World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.org/
Original Article

Influence of different grades and concentrations of hydroxypropyl methyl cellulose on the release of metformin hydrochloride

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Received: 23-07-2014 / Revised: 30-07-2014 / Accepted: 15-08-2014

Abstract

The main purpose of this work is to investigate drug release from matrix based metformin tablets prepared from Hydroxypropyl Methyl Cellulose of different grades: HPMCK4M, HPMCK15M and HPMCK100M of varying concentrations. Metformin tablets prepared by wet granulation using 11, 15, 20, 25 and 30% concentrations of above three grades were subjected to dissolution in USP Type I apparatus at 100 rpm medium being phosphate buffer (pH 6.8). Aliquots of sample were withdrawn at 1 hr, 3 hr, 6 hr and 10 hr and percentage drug release was analyzed in UV Spectrophotometer. The formulation was then optimized on basis of Indian Pharmacopoeia 2010 and drug release was compared with the marketed sample. Compatibility study using IR and three months stability studies were also performed. The results showed that at a fixed polymer level, drug release from the higher viscosity grade, K100M was slower as compared to the lower viscosity grades, K15M and K4M. Further, increasing concentration of same grade polymer showed decreased release rate. The release retarded with increase in polymer concentration because of swelling and gelling of HPMC which resulted in slowing penetration from the matrix due to increase in diffusional path length. High viscosity grade polymer can sustain the drug release at lower concentration than that of lower grades.

Key words: Metformin, Sustained release, Viscosity, Swelling, Diffusion, Grades

INTRODUCTION

Extended release (ER) dosage form categorized under the term Modified release dosage forms is one of the drug products (FDA, 1997) which are formulated to make the drug available over an extended period after ingestion; thus, it allows a reduction in dosing frequency compared to a conventional type i.e. immediate release (IR) dosage form. Products that alter the timing and rate of release of drug substance are termed as modified- release dosage forms. A modified-release dosage form is defined "as one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosages forms [1]. The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug [2]. Matrix tablets are considered to be the commercially feasible sustained action dosage forms that involve the least processing variables, utilize the conventional facilities and accommodate large doses of drug. It is of great interest to develop novel formulations that allow for sustained the drug release using readily available, inexpensive excipients by matrix based formulations [3]. The importance of the use of sustained-release technology in the formulation of pharmaceutical product is increasing. Sustained drug delivery involves the application of physical and polymer chemistry to produce well characterized and reproducible dosage forms, which control drug entry into the body within the specifications of the required drug delivery profile [4]. Though this type of dosage forms is influenced by external conditions, such as pH, enzymes, ions, motility and physiological conditions, the rate of drug release is mainly controlled by the delivery system itself [5]. Despite that, drug release from matrix tablet depends on other factors such as pore permeability, shape and size of matrix, drug solubility, polymer

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molecular weight, drug loading, compression force and hydrodynamic conditions [6]. The compression force has major control over the porosity, which directly influences the release characteristic of the tablet [7,8].

Drug solubility, hydrophilicity of the polymer and tablet porosity determines the rate of liquid penetration into the tablet, and thus influences drug release rate. It has been found that pore size distribution of the matrix and the permeation pressure of the release media is defined by its surface tension and contact angle [9]. Swelling of matrix tablet is influenced by the initial wetting of the surface of matrix tablet, hydrophobicity of the drug and the amount and type of polymer in the matrix tablet. The property of the gel layer formed by swellable polymers is the key factor for prediction of the kinetics of matrix swelling [10]. The growth of erosion front, diffusion front, and swelling front decrease with the increase in polymer proportion because of the formation of a stronger gel layer, which makes the entry of medium into the matrix difficult [11]. The drug release rate decreases with the increase in polymer proportion because the polymer swells and the resultant gel blocks the pathway of the medium and the drug, thus slowing down medium penetration and drug release. Since the above factors are important in designing of sustained-release matrix tablet, they deserve in-depth studies.

The reasons for developing the SR matrix DDS are:

- To extend the duration of action of the drug
- To reduce the frequency of dosing
- To minimize the fluctuations in plasma level
- Improved drug utilization
- Less adverse effects

MATERIALS AND METHODS

Materials: All the excipients along with Metformin Hydrochloride were obtained as a gift sample from Lomus Pharmaceuticals Pvt. Ltd. Other laboratory reagents were provided by National Model College for Advance Learning. Equipments and materials used during this work are listed in table 1 and 2 respectively.

Methods

Drug-excipients Compatibility study: Physical compatibility was assured by keeping 1:1 ratio of drug and excipient in humidity chamber maintained at temperature 40±2ºC and RH 75±5%. Any change in color, odor was noted periodically for a period of 3 months. Infrared spectrum was taken by scanning the samples of pure drug and the mixture with polymers in the ratio of 1:1 over a wave number range of 4000 to 400cm–1 using Fourier transform infrared spectrophotometer. The change in spectra of the drug in the presence of polymer was investigated to ascertain that there was no any significant alteration in major peaks [12].

Preparation of Metformin Hydrochloride matrix tablets:

At first the Preliminary Trial Batch of five formulations with varying concentration of HPMC (from 10% in increasing order) and EC (from 1% in increasing order) was studied to predict release pattern as in table 3. The wet granulation method was followed to fabricate the batches. The API was weighed, sieved through 30 mesh size and coated with the ethyl cellulose dissolved in Methylene chloride. It was then allowed to air dry. All the ingredients except lubricants were passed through mesh size 30, mixed properly with coated API and granulated with binder dissolved in Isopropyl alcohol. Then the wet mass was sieved through 12 mesh size, allowed for air drying for 10-15 minutes and dried in tray drier at 45ºC for 20 minutes. The dried mass was then sieved through 20 mesh size followed by lubrication with magnesium stearate and P.talc after passing through 80 mesh size.

This final blend was then analyzed for pre compressional parameters and finally compressed into tablets using 16 station rotary tablet press using DS punch of length 20+1.0 mm. The trail batches comprising higher amount of ethyl cellulose (i.e. PTB1, PTB2 and PTB4) showed various problems like sticking and drying problems along with tablet bursting during dissolution. Among PTB3 and PTB5, the release pattern of PTB5 that comprised of 22.22% HPMC K100M was found best. So, HPMC was only scaled up other excipients keeping constant assuming PTB5 as a basis. The concentrations of other HPMC grades were tentatively fixed as 11%, 15%, 20%, 25% and 30% based on above preliminary study as in table 4.

Evaluations of tablets: The prepared matrix tablets were analyzed immediately after compression for hardness, weight variation, thickness, friability and drug content. Weight variation of matrix tablets (n=20) was evaluated using an electronic balance (*Indian Pharmacopoeia*, 1996). Hardness tablets (n=6) from each formulations was determined by tablet hardness tester (Campbell Electronics, India). Friability (wt.≥ 6.0gm) was determined by a Roche friabilator for 4 minutes at a speed of 25 rpm. The thickness of tablets was measured by vernier caliper. Drug content was analyzed by measuring the absorbance of standard and samples at λ=232 nm using UV/Visible spectrophotometer [13].

***In-Vitro* drug release studies:** The *in vitro* release of Metformin HCl tablets was performed using IP dissolution apparatus Type II (Basket).The test was carried out using 1000ml of phosphate buffer solution pH 6.8 (prepared by dissolving 27.22 g of *monobasic potassium phosphate* in 1000 ml of water and taking 250 ml of that solution and adding 112 ml of 0.2*M sodium hydroxide solution,* then diluted to 1000 ml with water.) as dissolution medium. The test was performed at a temperature of 37 ± 0.5° C and 100 rpm speed for 10 hours. Tablets was in dissolution jar and the samples were taken at 1h, 3h, and 10 hour intervals. The samples were withdrawn, filtered and diluted to suitable concentration and analyzed for Metformin HCl content at 233nm by using UV spectrophotometer [13].

Release kinetics: Different kinetic equations (Zero-order, first-order, Higuchi's equation and Krosmeyer-Peppas Model) were applied to interpret the release rate of drug from matrix systems.

Zero order release kinetics can be expressed by the equation:

$Q_1 = Q_o + K_o t$

Where, $Q_{1=}$ Amount of drug dissolved in time t and the Q_o = Initial amount of drug in the solution, which is often zero and K_o is the zero order release constant.

It is independent of the amount of drug present in the dosage form and there is a constant release rate of drug. This is the ideal method of drug release to achieve prolonged pharmacological action [14].

First order release kinetics can be expressed by the equation:

$Q_t = Q_o e^{-kt}$

Where Q_t is the amount of drug released in time t. Q_o is the initial amount of drug in the solution and k is the first order release constant. The above equation in decimal logarithm will take the form

$\log Q_t = \log Q_o + kt/ 2.303$

This equation implies that a graphic of the decimal logarithm of the amount of drug versus time will be linear. The dosage forms that follow this dissolution profile release the drug in a way that is proportional to the amount remaining in the interior of the dosage form, in such a way that the amount of drug released by unit of time diminishes [14].

Higuchi model can be represented as follows:

$M = kt^{1/2}$

Where, k is the constant, so that a plot of amount of drug released versus the square root of time should be linear if the release of the drug from the matrix is diffusion- controlled [14].

Krosmeyer-Peppas Model is mathematically expressed in the following way:

$Mt / M\infty = kt^n$

Where, Mt & $M\infty$ are the absolute cumulative amounts of drug released at time t and infinity respectively k is a constant incorporating structural and geometrical characteristics of the device, and n is the exponent, indicative of the mechanism of drug release [14].

RESULTS

Compatibility study: Metformin Hydrochloride showed two typical bands at 3369 and 3296 cm^{-1} due to N-H primary stretching vibration and a band at 3170 cm^{-1} due to N-H secondary stretching. Characteristics bands at 1626 and 1567 cm^{-1} assigned to C=N stretching. FTIR studies revealed that there is no significant distortion or reduction in the intensity of the FTIR bands of Metformin Hydrochloride.The IR spectrum of metformin tallied with 1:1 ratio of metformin and excipients is shown in figure 1.

Physicochemical properties: The angle of repose for the formulated batches ranged from 36º to 39º. The results of the bulk density measurements of the different batches of granules prepared for compression are shown in table 5. The value for Hausner's ratio ranged from 1.159 to 1.191 indicating a good flow of the granules. The Carr's index obtained ranged from 13.03% to 16.07%. The angles of repose obtained also ranged between 36.68 º and 39.28 º. The average weight of tablets ranged from 1333mg to 1355mg in formulations using 11%, 15% and 20% polymer. In the formulations, F4, X4 and Y4 where the polymer was used in 25% concentration, the average weight ranged from 1381mg to 1401mg to accommodate the higher concentration of polymer. Similarly formulations using 30% of polymer had the average weight in the range of 1476mg-1479mg. The weight variation of all the batches passed the pharmacopoeial requirement. The average length of tablet ranged from 20.77mm to 20.86mm and the breadth from 9.80mm to 9.83mm. But the thickness ranged from 7.41mm to 8.1mm to compensate the total weight as indicated in table 6.

The friability of the different batches of tablets ranged from 0.4% to 0.97%. The swelling of matrix was progressive for 13hrs in all formulations as represented in figures 2-6.

***In Vitro* Dissolution Study**

Effect of different grades of HPMC: The low viscosity grade HPMC was not found to be so effective to sustain the release of drugs from their matrices since medium can penetrate easily. Upon

increasing the viscosity grade of the polymer, the release rate has been found to be sustained as in table 7 and figures 7-11.

Effect of different concentrations of HPMC: Initial burst release of drug was observed with formulations containing comparatively low viscosity grade HPMC K4M. With increase in polymeric concentration this burst effect and the drug release in later hours of dissolution were reduced significantly as illustrated in figures 12-14.

Drug content: The assay percentage of all the formulated batches were found in the range of 97.8% to 104.125% which was within the limit which is depicted in table 6 and figure 15.

Stability: The stability study showed that the assay percentage of the optimized formulation (Y3) decreased by 0.51% in three months. There was no large variation in the dissolution profile during 3 month stability study. It is illustrated in figures 16 and 17.

Drug release kinetics: The dissolution data were fitted to Zero Order, First Order, Higuchi Model and Peppas Model. The rate constants and R^2 values for Zero Order, First Order, Higuchi Model and "n" value for power law of all the formulated matrix tablets are given in table 8.
The correlation coefficient (R^2) values obtained from the different kinetic equations revealed that the drug release from the formulated matrix tablets was found to follow Higuchi model.

Diffusion exponent "n" values thus obtained in the range from 0.222 to 0.5724 for different formulations. For the formulations with "n" values less than 0.45 i.e. F1, F2, X1, X2, X3 and Y1 indicates drug diffusion partially through swollen matrix and water filled pores in the formulation. For the formulations F3, F4, F5, X4, X5, Y2, Y3, Y4 and Y5 the "n" value is greater than 0.45 suggesting that the release of drug from these formulations follows non-frickian diffusion mechanism. The power law revealed that at the grades and concentration of polymer alters the diffusion mechanisms for the release of drugs.

Statistical Analysis: The similarity and difference factor of all formulations was obtained with the marketed product. It was found that the greatest similarity factor (72.91) and lowest difference factor (4.501) with the marketed product was of Y3 i.e. the formulation containing 20% HPMC K 100M. Further, this optimized formulation was tested for correlation with marketed product and was found good correlation in dissolution profile with R^2 value 0.981 as in figure 18. When the drug release profiles of optimized and marketed product were analyzed by two tailed t-test, it showed that the correlation is significant at the 0.01 level.

DISCUSSION

Compatibility study: There was no change in the physical appearance and odor which concluded that the drug and excipients are physically compatible. FTIR studies revealed that there is no significant distortion or reduction in the intensity of the FTIR bands of Metformin Hydrochloride. Hence it can be presumed that Metformin Hydrochloride is compatible with the excipients used during formulation development.

Physicochemical properties: The pre compressional parameters were evaluated by finding the Angle of repose of the blended powder, Tapped density, Bulk density, Carr's Index and Hausner ratio. The angle of repose for the formulated batches ranged from 36º to 39º. As a general guide, powders with angle of repose greater than 50º have unsatisfactory flow properties, whereas minimum angles close to 25º corresponds to very good flow properties [15]. The Hausner's ratio and the Carr's index or percent compressibility, which are measures of interparticle friction and the potential powder arch or bridge strength and stability, respectively, have been widely used to estimate the flow properties of powders and extrapolated to that of granules. According to Aulton (2002), a Hausner's ratio value of less than 1.25 is indicative of good flowability of the material, whereas a value of 1.25 or higher suggests a poor flow display by the material. According to Carr (1965), a Carr's index between 5 and 15, 12 and 16, 18 and 21, and 23 and 28 indicates excellent, good, fair, and poor flow properties of the material, respectively.

The results of the bulk density measurements of the different batches of granules prepared for compression shows that the value for Hausner's ratio ranged from 1.159 to 1.191 indicating a good flow of the granules. The Carr's index obtained ranged from 13.03% to 16.07% which also indicates a good flow of the granules. The angles of repose obtained also ranged between 36.68 º and 39.28 º. This shows that the granules had a good flow because powders with angle of repose greater than 50º have unsatisfactory flow properties [15]. The uniformity of weight test carried out on tablets prepared with different concentrations of the HPMC showed that all the formulated tablets had uniform weight. This is indicative of the good flow properties of the granules. The uniformity of weight test gives an indication of how the weights of the individual tablets are scattered about the

average weight. By British Pharmacopoeia standards for uncoated tablets, the permitted percentage deviation for a tablet of weight greater than 250 mg is 5 % and not more than two of the individual tablets should deviate from the average weight by more than the permitted percentage deviation and none should deviate by twice the permitted deviation. From table 6, none of the batches of tables failed the uniformity of weight test.

The average weight of tablets ranged from 1333mg to 1355mg in formulations using 11%, 15% and 20% polymer. In the formulations, F4, X4 and Y4 where the polymer was used in 25% concentration, the average weight ranged from 1381mg to 1401mg to accommodate the higher concentration of polymer. Similarly formulations using 30% of polymer had the average weight in the range of 1476mg-1479mg. The weight variation of all the batches passed the pharmacopoeial requirement. The results could be due to the good flow properties exhibited by the granules prepared and the uniform compression force used in tablet compression.

The average length of tablet ranged from 20.77mm to 20.86mm and the breadth from 9.80mm to 9.83mm. But the thickness ranged from 7.41mm to 8.1mm to compensate the total weight. The friability of the different batches of tablets ranged from 0.4% to 0.97%. The maximum permitted loss in weight of a batch of tablets subjected to friability testing is 1 % [16]. This parameter assesses the ability of the tablet to withstand stress and abrasion associated with handling, packaging and transportation and chipping. This property of the tablet is affected by the nature and amount of binder used. Binders impart the cohesive nature to the particles in the tablets. From the results obtained, all the batches of tablets passed the friability test.

The swelling of matrix was progressive and reached maximum in 12-13 hours for all of the formulations. The swelling index for two formulations which comprised of same grade polymer in different concentration revealed that the swelling index remained similar for initial 2 hours but later it increased with the increase in concentration. It was also seen that the swelling index gradually decreased after 13th hour in both cases. With increase in HPMC concentration, swelling index increased in all the batches. This may be attributed to rapid hydration and gel layer formation by HPMC around the surface of the tablet. As the proportion of the HPMC increases, proportion of the diluent decreases. The diluent MCC is very porous and weakly swellable polymer. Therefore MCC does not form gel layer around the surface. In the batches with high the proportion of MCC, swelling index observed is much less in these cases as compared to other batches in the same series [17].

This result revealed that even at the same concentration of various grades of HPMC, the swelling index differed. The swelling index for initial hours is same but later it differed according to the viscosity grades and after 13th hour the swelling index gradually decreased due to erosion of the matrix. With increase in viscosity of HPMC, swelling index increased in all the batches. In formulations comprising smaller grades polymer, swelling index increased up to a maximum level in 8th hr. and then onwards it started decreasing. This may be due to the low viscosity grades of HPMC used in these formulations, which results in loss of matrix integrity and hence rapid erosion. In the formulation formulated with higher viscosity grade, the swelling index showed increments up to 10th hr. The formulation in which the viscosity of HPMC grade is much higher resulted in more hydration and gel formation around the surface of the tablet, attributing to high swelling index. Due to high viscosity, matrix integrity is maintained for a longer duration leading to least erosion [17].

***In Vitro* Dissolution Study**

Effect of different grades of HPMC: The low viscosity grade HPMC was not found to be so effective to sustain the release of drugs from their matrices since medium can penetrate easily. Upon increasing the viscosity grade of the polymer, the release rate has been found to be sustained. This is because, with the increase in the viscosity of the polymer, the penetration of the medium decreases due to higher viscosity and thus leads to the retardation of the drug release [9].

In this study, since the Metformin hydrochloride is highly hydrophilic in nature, the low viscosity grade HPMC K4M was not found as effective as other grades in comparison. Though the release pattern seems to be similar, the rate of drug release has been highly influenced by the viscosity grades i.e. upon increasing the viscosity grades rate of drug release has been decreased.

Effect of different concentrations of HPMC: Initial burst release of drug was observed with formulations containing comparatively low viscosity grade HPMC K4M. With increase in polymeric concentration this burst effect and the drug release in later hours of dissolution were reduced significantly. This may be attributed to greater gel formation resulting in increased diffusional path length for drug release [18]. It is

also clear that HPMC K4M cannot control the initial drug release as much as the lower viscosity grades at least up to initial 3 hrs. Then, it starts releasing drug in a more sustained manner than its counter parts irrespective of the polymer concentrations. This may be attributed to the increasing swelling index of HPMC K4M over the entire dissolution time and at the same time decrease in swelling index was seen after a certain point of time in case of lower viscosity grades. It may also be assumed that increase in amount of lower grade polymers delays the onset of matrix erosion of the formulation, since higher the low grade polymer concentration, longer would be the time taken to obtain the optimum swelling index. The permeability increased at higher HPMC concentrations as upon hydration of the film water channels within the film become the major pathway for drug release [19].

But from a comparison of various polymers, it was found that one important polymer property should be that the polymer must hydrate quickly to form a gel layer before the contents of the tablet can dissolve prematurely. 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. 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. 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 diffusional layer that is resistant to diffusion or erosion.

Ultimately this will slow drug release which concluded [20].

1. Drug release became more sustained with increasing polymer concentration or viscosity grade;
2. Different levels of methyl and hydroxypropoxy substitution resulted in intrinsically different hydration rates, which affected the performance of the polymer in the initial stages of tablet hydration; and
3. Different substitution levels gave rise to different drug release profiles, principally as a result of differences in gel strength and susceptibility to erosion.

Size and shape (e.g. tablet or capsule) of matrix are 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.

Drug content: The assay percentage of all the formulated batches were found in the range of 97.8% to 104.125% which was within the limit. Metformin Hydrochloride tablets contains not less than 95.0% and not more than 105.0% of metformin hydrochloride [21].

Stability: The stability study of the optimized formulation (Y3) was conducted on the cumulative percentage drug release (Dissolution), assay percentage and thus is compared with the market sample as shown in figure 16. The stability study showed that the assay percentage of the optimized formulation decreased by 0.51% in three months. A significant change is considered to have occurred if the assay value shows a 5% decrease as compared with the initial assay value of the batch [22].

The stability study conducted in dissolution profile in 0, 1, 2 and 3 months is depicted in figure 17.There was no large variation in the dissolution profile during 3 month stability study. A significant change is considered to have occurred if the specification limits for the dissolution of 12 capsules or tablets are no longer met [22].

Drug release kinetics: The dissolution data were fitted to Zero Order, First Order, Higuchi Model and Peppas Model. The rate constants and R^2 values for Zero Order, First Order, Higuchi Model and "n" value for power law of all the formulated matrix tablets were determined. The correlation coefficient (R^2) values obtained from the different kinetic equations revealed that the drug release from the formulated matrix tablets was found to follow Higuchi model. Diffusion exponent "n" values thus obtained in the range from 0.222 to 0.5724 for different formulations. For the formulations with "n" values less than 0.45 i.e. F1, F2, X1, X2, X3 and Y1 indicates drug diffusion partially through swollen matrix and water filled pores in the formulation. For the formulations F3, F4, F5, X4, X5, Y2, Y3, Y4 and Y5 the "n" value is greater than 0.45 suggestion that the release of drug from these formulations follows non-frickian diffusion mechanism.

The power law revealed that at the grades and concentration of polymer alters the diffusion mechanisms for the release of drugs. From the above fact it can be assumed that:

1 Low grade polymer (HPMC K4M) upto 20% concentration follows frickian mechanism and beyond that concentration it follows non frickian diffusion mechanism.

2 Upon increasing the grade i.e. HPMC K15M, the formulation comprising upto 15% of polymer only showed non frickian diffusion mechanism.

3 Further increase in grade i.e. HPMC K100M, the only formulation that follows frickian mechanism is Y1 (11% polymer). Beyond 11% of high grade polymer followed non frickian diffusion mechanism.

Statistical Analysis: A model independent mathematical method was developed to compare dissolution profiles using two factors, f_s and f_d. The factors f_s and f_d are known as the similarity factor and difference factor which measures the closeness between the two profiles. The similarity and difference factor of all formulations was obtained with the marketed product. It was found that the greatest similarity factor (72.91) and lowest difference factor (4.501) with the marketed product was of Y3 i.e. the formulation containing 20% HPMC K 100M. Further, this optimized formulation was tested for correlation with marketed product and was found good correlation in dissolution profile with R^2 value 0.981. When the drug release profiles of optimized and marketed product were analyzed by two tailed t-test, it showed that the correlation is significant at the 0.01 level.

CONCLUSIONS

The finding of the present study demonstrate that the hydrophilic matrix of HPMC of low viscosity grade could not control the release of Metformin HCL effectively for 10 hours whereas polymer of higher viscosity could slow down the release of drug from the matrices. Thus high viscosity polymer is employed for the formulation of sustained release matrix tablets. Diffusion coupled with erosion might be the mechanism of drug release from matrix tablets.

ACKNOWLEDGEMENTS

The authors are thankful to Lomus Pharmaceuticals Pvt. Ltd. for providing Metformin Hydrochloride and various grades of HPMC as a gift samples and National Model College for Advance Learning for providing necessary facilities to carry out this work.

Table 1: List of equipment used

Name of the equipment	Model No.	Origin
Analytical balance	AR-3130/ *OHAUS*	Germany
Weighing balance	98-110/Scaltec	Germany
Tray Drier		
Tablet compression machine	-	
Dissolution Tester (USP)	TDT-80/ Electro lab	India
Friability test Apparatus	C-FTA 20 /Thermonik	India
Tapped density tester	-/ Thermonik	India
Digital Vernier calipers	-/ Mitutoyo	Japan
Digital Tablet Disintegration Test Machine	(IP/BP/USP std)	India
UV-Spectrophotometer	UV-2450/Shimadzu	Japan
pH meter	420 A/ Thermo Orion	USA
Tablet Hardness Tester	C-DHT 200/ Thermonik	India
FTIR	-/Shimadzu	Japan
Sonicator	PCI	India

Table 2: List of materials used

Materials	Functionality
Metformin HCl	API
HPMC K4M	Polymer
HPMC K4M	Polymer
HPMC K4M	Polymer
Dibasic Calcium Phosphate (Dihydrate)	Diluent
PVPK-30	Binder
Ethyl Cellulose	Coating agent
Magnesium stearate	Lubricant
P.Talc	Glidant

Table 3: Compositions of preliminary trial batches

Items	PTB-1	PTB-2	PTB-3	PTB-4	PTB-5
Met. HCl	1000 mg	1000 mg	1000 mg	1000 mg	1000 mg
EC	150 mg	70 mg	40 mg	100 mg	13.5 mg
PVPK 30	27 mg	27 mg	27 mg	27 mg	27 mg
HPMC K100M	150 mg	200 mg	250 mg	100 mg	300 mg
DCP	-	29.86 mg	9.86 mg	99.86 mg	-
P.Talc	11.57 mg	11.57 mg	11.57 mg	11.57 mg	11.57 mg
MST	11.57 mg	11.57 mg	11.57 mg	11.57 mg	11.57 mg
Total Wt./Tab	1350 mg	1350 mg	1350 mg	1350 mg	1363.64 mg

Table 4: Formulation compositions using three grades in different proportions.

Code	Met.HCL	E.C.	HPMC K4M	HPMC K15M	HPMC K100M	PVPK 30	P. TALC	MST	DCP	Total Weight
F1	1000	13.5	-	148.5	-	27.0	11.57	11.57	137.86	1350.0
F2	1000	13.5	-	202.5	-	27.0	11.57	11.57	83.86	1350.0
F3	1000	13.5	-	270	-	27.0	11.57	11.57	16.30	1350.0
F4	1000	13.5	-	337.5	-	27.0	11.57	11.57	-	1401.0
F5	1000	13.5	-	405	-	27.0	11.57	11.57	-	1468.0
X1	1000	13.5	148.5	-	-	27.0	11.57	11.57	137.86	1350.0
X2	1000	13.5	202.5	-	-	27.0	11.57	11.57	83.86	1350.0
X3	1000	13.5	270	-	-	27.0	11.57	11.57	16.30	1350.0
X4	1000	13.5	337.5	-	-	27.0	11.57	11.57	-	1401.0
X5	1000	13.5	405	-	-	27.0	11.57	11.57	-	1468.0
Y1	1000	13.5	-	-	148.5	27.0	11.57	11.57	137.86	1350.0
Y2	1000	13.5	-	-	202.5	27.0	11.57	11.57	83.86	1350.0
Y3	1000	13.5	-	-	270	27.0	11.57	11.57	16.30	1350.0
Y4	1000	13.5	-	-	337.5	27.0	11.57	11.57	-	1401.0
Y5	1000	13.5	-	-	405	27.0	11.57	11.57	-	1468.0

Table 5: Pre compression parameters of the formulated Metformin HCL sustained release tablets.

Formulations	Angle of Repose	Bulk Density	Tapped Density	Carr's Index	Hausners' ratio
F1	38.3	0.56	0.658	14.893	1.175
	38.5	0.562	0.658	14.589	1.17
F3	38.8	0.568	0.663	14.328	1.167
F4	37.6	0.556	0.645	13.798	1.16
F5	37.23	0.58	0.688	15.69	1.186
X1	39.01	0.604	0.7173	15.79	1.187
X2	37.95	0.596	0.707	15.7	1.186
X3	38.38	0.598	0.698	13.03	1.167
X4	38.79	0.554	0.644	13.97	1.162
X5	36.68	0.588	0.7	16	1.19
Y1	39.35	0.606	0.721	15.95	1.189
Y2	37.79	0.598	0.696	14.38	1.168
Y3	38.1	0.568	0.677	16.07	1.191
Y4	39.28	0.5602	0.6513	13.98	1.162
Y5	36.86	0.581	0.673	13.78	1.159

Table 6: Evaluation of physicochemical parameters of compressed tablets.

Formulation	Average Weight ± SD (mg) N=20	Average Length ± SD (mm) N=10	Average Breadth ± SD (mm) N=10	Average Thickness ± SD (mm) N=10	Average Hardness ± SD N=10	Friability %	Assay % of the Drug ± SD N=2
F1	1333.4±6.294	20.86 ± 0.031	9.983 ± 0.042	7.47 ± 0.105	7.65 ± 0.935	0.59	99.705 ± 0.9121
F2	1343.9± 7.73	20.79 ± 0.018	9.896 ± 0.017	7.431 ± 0.097	8.05 ± 0.897	0.40	99.58 ± 0.3252
F3	1355.95± 4.87	20.78 ± 0.021	9.88 ± 0.032	7.48 ± 0.041	8.0 ± 0.3829	0.54	99.45 ± 0.862
F4	1393.85 ± 8.96	20.80 ± 0.025	9.84 ± 0.05	7.858 ± 0.033	7.2 ± 0.288	0.91	99.97 ± 0.268
F5	1479.8 ±9.7	20.77 ± 0.037	9.835 ± 0.053	8.218 ± 0.046	7.05 ± 0.2753	0.97	99.155 ± 0.2757
X1	1355.2 ±5.89	20.815 ± 0.022	9.88 ± 0.016	7.468 ± 0.026	7.1 ± 0.2081	0.71	97.903 ± 0.5218
X2	1351.2 ±9.91	20.80 ± 0.017	9.856 ± 0.013	7.418 ± 0.030	6.714 ± 0.3023	0.45	100.315 ± 1.364
X3	1351.2 ±9.83	20.83 ± 0.021	9.865 ± 0.022	7.435 ± 0.064	6.77 ± 0.2984	0.90	99.294 ± 0.2665
X4	1381.8 ±9.25	20.80 ± 0.014	9.838 ± 0.0078	7.763 ± 0.019	6.957 ± 0.139	0.59	100.051 ± 0.5352
X5	1476.65 ± 8.95	20.79 ± 0.012	9.8 ± 0.033	8.108 ± 0.021	6.93 ± 0.2568	0.73	100.903 ± 0.447
Y1	1350.35 ± 9.72	20.85 ± 0.023	9.875 ± 0.036	7.45 ± 0.0789	7.217 ± 0.6733	0.68	101.73 ± 1.125
Y2	1355.3 ± 9.57	20.85 ± 0.046	9.851 ± 0.0435	7.423 ± 0.050	7.05 ± 0.386	0.86	104.125 ±1.725
Y3	1351.25 ± 9.16	20.806 ± 0.021	9.88 ± 0.025	7.486 ± 0.013	7.15 ± 0.5058	0.94	97.89 ± 0.5232
Y4	1401.3 ± 9.47	20.8 ± 0.04	9.853 ± 0.040	7.821 ± 0.034	7.0514 ± 0.446	0.37	100.32 ± 0.1414
Y5	1477.85 ± 8.61	20.78 ± 0.026	9.816 ± 0.041	8.11 ± 0.025	7.157 ± 0.3779	0.84	100.885 ± 0.4737

Table 7: The dissolution profile of the formulated products.

Formulations	**1st Hour**	**3rd Hour**	**6th Hour**	**10th Hour**
F1	56.89 ± 1.84	80.44 ± 1.529	91.12 ± 1.082	99.65 ± 1.046
F2	49.505 ± 1.963	69.7 ± 0.205	89.872 ± 2.016	99.257 ± 0.727
F3	31.042 ± 0.646	59.73 ± 0.652	82.658 ± 1.354	99.554 ± 2.305
F4	28.922 ± 1.323	51.595 ± 0.607	73.483 ± 0.823	93.302 ± 0.507
F5	26.96 ± 0.123	51.83 ± 0.162	74.813 ± 0.269	90.022 ± 0.392
X1	60.856 ± 1.25	91.113 ± 2.014	99.003 ± 0.29	100.403 ± 0.859
X2	42.268 ± 0.416	72.18 ± 1.578	93.33 ± 0.859	98.375 ± 0.711
X3	37.47 ± 0.471	64.045 ± 0.807	82.873 ± 1.428	98.295 ± 0.646
X4	35.33 ± 1.032	61.635 ± 1.629	86.693 ± 0.191	98.346 ± 0.284
X5	30.4 ± 0.163	55.44 ± 0.0899	76.5283 ± 1.735	92.601 ± 0.7121
Y1	51.331 ± 3.675	80.701 ± 0.506	91.38 ± 0.851	98.258 ± 0.508
Y2	32.798 ± 0.745	62.223 ± 1.944	82.384 ± 0.757	93.673 ± 1.123
Y3	29.348 ± 1.945	53.946 ± 0.948	78.878 ± 0.823	89.948 ± 1.021
Y4	28.236 ± 1.152	54.396 ± 1.279	76.06 ± 1.553	89.076 ± 1.643
Y5	23.87 ± 0.67	49.445 ± 0.093	69.958 ± 0.8134	88.766 ± 0.746
MKT	27.97±0.73	50.455± 1.03	72.66 ±0.972	96.95 ± 1.472

Table 8: The determination of coefficients and the relevant kinetic constants

Formula-tions	Zero Order Model		First Order Model		Higuchi Model		Power Law	
	R^2	K_o	R^2	K_1	R^2	K_H	R^2	n
F1	4.3689	0.854	0.7983	0.0561	0.9424	0.0488	0.9768	0.244
F2	5.3938	0.9155	0.8659	0.0734	0.9779	0.0417	0.9936	0.3092
F3	7.289	0.9313	0.8344	0.119	0.9877	0.0313	0.9902	0.5095
F4	6.4798	0.9469	0.863	0.1169	0.9932	0.0355	0.9963	0.4937
F5	0.8133	0.9383	0.8441	0.1248	0.9901	0.0336	0.9926	0.532
X1	3.813	0.6545	0.6211	0.0475	0.7887	0.0448	0.8839	0.2225
X2	5.9082	0.8224	0.7533	0.0858	0.9222	0.035	0.9614	0.3804
X3	6.4428	0.9278	0.8443	0.0988	0.9859	0.0353	0.9924	0.4209
X4	6.822	0.9099	0.8316	0.1066	0.9756	0.0328	0.9885	0.4568
X5	6.675	0.9414	0.8519	0.115	0.9918	0.0344	0.9944	0.4884
Y1	4.587	0.7084	0.6555	0.0621	0.8336	0.0338	0.9055	0.2865
Y2	6.3833	0.8828	0.7900	0.1059	0.9623	0.0343	0.9758	0.4627
Y3	6.9489	0.9333	0.8457	0.1204	0.9876	0.0328	0.9923	0.5131
Y4	6.610	0.9234	0.8273	0.119	0.9839	0.0343	0.9884	0.5112
Y5	6.9433	0.9529	0.8464	0.1345	0.9957	0.0333	0.9927	0.5724
MKT	7.4917	0.983	0.9051	0.1302	0.9994	0.0314	0.9830	0.74917

Table 9: Physical characteristics of Metformin Hydrochloride sustained release tablet (F3) during stability study

Time (months)	Weight (mg) Avg±SD N=20	Length (mm) Avg±SD N=10	Breadth (mm) Avg±SD N=10	Thickness (mm) Avg±SD N=10	Hardness (kg/cm^2) Avg±SD N=10	Friability %	Assay % N=3
0	1355.95±4.87	20.78 ± 0.021	9.88 ± 0.032	7.48 ± 0.041	7.011 ± 0.3829	0.54	97.89 ± 0.320
1	1351.2 ±3.97	20.83 ± 0.019	9.865 ± 0.022	7.435 ± 0.064	6.77 ± 0.2984	0.596	97.78± 0.268
2	1348.4±6.294	20.86 ± 0.031	9.983 ± 0.042	7.47 ± 0.105	6.965 ± 0.935	0.495	97.54± 0.2757
3	1351.7 ±6.91	20.80 ± 0.017	9.856 ± 0.013	7.418 ± 0.030	6.714 ± 0.3023	0.45	97.39± 0.447

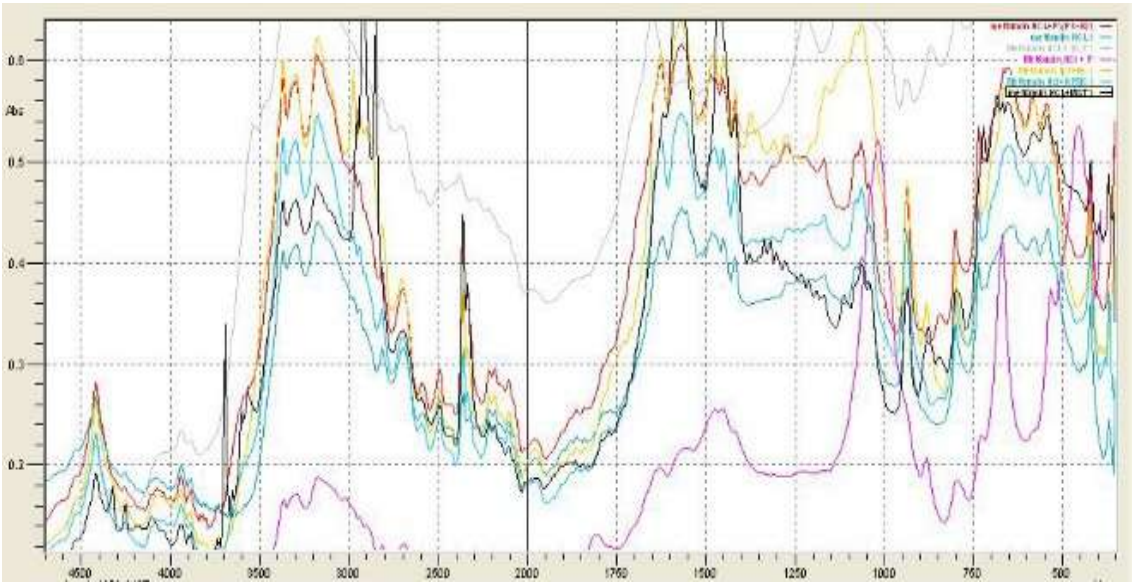

Figure 1: IR spectrum of 1:1 ratio of metformin and excipients.

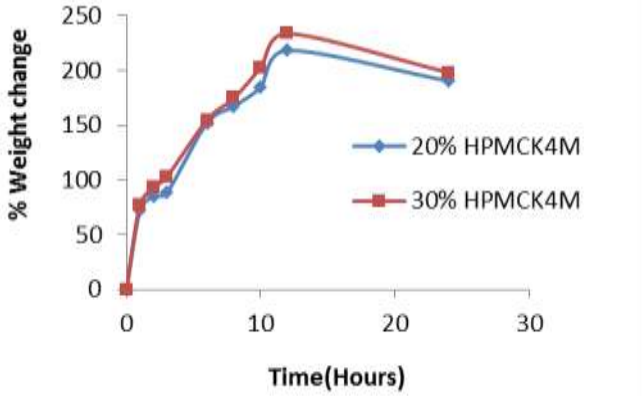

Figure 2: Swelling index of HPMC K4M at different concentrations

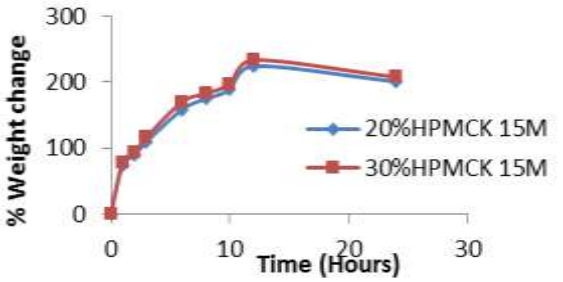

Figure 3: Swelling index of HPMC K15M at different concentrations

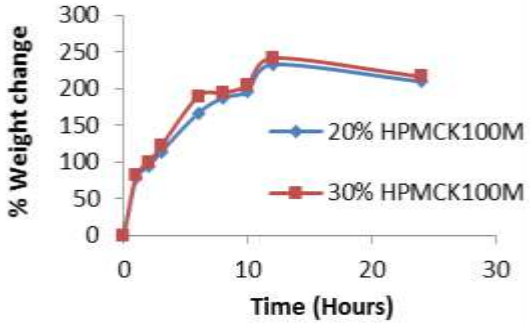

Figure 4: Swelling index of HPMC K100M at different concentrations

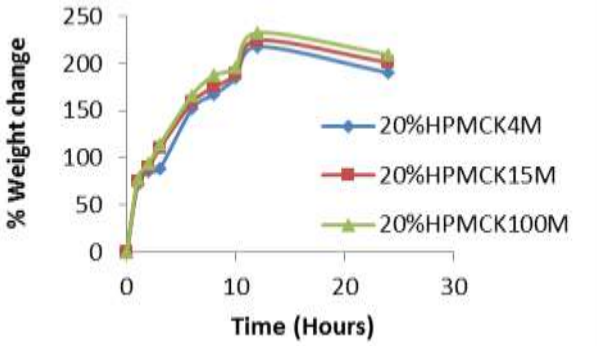

Figure 5: Swelling index of different grades of HPMC at 20% concentration.

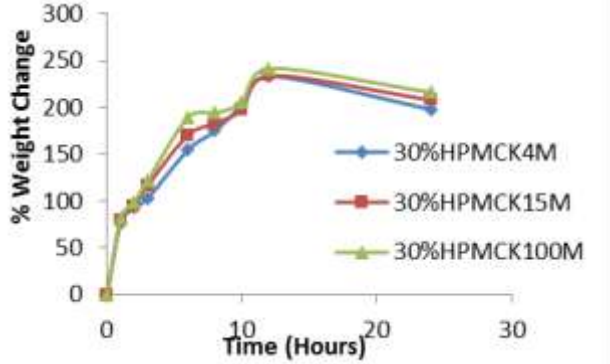

Figure 6: Swelling index of different grades of HPMC at 30% concentration.

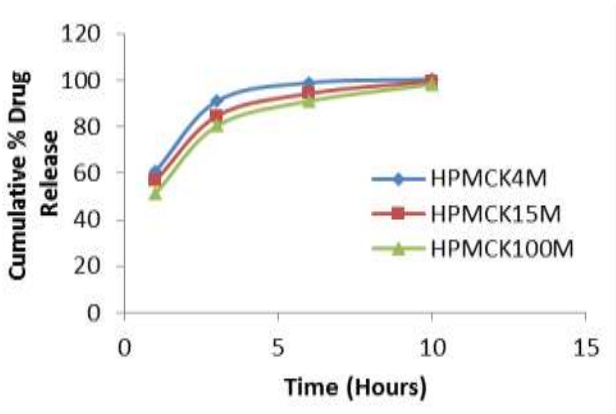

Figure 7: Cumulative % drug release from formulations containing 11% HPMC K4M, K15M and K100M respectively.

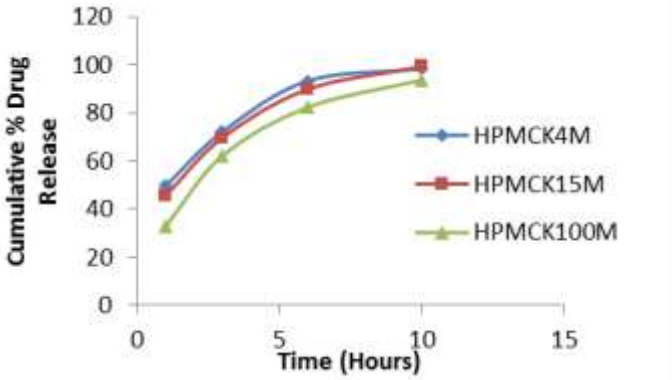

Figure 8: Cumulative % drug release from formulations containing 15% HPMC K4M, K15M and K100M respectively

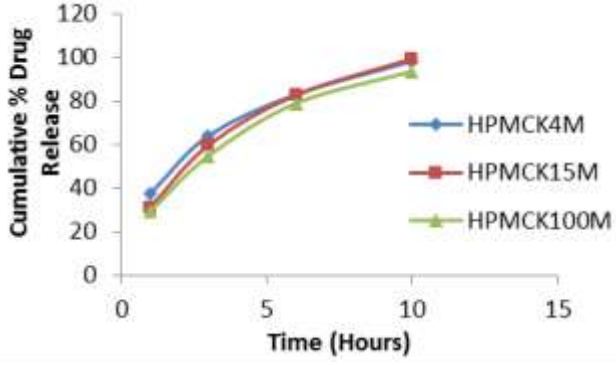

Figure 9: Cumulative % drug release from formulations containing 20% HPMC K4M, K15M and K100M respectively.

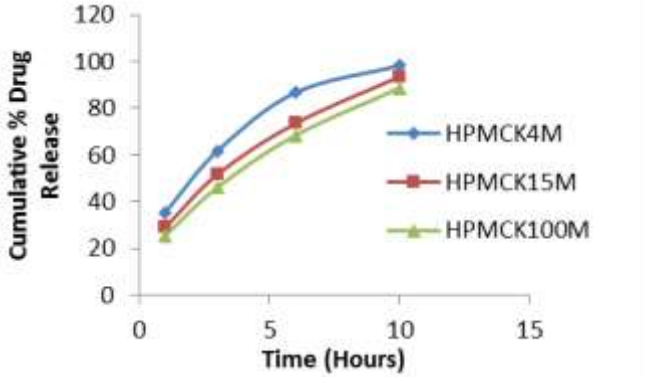

Figure 10: Cumulative % drug release from formulations containing 25% HPMC K4M, K15M and K100M respectively

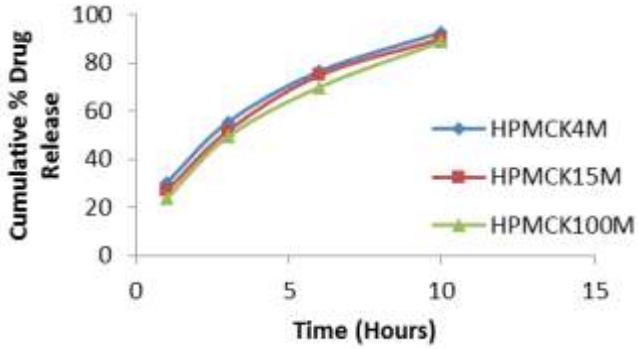

Figure 11: Cumulative % drug release from formulations containing 30% HPMC K4M, K15M and K100M respectively

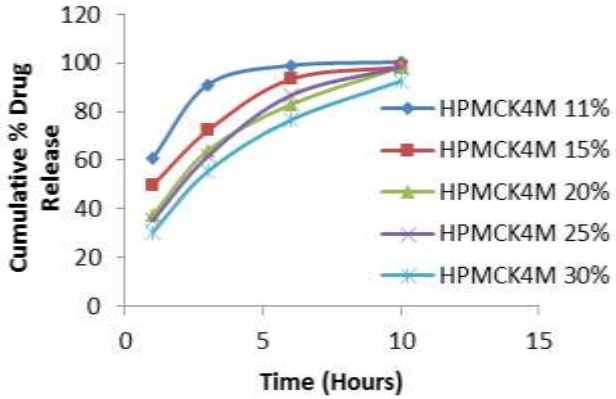

Figure 12: Cumulative % drug release from formulations containing different concentrations of HPMC K4M

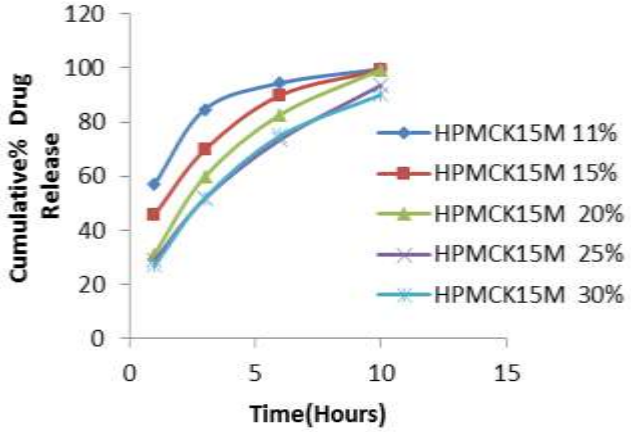

Figure 13: Cumulative % drug release from formulations containing different concentrations of HPMC K15M

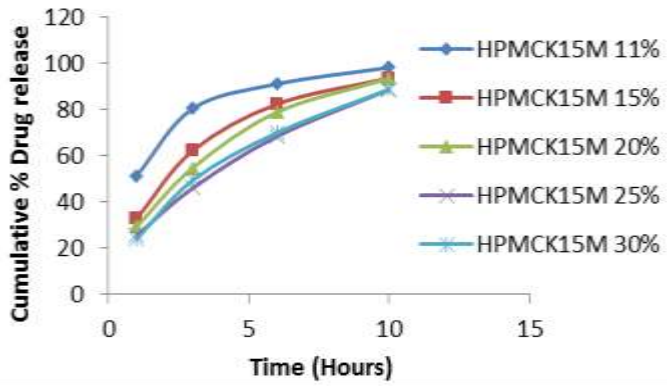

Figure 14: Cumulative % drug release from formulations containing different concentrations of HPMC K100M

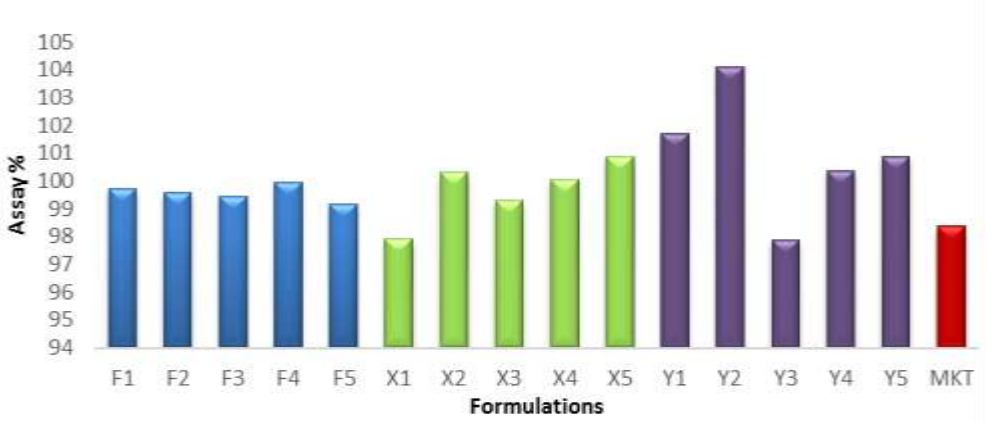

Figure 15: Assay percentage of various formulated and marketed sample.

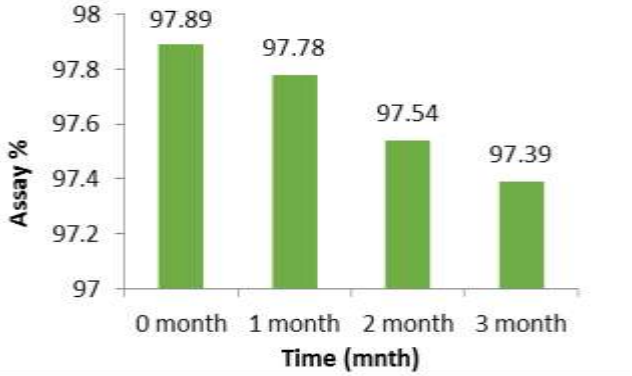

Figure 16: Assay of formulation (Y3) during three month accelerated stability study each conducted at one month interval.

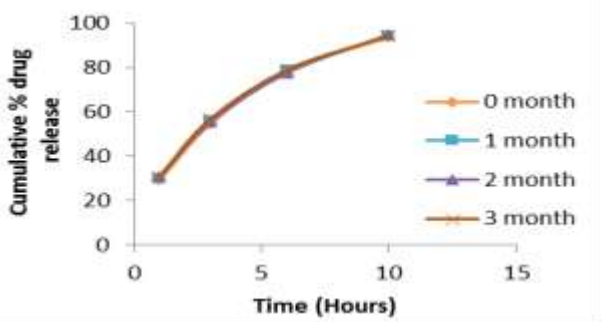

Figure 17: Dissolution profile of optimized formulation during three month accelerated stability study each conducted at one month interval.

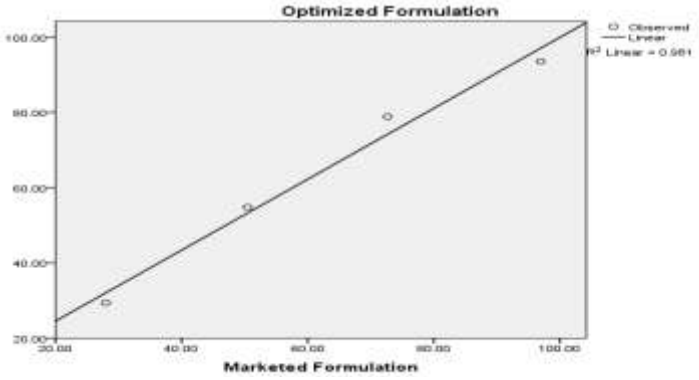

Figure 18: Correlation of optimized formulation with marketed sample.

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