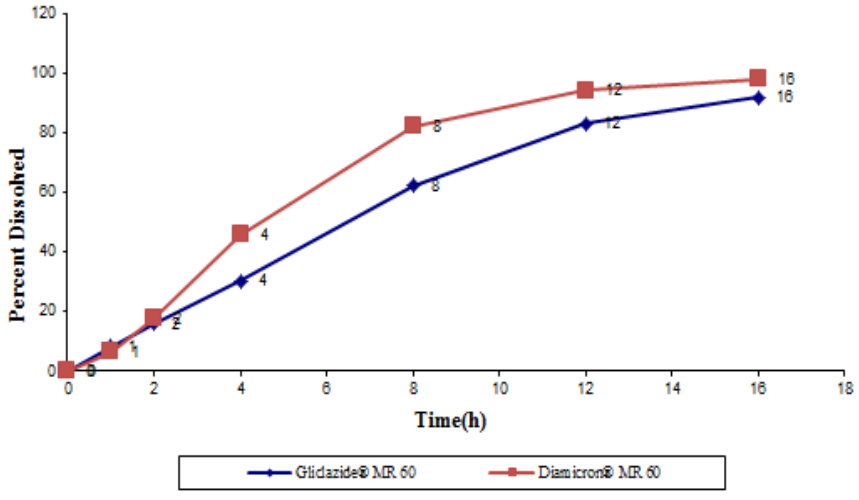

Fig. 6 Dissolution profiles of half of a modified release gliclazide 60 mg tablet after passing of the granule through oscillating granulator with 24-mesh screen with average hardness of 6.4 kp and Diamicron MR 60 tablets

Skoug et al. reported that two halves of a SR tablet had an increase in the surface area to volume ratio of about 16% relative to whole tablets [5]. The halves of a tablet have faster drug release relative to the whole tablet.

When we compared dissolution profiles of two tablets modified-release Gliclazide 30 mg tablet (Granule passed through mesh screen 24) and half of a modified-release gliclazide 60 mg tablet, f2 and f1were obtained as 61.01 and 7.95, respectively, while the whole gliclazide 60 mg tablet has f2 and f1 which are equal to 45.65 and 16.55, respectively. It indicates that half of a gliclazide 60 mg tablet (in comparison of the whole 60 mg tablet) is more similar to modified-release gliclazide 30 mg tablet.

3. Investigation of HPMC K4M in Internal and External Phase of Blending

Studies about manufacturing of modified-release gliclazide 60 mg tablet showed that adding HPMC K4M intragranular or extragranular (before or after granulation process) had significant effect on drug release profile. Therefore, we can control the rate of drug release by adjusting the ratio of HPMC K4M content in the internal or external phase of blending process.

4. Estimation of the Percentage of HPMC in Modified Release Gliclazide Tablet 60 mg

In our previous work, we obtained a mathematical model to describe the behavior of optical sensors [10] which is based on Fick's diffusion laws and reaction kinetic at the sensor surface.

When drug released from a matrix is controlled by diffusion through the polymeric matrix, its release kinetics obey Fick's 1st and 2nd laws [11].

$$J = -D\frac{\delta C}{\delta x} \quad (1)$$

$$\frac{\delta C}{\delta t} = -D\frac{\delta^2 C}{\delta x^2} \quad (2)$$

where J represents the diffusional flux of the drug, D is the diffusion coefficient of the drug, C is the concentration of the drug, and x is the distance of diffusion. For a planar matrix, whose shape is close to a flat thin tablet, with drug loading lower than or equal to drug solubility ($C_0 \leq C_s$), the fraction of drug released from matrix into a perfect sink by time t is described by Crank [11].

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} \exp\left[\frac{-D(2n+1)^2\pi^2 t}{a^2}\right] \quad (3)$$

where $\frac{M_t}{M_\infty}$ is the fraction of drug release, a is the thickness of the matrix, and D is the diffusion coefficient. A simplified equation can be used for early time, e.g. $\frac{M_t}{M_\infty} \leq 0.6$ [11].

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi a^2}\right)^{1/2} \quad (4)$$

Modified release gliclazide 60 mg tablets were produced with different content of HPMC (10%, 12%, 12.5%, 15% and 20% in formulation) and average hardness of 6.0 kp. Fitzmill with mesh screen 16 was used for fining of the granule. Drug release profiles were obtained as shown in Fig. 7.

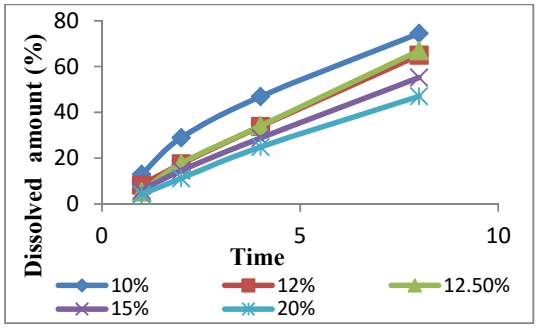

Fig. 7 Dissolution profiles of modified release Gliclazide 60 mg tablets with different content of HPMC in formulation after passing of the granule through oscillating granulator with 24-mesh screen with average hardness of 6.4 kp and Diamicron MR 60 tablets

As expected, drug release is decreased by increasing HPMC content in formulation. Drug release of both of modified release gliclazide 30 and 60 mg tablets obeyed from Higuchi equation $Q=k_H t^{0.5}$, where Q is the percent of drug released at time t, and K_H is a respective coefficient (R^2 from plotting of dissolution (%) versus $t^{0.5}$ was obtained as 0.9902 and 0.9903 for modified release Gliclazide 30 and 60 mg, respectively). From equation of Pepass ($Q=k_p t^n$), n was obtained as 0.91 and 0.89 for modified-release gliclazide 30 and 60 mg, respectively. It shows that non-Fickian transport (erosion of polymer) controls the drug release. So, by assuming that the erosion of HPMC is predominant step of drug release, (5) can be used to describe drug release. According to this equation, the percent of dissolved amount of modified release gliclazide 60 mg tablet has a relationship with the amount of HPMC in percent.

$$Dissolution\ (\%) = KX^n \quad (5)$$

where K is a constant, and X is the HPMC content in percent. In initial times of 1 and 2 hours, by plotting Ln (Dissolution (%)) versus Ln(X), n (average) was determined as -1.45 from the slope of the curves. According to (4) and Higuchi equation, drug release is proportional to $t^{1/2}$. As Pepass equation shows for insoluble drugs (such as Gliclazide), we can consider that the drug release is controlled by polymer erosion. Therefore, it can be concluded polymer erosion is proportional to $t^{-1/2}$. By substitution of X in (5) by $X_0 t^{-1/2}$, (6) was obtained which X_0 is HPMC content in percent in formulation.

$$Dissolution\ (\%) = K(X_0\, t^{-\frac{1}{2}})^{-1.45} \quad (6)$$

The dissolution (%) was obtained in initial times (1 and 2 h) for different HPMC content (10%, 12%, 15%, and 20%) in formulations using (6). Good results were obtained in comparison with real data. K (correction factor) was determined as 1.003964 as the average of ratio of data obtained from the model to the real data for different HPMC content. Therefore, final equation was obtained as (7).

$$Dissolution\ (\%) = 1.003964(X_0\, t^{-\frac{1}{2}})^{-1.45} \qquad (7)$$

The model was used to predict HPMC K4M content in four formulations. The results are summarized in Table I. As seen in Table I, the model can predict HPMC content in different formulations as well.

TABLE I
ESTIMATED VALUE OF HPMC CONTENT IN DIFFERENT FORMULATIONS USING THE PROPOSED MODEL

HPMC content (%)	10	12	15	20
Predicted value	9.34	12.9	15.54	19.19
Relative error (%)	-6.6	7.5	3.6	-4.05

This model can be used for the prediction of HPMC content in other formulations containing water insoluble drugs where erosion of HPMC K4M controls drug release. The estimation of HPMC K4M content in modified-release gliclazide 30 mg tablet was 19.3% which was so close to real content that we used in formulation (20%). We used the model for estimation of the HPMC K4M content in quetiapine extended-release tablets. By obtaining drug release profile of the reference tablet (Seroquel XR 200 mg) and using the proposed model, the polymer content was estimated, then by incorporating the correction factor because of the change in surface area to volume ratio (because modified-release gliclazide 60 mg tablet was a round convex tablet with 9.0 mm diameter and 3.92 mm thickness and quetiapine was an oblong tablet with 16.30 mm length, 7.5 mm width and 6.38 mm thickness),the tablet was designed, and dissolution profile was obtained. Table II shows the dissolution data of two kinds of tablets. Good results were obtained from dissolution data. It shows that two tablets have similar drug release, and the model predicts the amount of HPMC K4M in formulation with a good approximation (f_2 and f_1 for quetiapine and Seroquel 200 mg tablets were obtained as 60.74 and 2.30, respectively). Also, this shows that difference in solubility of insoluble drugs and also difference in dissolution media do not have significant effect on drug release profile in HPMC formulations, and polymer content and surface area to volume ratio of tablets are the key factors in drug release profiles.

TABLE II
DISSOLVED AMOUNT OF EXTENDED-RELEASE QUETIAPINE 200 MG TABLET IN DIFFERENT TIMES ACCORDING TO THE HPMC CONTENT ESTIMATION IN EXTENDED-RELEASE SEROQUEL 200 MG TABLET

Time (h)	1	2	4	6	8	10	12	16	20	24
Seroquel	8.73	18.03	38.03	51.85	57.07	60.62	63.84	69.04	75.18	80.37
Quetiapine	11.68	18.66	33.84	45.64	53.68	61.46	67.52	75.82	77.51	88.97

IV. CONCLUSION

In this study, the effect of important factors on drug release profiles of modified-release gliclazide tablets with HPMC in formulation was investigated. Surface area to volume ratio is a key factor in HPMC used controlled release tablets. Fining of powder particles of tablets, increasing of hardness and halving of tablets increases surface area to volume ratio and therefore increases the drug release. A mathematical model was developed for estimation of HPMC K4M content (%) in modified-release gliclazide tablet formulation. By this formula, we can predict the HPMC K4M content with a good approximation. This model was used to predict HPMC K4M in extended release quetiapine 200 mg tablet formulation. According to the dissolution results, good estimation was achieved. Also, this model can be used to predict HPMC K4M in other insoluble drug formulations which use HPMC K4M as a drug release retarding agent. This model can be useful for formulation scientists to optimize HPMC content in formulations.

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DECLARATION OF INTEREST

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