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Research Article

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Evaluation of Drug Release and Performance Parameters for Metformin Extended Release Tablets

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Abstract

The objective of the current investigation was to evaluate the release of metformin from extended-release hydrophilic tablets and to assess their swelling, textural, and erosional behavior. Drug release from the matrix tablets was assessed using USP 26 apparatus II (paddle) modified with the insertion of mesh. The swelling and erosion behavior was investigated by textural analysis of the swollen tablets using a TA. XT2i texture analyzer. The release of metformin was pH-independent with a burst effect observed during the first two hours of the release. The rapid increase in swelling initially may be responsible for the burst effect in drug release. In HCl/KCl buffer, the drug release followed non-fickian (anomalous) release, while it followed Fickian (Case I) diffusion in phosphate buffer. The drug release was diffusion controlled rather than first-order kinetics. The rate of water uptake followed an anomalous or complex behavior. Increased swelling and water uptake increased the drug release, while decreased work of penetration through the polymeric matrix decreased the drug release. Erosion was also one of the mechanisms that occurred in HPMC-matrix tablets. It is interesting to note that swelling and water uptake played a more important role than erosion during drug release.

Keywords: Metformin; drug release; axial swelling; water uptake; erosion.

Introduction

Metformin Hydrochloride is an orally administered biguanide that has been widely used in the treatment and management of non-insulin dependent diabetes mellitus (NIDDM). It lowers both basal and postprandial elevated blood glucose in patients with NIDDM when hyperglycaemia cannot be satisfactorily managed on diet alone [1-4].

Metformin became commercially available in 1959 and in the United States in 1995 [2]. The marketed product of metformin, Glucophage®, is an immediate-release (IR) tablet that is administered 2-3 times daily. The drug is commonly administered at high doses to achieve effective glucose lowering treatment. Metformin therapy is usually associated with a high incidence of gastrointestinal side effects, which occur in about 30% of patients. The GI side effects include abdominal discomfort, nausea and diarrhoea. These side effects occur especially during the initial weeks of therapy. Side effects and the need to administer the drug 2-3 times daily especially at high doses can also decrease patient compliance. An extended-release formulation may reduce GI symptoms due to lower peak exposure of intestinal tissue to metformin. While increased GI tolerability problems with increased dose limit the current IR formulation dosing, extended release (ER) formulations with improved GI tolerability may permit single dosing of metformin daily. This could also reduce the dosing frequency and improve patient compliance [1,2].

Once daily dosing of extended-release metformin formulation also helps maintain the plasma levels of the drug for 10 to 16 hours. The maintenance of plasma levels of metformin helps to maintain the pharmacological effects of the drug as long as 24 hours as the pharmacological

effects appear to exceed the persistence of drug concentrations in plasma [2].

Oral controlled-release (CR) formulation of metformin is also supported by the first pass pharmacodynamic effect of the drug. The drug produces an augmented pharmacological effect when it reaches the systemic circulation following oral administration and intestinal absorption, in comparison to administering the drug directly to systemic circulation via intravenous injection. Thus, the pre-systemic sites of metformin glucose lowering action that are located in the GI tract and the liver are of major importance for the overall effect. The glucose lowering action is also mode-of-administration dependent; when metformin is administered as an oral CR formulation, sustained exposure of presystemic sites to the drug improves glucose lowering effect of glucose [3].

There is a pharmaceutical challenge in developing CR dosage forms for metformin due to the clinically used high dose of the drug. Since immediate release metformin tablets contain 500-1000mg of the drug, the CR tablet's dimensions containing the same amount of drug would be close to the upper limit of the size that is plausible for patient intake [3,4].

As Metformin has a very high solubility in water, it can be difficult to formulate into a controlled release oral dosage form. Solubility is a driving force for a drug substance to dissolve in water; the greater the solubility, the greater the rate of dissolution when all other factors are maintained constant. In a controlled release formulation, the rate of dissolution can be reduced by embedding the drug in a polymeric matrix or surrounding it with a polymeric barrier membrane through which the drug must diffuse out to be released for absorption. To reduce the rate of release of drug from the dosage form to an appropriate level consistent with the blood level profile desired for a drug possessing high water solubility, very large amounts of polymer would be required for the matrix or barrier membrane. If the total daily dose of drug to be delivered is of the order of only a few milligrams this may be feasible, but many drugs having the solubility properties described require total daily doses of the order of many hundreds of milligrams. Whilst it is possible to create oral controlled release dosage forms for such products by use of large amounts of polymer, an unacceptably large dosage form may result [3-5].

A further problem with highly soluble drugs formulated into a controlled release dosage form is that a significant and variable "burst" of drug can occur from these systems. The burst of highly water soluble drug is the initial rapid release of drug that occur when first contacting fluid, such as gastric fluids, prior to release controlling mechanisms establish themselves and a stable release rate is provided. Hydration of any polymer matrix used to formulate the dosage form is a pre-requirement of establishing a stable release rate. Thus, a readily hydrating polymer is required to establish the desired stable release rate. However, if the polymer used is slow to hydrate, then an undesirable variable burst can occur [5].

The purpose of the current investigation is to evaluate the release of metformin from extended release hydrophilic Glucophage® XR tablets, and to assess their swelling, textural, and erosional behaviour during the drug release process.

Materials and Methods

Product Studied

Glucophage® XR tablets (batch no. 6063) was manufactured by Bristol Myers Squibb. Glucophage® XR contains 500mg metformin as the active ingredient. Each tablet also contains the following polymers: Sodium carboxymethylcellulose(binder),hydroxypropylmethylcellulose (matrix former), and microcrystalline cellulose. The lubricant used in each tablet is magnesium stearate [4].

Glucophage® XR tablets comprise a dual hydrophilic polymer matrix systems. Metformin hydrochloride is first combined with a drug release controlling polymer to form an "inner" phase. This "inner" phase is then incorporated as discrete particles into an "external" phase of a second polymer [4].

Materials

Metformin hydrochloride was obtained from Sigma-Aldrich Co., St. Louis, MO. It was used to construct the calibration curves in the different buffers used. The buffers were made from the following materials: sodium hydroxide (Fisher Chemicals, Fair Lawn, NJ); monobasic potassium phosphate, NF grade (Spectrum Chemical Mfg. Corporation, New Brunswick, NJ); potassium chloride (Spectrum Chemical Mfg. Corporation, New Brunswick, NJ); hydrochloric acid (37% w/w, Mallinckrodt-Baker, Inc., Kentucky). The pH of the two different buffers used was adjusted using an Accumet® pH meter 25 (Fisher Scientific).

In Vitro Dissolution Studies (Drug Release Testing)

The drug release studies were carried out using the dissolution tester (Vankel VK 7000) using USP apparatus II (paddle) modified with mesh [6]. The dissolution medium was 1000ml KCl/HCl buffer (pH 2.2) or phosphate buffer (pH 6.8) at 37°C with a stirring speed of 100rpm. Samples (3ml) were withdrawn at pre-selected time intervals and replaced by an equivalent volume of fresh solvent. The collected samples were diluted and the absorbance measured spectrophotometrically using HP 8453 UV/VIS spectrophotometer at λ=200nm (HCl/KCl buffer) or λ=276

nm (phosphate buffer). The released drug concentrations were calculated using a calibration curve. The dissolution data were corrected for the dilution effect. Two tablets were used to obtain the dissolution data in the selected buffer [1,7].

Textural Profiling of Hydrated Matrices

Textural analysis associated with the dynamics of matrix swelling was evaluated using a Textural Analyzer, TA-XT2i (Texture Technologies Corp, Scarsdale, NY). The tablets were placed in dissolution vessels containing 1000ml buffer medium, at 37˚C during separate tests. The paddle speed was set at 100rpm to simulate the actual tablet dissolution process. At predetermined time intervals, the tablets were removed and subjected to textural analysis.

The textural analyzer instrument had the ability to draw force-displacement-time profiles at a rate of 200 points/s via the Texture Expert for Windows software, version 1.20. A flat-tipped steel probe, 2mm in diameter, was connected to a force transducer within the analyzer that measured the force of resistance encountered by the probe during the advancement through the sample. During a typical test, the probe advanced at a predetermined velocity into the sample according to the following parameter: pre-test and post-test speeds, 1mm/s; test speed, 0.5mm/s; maximum compression force, 40N; and the trigger force is 0.005N.

The force-displacement-time profiles at different times were utilised to determine % axial swelling and the total work of penetration according to the following equations:

$$\text{Total work of penetration} = W_T = \int F.dD \ldots . 1$$

$$\%\ \text{axial swelling} = \frac{100(\text{swollen thickness} - \text{origional thickness})}{\text{origional thickness}} \ldots\ldots 2$$

Degree of hydration and erosion were determined gravimetrically according to the following equations:

$$\%\ \text{Weight Gain or}\ \%\ \text{water uptake} = \frac{100(\text{wet weigh t} - \text{dry weigh t})}{\text{dry weight}} \ldots . 3$$

$$\%\ \text{erosion} = \frac{100(\text{origional weight} - \text{dry weight} - \text{drug released})}{\text{origional weight}} \ldots . \quad 4$$

Swelling of polymer matrix depends on the rate of penetrant entry into the matrix. The penetrant uptake measurement is used primarily for evaluation of the effect of polymer-penetrant interaction that enables the release of the drug to take place at a constant rate. The swelling behaviour indicates the rate at which the polymeric matrices absorb water and swell [8].

The water uptake data were subjected to the Vergnaud model to determine the rate of water uptake. The generalised equation of the Vergnaud model is as follows [8]:

$M_t = kt^n$ …….. 5

M_t represents the amount of liquid transferred at time, t

k is the swelling constant which depends on the amount of liquid transferred after infinite time, the porosity of the matrix (this term was substituted for the shape of the polymer in the original equation), and diffusivity [8].

The exponent, n, indicates the mechanism of water uptake. A value of ≤0.5 for n indicates a diffusion-controlled mechanism in which the rate of diffusion of the liquid is much less as compared with the rate of relaxation of the polymer segment. A value of one for n (n=1) suggests that the stress relaxation process is very slow as compared with the rate of diffusion. This means that the liquid diffuses through the polymer matrix at a constant velocity showing an advancing front marking the limit of liquid penetration. A value of n between 0.45 and 1, indicates an anomalous or complex behaviour in which the rate of diffusion of the liquid and that of relaxation are of the same magnitude. High values of swelling constant, k, suggests burst swelling or water uptake, while low values of k suggest absence of burst effect in polymer swelling or water-uptake [8].

Drug Release mechanism and Drug Release Rate

The polymeric matrix tablets, on contact with water, builds a gel layer around the tablet core, thus governing the drug release. It is known that the drug release from HPMC matrices is controlled for water-soluble drugs by diffusion through the gel layer. Therefore, the kinetics of swelling is important, because of the gel barrier is formed with the water penetration [9].

The following mechanisms are the mechanisms by which drug release from a polymeric matrix may occur: (a) the first and the most often encountered mechanism is drug diffusion through the outside layers of the matrix, also known as “Fickian” release of “Case I” mechanism; (b) non-fickian or anomalous transport where drug diffusion through the polymeric matrices and the polymeric chains

relaxation affect drug release. In this case, the dry, hydrophilic glassy polymers become rubbery as they swell once they come in contact with water. This is due to the rearrangement of macromolecular chains of the polymers; (c) "zero-order" release or "case II" mechanism, which is a special case of non-fickian diffusion. The basis for these models is the possible competition between water diffusion and polymer chain relaxation [8,9].

However, in practice, polymeric matrices release the drug via a combination of mechanisms. In such situations, the following general equation may be used to characterise drug release for water soluble molecules [8,9]:

$M_t / M_\infty = kt^n$ 6

M_t is the amount of the released drug at time t,

M_∞ is the overall amount of the drug (whole dose)

M_t / M_∞ is the fraction of drug released at time, t

k is the proportionality constant which accounts for structural and geometric properties of the matrix, and n is the diffusional exponent indicative of the mechanism of the drug release. The values of the release parameters, n and k, are inversely related. A higher value of k may suggest burst drug release from the matrix. The equation is, however, valid only for the early stages (≤70%) of drug release. According to the criteria for release kinetics from swellable systems, a value of release exponent, n=0.45, 0.45<n<0.89, and 0.89<n<1.0 indicates Fickian (Case I) diffusion, non-Fickian (anomalous) diffusion and zero-order (Case II) transport, respectively. Fickian (Case I) behaviour indicates that the drug partially diffuses through the swollen polymer matrix and partly through the water-filled pores and channels in the matrix channel. While non-Fickian (anomalous) behaviour indicates that the drug partially diffuses through the swollen polymer matrix and also partly through the gradually expanding hydrated matrix with increasing diffusional path-length [8,9].

The passage of a water-soluble drug through the hydrated gel layer around the matrix tablet is approximately dependent on the square root of time and can be described in the following equation form [8-10]:

$Q_t = kt^{1/2}$ 7

Q_t is the amount of released drug in time t

k is the kinetic constant that accounts for several factors including solubility and diffusion coefficient of the drug in permeating fluid, porosity, and turtuosity of the matrix

t is time

This simple equation is useful for the determination of the drug release rate [8-10].

Equation 7 is a simplified form of Higuchi's equation describing the diffusion-controlled mechanism from various controlled-release preparations. It takes the following form [10]:

$$Q_t = \frac{D\,\varepsilon\,C_s}{\tau}(2A - \varepsilon\,C_s)\,t^{1/2} \quad \ldots\ldots 8$$

where: Q_t = mass of drug released at time, t, per unit exposed surface

A = initial mass of drug present in the matrix per unit volume

C_s = solubility of drug in the dissolution fluid

ε = porosity of the matrix

τ = tortuosity factor for the capillary system of the matrix

Although equations 7 and 8 are based on the release from a single surface, they can be used to describe diffusion-controlled from all surface tablets [10].

Another method to confirm that the presence of diffusion-controlled release mechanisms is provided by the use of the logarithmic form of the diffusion equation (equation 7). The logarithmic form can be written as the following equation [10]:

$$\log Q = \log k + 0.5 \log t \ldots\ldots\ldots 9$$

According to equation 9, the plot of log Q versus log t will give a straight line with a slope of 0.5 and an intercept equal to log k [10].

When the drug is released from the matrix via diffusion, the drug is assumed to be leached out by fluid around the matrix. The fluid surrounding the matrix enters the pores through the pores, cracks, and intergranular spaces. The drug is presumed to dissolve slowly into the permeating fluid, and then it diffuses out of the system along the cracks and capillary channels which are already filled with the solvent. Intragranular diffusion is insignificant [11].

Results and Discussion

The dissolution of metformin XR tablets was done in HCl/KCl buffer (pH 2.2) and phosphate (pH 6.8) buffer - figure 1.

It was observed that during dissolution, the Glucophage® tablets gently floated over the mesh for about 20 hours, after which time the tablets freely moved to the top of the dissolution medium in the vessel. The fact that the floating tablets remained near the bottom of the vessel near the mesh due to the presence of large amounts of sodium carboxymethylcellulose, which absorbs a lot of water per 1g of the polymer upon contact with the dissolution medium thus increasing the weight of the tablet. After twenty hours, the tablets floated to the top as most of the drug and some of the polymers dissolved in the media.

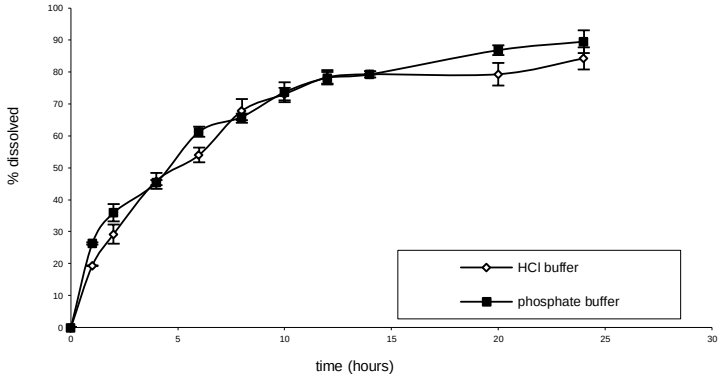

Figure 1: Dissolution Profile of Metformin XR tablets in phosphate buffer (pH 6.8) and HCl. / KCl USP buffer (pH 2.2) (n=2).

As observed from figure 1, the release of Metformin is pH independent. This may be due to the fact that all the polymers used are non-ionic and should not be affected by the pH changes within the GIT. A burst effect is observed during the first two hours in both buffers. This effect may be due to the high solubility of metformin and the fact that HPMC polymers are known to hydrate slowly before a gel layer is formed and a more consistent release begins. From 2 hours up to 12 hours, the release of metformin followed linear kinetics. A tailing of the release was observed from 14 up to 24 hours.

It can also be concluded that the release of metformin is related to the square root of time (up to 80% of the drug being released) as seen in figure 2. From figures 2 and 3, it can be concluded that the metformin release from Glucophage XR tablets is diffusion controlled. This fact is also confirmed by the fact that the drug release is affected to a larger extent by axial swelling (figure 4) and water uptake (figure 5) rather than erosion (figure 8).

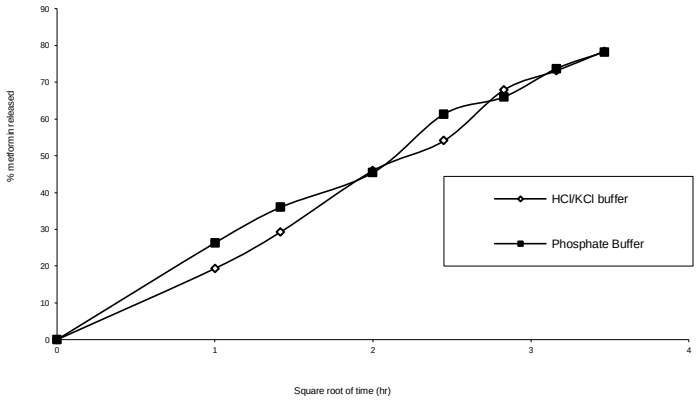

Figure 2: % released of metformin versus the square root of time.

From figure 2, the release rate of metformin can be calculated from the slope of the line. The release rate of metformin in HCl/KCl buffer is 23.579 (%/√hr) with a correlation coefficient equal to 0.9974 while the release rate in phosphate buffer is 22.604 (%/√hr) with a correlation coefficient equal to 0.9966. This is another example that the release of metformin from Glucophage XR tablets is pH-independent. It could also be concluded from figure 2, that the release of metformin is a diffusion-controlled mechanism as there is a linear square root of time plot (Higuchi Kinetics) both in HCl/KCl buffer and phosphate buffer.

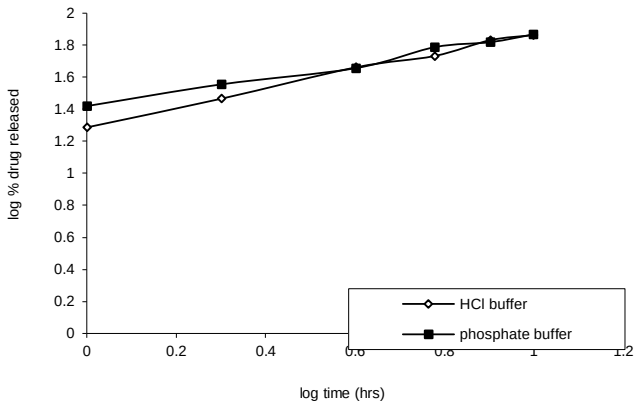

Figure 3: Plot of log percent drug released from Glucophage XR tablets as a function of log time.

The values of release parameters, n and k, for Glucophage XR tablets were determined from the slope and intercept of the plot of percent drug released (M_t/M_∞) as a function of time according to equation 6 on a logarithmic scale as shown in figure 3 and table 1.

Buffer System	Kinetic Parameter (k)	Release Exponent (n)	Correlation Coefficient (r^2)
HCl/KCl USP	19.566	0.5840	0.9983
Phosphate BP	26.0495	0.4496	0.9953

Table I: Kinetics based on equation 6 for Glucophage XR tablets in HCl/KCl and phosphate buffer.

From Figure 3 and table 1, it can be concluded that Metformin release in HCl/KCl buffer follows non-fickian or anomalous diffusion (n=0.58036), while it follows Fickian (Case I) diffusion in phosphate buffer (n=0.44958). The difference in the n values may be due to the fact that Glucophage XR tablets are made of several polymers which tend to interact with the fluid intake differently according to the surrounding media. In both buffer systems, the value of release constant, k, is high suggesting burst drug release from Glucophage XR tablets at both pH values (table 1). The fact that the slope in both buffers (figure 3) is close to 0.5 confirms that metformin is released via a diffusion-controlled mechanism. The profile can be described by equation 9. The equation for the straight line obtained in the HCl/KCl buffer is $y = 0.5840x + 1.2915$ ($r^2 = 0.9983$). While the line equation in the phosphate buffer is $y = 0.4496x + 1.4158$ ($r^2 = 0.9953$).

In an attempt to relate the % dissolved to the swelling and hydration behaviour of the tablets, textural analysis was done at several time points. From the textural analysis work, it can be concluded that the swelling of the tablets increases up to 12 hours as the distance moved by the probe increases. The total work of penetration, represented by the area under the curve of each profile, decreases as time increases indicating that the gel layer is getting larger and the dry core is replaced by the gel barrier thus the work need by the probe to pass through the tablet decreases with time. From the textural analysis work along with the weight changes before and after textural analysis, % axial swelling, % erosion, % hydration or weight gain, and the total work of penetration can be calculated. Figure 4 represents % axial swelling data, while figure 5 represents % water uptake data. Work of Penetration is represented in figure 7, while figure 8 represents % erosion data.

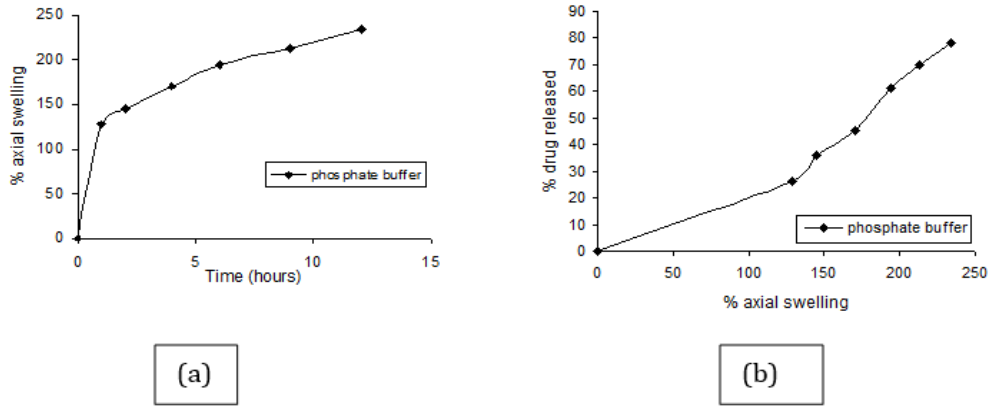

Figure 4: (a) % Axial swelling versus time (hr), (b) % drug release versus % axial swelling.

From figure 4(a), there is a linear increase in the axial swelling of the matrix tablets but at two different rates. There is a rapid increase in axial swelling during the first two hours followed by a slower increase in swelling from 2 till 12 hours. This phenomenon may be responsible for the burst effect observed during the first two hours of the dissolution profile. Thus the % drug released is dependent on the axial swelling or the formation of the gel layer around the matrix tablet (figure 4b). During the first hour, 15% of drug is released, then the rate of drug release decreases and becomes more consistent as the rate of gel formation occurs at a slower and a more consistent rate after the first hour of the dissolution while the amount of drug being released increases as the percentage of axial swelling increases.

Figure 5 represents the % water uptake data with time and its relation with % drug released in phosphate buffer.

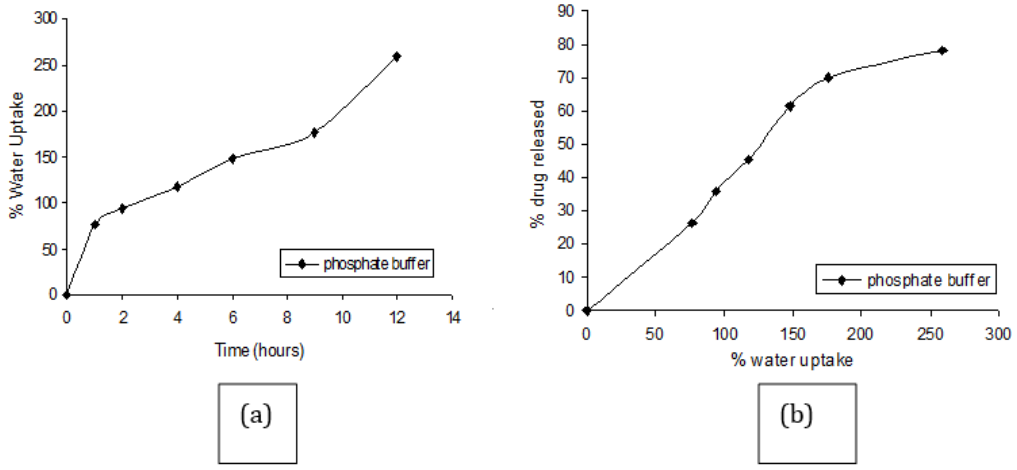

Figure 5: (a) % Water Uptake versus time (hours), (b) % drug released versus % water uptake.

The rate of water uptake through the matrix tablet changes with time (figure 5a). During the two hours, there is a rapid increase in % water uptake followed by a slower increase in the water uptake from 2 till 9 hours. After 9 hours, there is also a rapid increase in water uptake probably after all the tablet is being hydrated. This will reflect on the % drug released with time (figure 5b). During the first two hours, about 27% of the drug is released followed by a slower drug release rate due to decreased rate of hydration to allow the drug to be released over an extended period of time. After 9 hours, most of the drug has been released so an increased rate of hydration will help the remaining drug present in the matrix tablet to be released. The water uptake data were subjected to the Vergnaud model according to equation 5 as shown in figure 6.

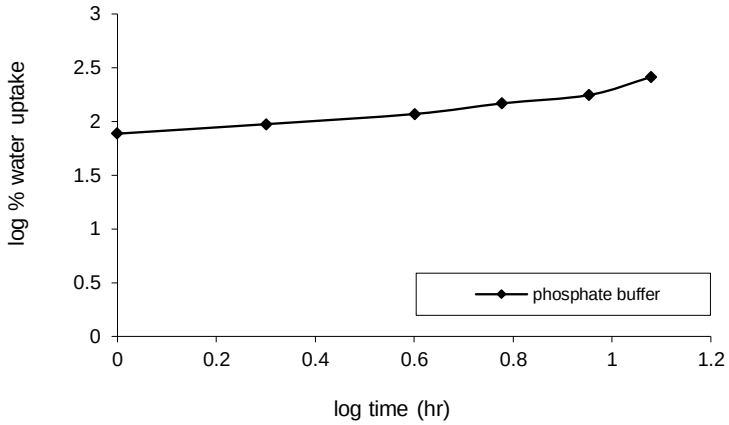

Figure 6: Plot of percent water uptake as a function of log time (Vergnaud Model).

The characteristic values of the Vergnaud model were calculated by fitting the water uptake data in equation 5. The value of exponent n is 0.4520 (r^2 = 0.9659). The n value indicates anomalous or complex behaviour in which the rate of diffusion of the liquid and that of relaxation are of the same magnitude. The dominant mechanism of drug release is drug polymer relaxation. Both axial swelling and % water uptake are also reflected in the tablet through the work of penetration (figure 7).

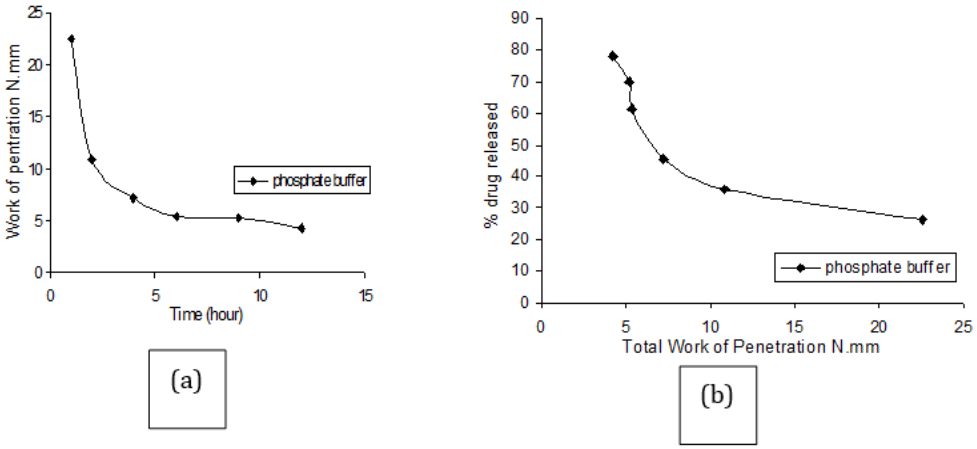

Figure 7: (a) Work of Penetration versus time, (b) % drug released versus work of penetration.

As the gel layer of the matrix tablet is being formed due to increased water uptake and hydration, the inner core of the tablet decreases in size and the gel layer increases thus the work of penetration decreases with time (figure 7a). The work of penetration decreases drastically during the first two hours then reaches a plateau after about 6 hours of hydration. As the work of penetration decreases, the rate of drug released also decreases (figure 7b) probably due to the fact that the amount of drug present in the tablet is reduced. In this case, the decreased work of penetration with time will help hydrate the tablet more easily in order to release what is left of the drug more easily to keep a consistent level of drug release. All these changes in the matrix tablets are also accompanied with a change in the rate of erosion of the polymeric tablet (figure 8).

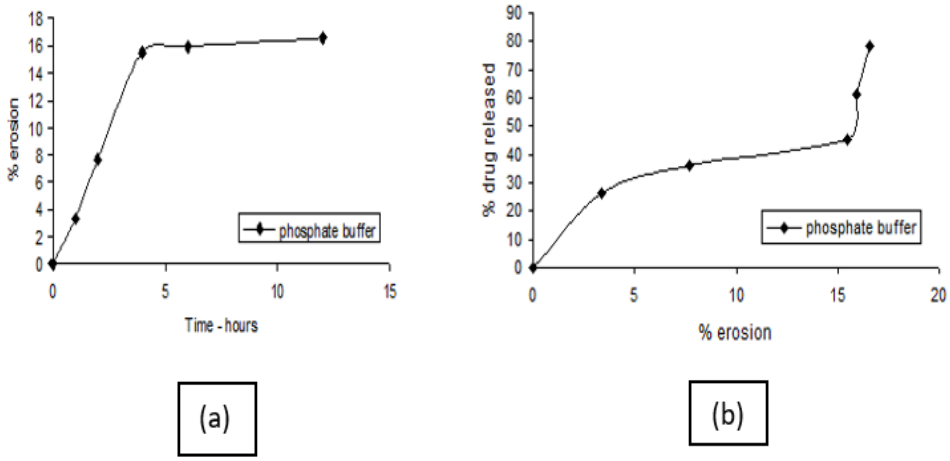

Figure 8: (a) % erosion versus time, (b) % drug released versus % erosion.

Erosion is one of the main mechanisms that will take place along with swelling in matrix tablets containing HPMC (Figure 8). As time passes by, there is a linear increase in % erosion taking place mainly during the first four hours after which there is a plateau reached after about 4 hours (figure 8a). This will have an effect on the drug release as well (figure 8b). During the beginning of the swelling process, as erosion increases, the drug release also increases but not to a large extent until a plateau is reached. There is a tremendous increase in the release of the drug towards the end of the swelling-erosion process as the amount of drug still present in the polymer is small and seems to be more affected by the erosion process. It is worth noting that the swelling process affected the drug release to a larger extent than the erosion process as metformin is a water-soluble drug.

Conclusion

Evaluation of extended-release commercial formulations was done using both dissolution and textural analysis. From the dissolution, the performance of the drug in acidic and basic media was evaluated. The release of metformin from controlled release tablets was not affected by the pH of the media. The evaluation of drug release from the dissolution profile was done according to different release mechanisms. The drug-release from controlled release preparations follows either diffusion-controlled mechanism (Higuchi equation) or first-order kinetics (according to Wagner). From the textural analysis profile along with the tablet weight changes accompanying the textural analysis, the % axial swelling, % erosion, % hydration or weight gain, and the total work of penetration were calculated. All these calculations demonstrated the main mechanisms of drug release from the tablet. In case of water soluble drugs like metformin, the swelling of the polymers affects the drug release to a larger extent than the erosion process thus metformin was mainly released from the hydrophilic polymers via diffusion.

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