Original Article

Formulation and design of sustained release matrix tablets of metformin hydrochloride: Influence of hypromellose and polyacrylate polymers

Harekrishna Roy, Chandan K Brahma, Sisir Nandi[1], Kirti R Parida[2]

Department of Pharmatechnology, Vikas College of Pharmaceutical Sciences, Suryapet, Nalgonda, Andhra Pradesh, [2]Jeypore College of Pharmacy, Rondapalli, Koraput, Odisha, India, [1]Department of Medicinal Chemistry, Laboratory of Chemometrics, National Institute of Chemistry, Hajdrihova 19, SI-1000, Ljubljana, Slovenia, Europe

Abstract

Aim: The current paper was an attempt to design a sustained release dosage form using various grades of hydrophilic polymers, Hypromellose (hydroxyl-propyl methylcellulose [HPMC] K15M, HPMC K100M and HPMC K200M) and Polyacrylate polymers, Eudragit RL100 and Eudragit RS100 with or without incorporating ethyl cellulose on a matrix-controlled drug delivery system of Metformin hydrochloride. **Materials and Methods:** Laboratory scale batches of nine tablet formulations were prepared by wet granulation technique (Low shear). Micromeritic properties of the granules were evaluated prior to compression. Tablets were characterized as crushing strength, friability, weight variation, thickness, drug content or assay and evaluated for *in-vitro* release pattern for 12 h using Phosphate buffer of pH 6.8 at 37 ± 0.5°C. The *in-vitro* release mechanism was evaluated by kinetic modeling. **Results and Discussion:** The results obtained revealed that HPMC K200M at a concentration of 26% in formulation (F6) was able to sustain the drug release for 12 h and followed the Higuchi pattern quasi-Fickian diffusion. With that, combined effect of HPMC K15M as an extragranular section and Eudragit RS100 displayed a significant role in drug release. Dissolution data were compared with innovator for similarity factor (*f*2), and exhibited an acceptable value of ≥50 Three production validation scale batches were designed based on lab scale best batch and charged for stability testing, parameters were within the limit of acceptance. There was no chemical interaction found between the drug and excipients during Fourier Transform Infrared Spectroscopy (FTIR) and Differential scanning calorimetry study. **Conclusion:** Hence, combinely HPMC K200M and Eudragit RS100 at a suitable concentration can effectively be used to sustain drug release.

Key words: Hydrophilic polymer, innovator, Metformin hydrochloride, micromeritic properties, sustained release tablet matrix

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Introduction

Oral drug delivery is the most widely utilized routes for administration of drugs, which has been explored for systemic delivery via various pharmaceutical products as different dosage form.[1] In long-term therapy for the treatment of chronic disorders, conventional formulations are required to be administered frequently in multiple dosage regimens, and therefore have several undesirable effects. Hence, in order to reduce the drawback associated with multiple dosing, controlled or sustained release solid unit dosage forms as tablets were developed.[2] They often produce better patient compliance, maintain uniform drug therapeutic level, are cost-effective, have broad regulatory acceptance, reduce dose as well as side-effects, and increase the safety margin for high-potency therapeutic agents.[3]

Diabetes mellitus, simply referred to as diabetes, is a group of metabolic diseases in which a person has high level of blood sugar. The possible causative reason maybe that the

Address for correspondence: Asst. Prof Harekrishna Roy, Department of Pharmatechnology, Vikas, College of Pharmaceutical Sciences, Nalgonda, Andhrapradesh, Hyderabad, India.
E-mail: hareroy@gmail.com

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body does not produce enough insulin, or cells do not respond to the insulin that is produced by the pancreatic cells.[4] In developing countries, the majority of people suffering from diabetes are in the 45-64 year age range.[5] As per the World Health Organisation (WHO) report, the total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030.[6,7]

Metformin hydrochloride is the first-line drug of choice for the treatment of type II diabetes, especially, in overweight and obese people and those having normal kidney function.[8] Metformin helps to improve hyperglycemia primarily by suppressing glucose production by the liver (hepatic gluconeogenesis). It does activate adenosine monophosphate-activated protein kinase, an enzyme that plays an important role in insulin signaling, maintains whole body energy balance, metabolism of glucose and fats, helps to increase the expression of small heterodimer partner. The conventional form of Metformin tablets have been found to have many associated drawbacks such as gastrointestinal upset, including diarrhea, cramps, nausea, vomiting, and increased flatulence.[9] So as to reduce the above mentioned side-effects and to enhance patient compliances, sustained release formulation of Metformin was developed. Numerous studies have been reported in literature investigating the hydroxyl-propyl methylcellulose (HPMC) matrices to control the release of variety of drug from matrices.[10,11] The most commonly used method for fabricating drugs in a controlled-release formulation is to formulate a matrix containing either hydrophilic or hydrophobic rate-controlling polymers. Previous studies proved the use of hydrophilic polymers such as HPMC, methylcellulose, sodium carboxymethyl cellulose, carbopols, and polyvinyl alcohol provide gelling network and act as a barrier to retard the drug release mechanism. Report shows various grades of HPMC were used to fabricate the drug as sustained release doses form.[12]

Thus, an attempt has been made to formulate the extended-release matrix tablets of Metformin Hydrochloride and tested for controlled delivery of drug using hydrophilic matrix polymer, Hypromellose or (HPMC K15M, HPMC K100M, HPMC K200M) and Polyacrylate polymers (Eudragit RL100 and Eudragit RS100) alone or in combination with hydrophobic ethyl cellulose to produce additive antidiabetic activity, resulting in reduction in the dose of Metformin HCl and there by its dose-related side effects.

Materials and Methods

Materials

Metformin HCl was procured from Tocris bioscience (USA). HPMC K15M, HPMC K100M, and HPMC K200M and Ethyl cellulose (Aqualon T10 Pharm EC) were purchased from Ashland Aqualon Functional Ingredients (Wilmington, DE, United states). Anhydrous dicalcium phosphate and Eudragit RS100/RL 100 were purchased from Emzor exports Pvt. Ltd (Ahmedabad, India). Polyvinyl pyrrolidone (Kollidon CL-SF and Kollidon 30 were purchased from BASF Global (Germany). Colloidal silicon dioxide (Aerosil-R 972) and glyceryl behenate were purchased from Tangmin industry Ltd. (China). Iso propyl alcohol (IPA) was purchased from Triveni Interchem Pvt. Ltd. All chemicals and solvents used were of high analytical grade.

Method for preparation of tablets

Metformin HCl, HPMC K100M, HPMC K200M, anhydrous dicalcium phosphate, Eudragit RS100, Eudragit RL 100, and kollidon CL-SF were passed through #40 mesh and collected separately in a polyethylene bag. Wet granulation technique was applied for the batch preparation of matrix tablets.[13] All the materials were sifted to rapid mixing granulator (Ganson Ltd, India) and mixed for 20 min at optimized speed. Kollidon-30 was dissolved in the mixture of IPA and Water (1:0.5) with the help of a mechanical stirrer. The above binder solution was added to dry mix and mixed for 15 min to get wet mass. Then, the resultant wet mass was dried at inlet temperature of 45°C to 65°C for 45 min and passed through multi mill (Propack Techno Pvt. Ltd, India). The resultant dried granules were sifted through #20 mesh and milled through multi mill. The comminuted granules were lubricated with Aerosil-R 972 which was passed through #40 mesh and HPMC K15M for 5 min, further lubricated with glyceryl behenate (sifted through #60 mesh) for 5 min in Octagonal Blender (Mevish engineering, India). Finally, the lubricated granules were compressed to formulate tablets using a tablet compression machine (Cadmach Machinery Pvt. Ltd, India) with 18.5 mm × 6.5 mm capsule-shaped punches. The compositions of various formulations designed in the present study are given in Table 1.

Micromeritic properties of prepared granules

Prior to compression, granules were evaluated for their characteristic parameters.[14] Angle of repose was determined by funnel method. Bulk density (BD) and tapped density (TD) were determined by cylinder method, and Carr's index (CI) was calculated using the following equation

$$CI = (TD\text{-}BD)/TD \times 100 \quad (1)$$

Hausner's ratio (HR) was calculated by the following equation

$$HR = TD/BD \quad (2)$$

Physical characterization of matrix tablets

The physical properties such as crushing strength, friability,

Table 1: Composition of tablet formulation (mg)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Intragranular preparation (mg)									
Metformin hydrochloride	500	500	500	500	500	500	500	500	500
Anhydrous dicalcium phosphate	80	80	80	80	80	80	80	80	80
HPMC K100M	210	5	-	-	-	-	-	-	-
HPMC K200M	-	5	160	165	210	265	225	245	280
Aqualon T10 pharm EC	-	165	-	-	-	-	-	-	-
Eudragit RL 100	10	10	10	10	10	-	-	-	-
Eudragit RS100	-	-	-	-	-	10	10	10	10
Kollidon CL-SF	10	10	10	10	10	10	10	10	10
Granulating solution									
Kollidon 30	50	50	50	50	50	50	50	50	50
Isopropyl alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Extra granular preparation (mg)									
HPMC K15M	110	145	160	155	110	55	95	75	40
Aerosil R 972	10	10	10	10	10	10	10	10	10
Glyceryl behenate	10	10	10	10	10	10	10	10	10
Total weight (mg)	990	990	990	990	990	990	990	990	990

HPMC: Hydroxyl-propyl methylcellulose; EC: Ethyl cellulose

weight variation thickness, and assay of compressed matrix tablet for each formulation were determined.[15,16] Tablet crushing strength was determined for 10 tablets using digital tablet hardness tester (Erweka TBH-28) and the data reported is the mean of three individual determinations. Friability test was performed to assess the effect of friction and shocks, which may often cause the tablet to chip, cap, or break. Preweighed, randomly selected twenty tablets were placed in a Roche friability tester and operated for 4 min at 25 rpm. Compressed tablets should not lose more than 1% of their weigh. A weight variation test was performed according to United States Pharmacopeia (USP) 30 NF25 on 20 tablets by taking samples from a batch after production of every 100 tablets and randomly from a total batch of 300 tablets using an electronic balance (Contech Instruments CA 224, India). The thicknesses of tablets was measured by Vernier callipers (Mitatoyo, Japan). The drug content in terms of assay of each batch was determined in triplicate. For each batch, 20 tablets were weighed and crushed to fine powder using mortar and pestle. An accurately weighed 500 mg of the powder was taken and suitably dissolved in water and analyzed by High performance liquid chromatography (HPLC) after making appropriate dilutions. The procedure was carried out on Shimadzu LC-10AT (Phenomenex C_{18}; 250 mm × 4.60 mm) with flow rate of 1.0 mL/min at ambient temperature.

In-vitro dissolution studies

Release rate of all designed formulations were studied up to 12 h. The procedure was determined using USP XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 1000 mL of Phosphate Buffer of pH 6.8 at 37 ± 0.5°C and 75 rpm. A sample of 10 mL of the solution was withdrawn from the dissolution apparatus at 1-h intervals with the replacement of fresh dissolution medium for 12 h. The samples were passed through a 0.45-µm membrane filter and diluted to a suitable concentration with phosphate buffer. The absorbance of these solutions was measured at 233 nm using a Shimadzu Ultra Violet (UV)-1601 UV/Vis double-beam spectrophotometer.[17-19]

Comparison of dissolution profile

The similarity factor (*f*2) given by scale up and post approval Changes guidelines for a modified release dosage form was used as a basis to compare dissolution profile.[20,21] The dissolution profiles are considered to be similar when *f*2 is between 50-100 and dissimilarity factor (*f1*) lies below 50. The dissolution profiles of product were compared to Innovator (Glumetza TM, Depomed Inc. USA) using *f*2 and *f1* which are calculated from the following formulae,

$$f2 = 50 \times \log \{[1+ (1/n) \sum_{t=1}^{n} | R_t - T_t |^2]^{-0.5} \times 100\} \quad (3)$$

$$f1 = \{[\sum_{t=1}^{n} | R_t - T_t |]/[\sum_{t=1}^{n} R_t]\} \times 100 \quad (4)$$

Where, n is the number of dissolution sample times and R_t and T_t are the individual or mean percent dissolved at each time point, *t*, for the innovator and test dissolution profiles respectively.

Statistical analysis

Analysis of variance followed by Tukey's test was used for statistical comparison of the data. Significance level was fixed at $P < 0.05$

Results and Discussion

Micromeritic properties of granules

Result shows that all the formulations produced optimal flow properties calculated in terms of compressibility. Table 2 depicts the micromeritic properties of the designed formulations. The angle of repose ranged from 30 ± 0.29-40 ± 0.12 which indicates optimal flow ability. In addition to that, the TD and BD for all formulation granules ranged between 0.712-0.781 and 0.609-0.624, respectively, whereas HR was obtained as 1.15-1.27.

Physical characterization of matrix tablets

The physical properties of the designed tablets are presented in Table 3. These properties were studied by determining crushing strength, friability, weight variation, drug content,

and thickness of the prepared tablets. Crushing strength of the prepared tablets ranged from 163.95 ± 1.65 newton to 190.22 ± 1.45 newton. It was observed that among all the formulations containing HPMC K100M as the intragranular polymer showed the highest hardness, this could be due to the higher binding capacity of HPMC K100M than HPMC K 200M.[22] The European and US pharmacopeias states that a loss up to 1% is acceptable for friability and can be decreased by increasing the extra granular polymer level. In the present study, the percentage friability for all formulations were below 1%, that is it ranged from 0.10% to 0.19%, indicating that the friability is within the prescribed limits. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the USP specifications for weight variation, drug content, hardness, and friability. All the formulations showed uniform thickness. In a weight variation test, the pharmacopeial limit for the percentage deviation for tablets of more than 250 mg is ± 5%. The average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the test for uniformity of weight as per official requirements. The average weight of each formulation tablet ranged from 990.6 ± 1.53 mg to 991.9 ± 1.57 mg. Satisfactory uniformity in drug content was found among different batches of the tablets, and the percentage of drug content was more than 96%.

Table 2: Micromeritic properties of prepared granules

Formulation code	Bulk density (X±SD)	Tapped density (X±SD)	Hausner's ratio	Carr's index	Angle of repose (X±SD)
F1	0.613±0.12	0.712±0.13	1.16	13.9	38±0.65
F2	0.624±0.01	0.772±0.43	1.23	19.1	40±0.12
F3	0.622±0.04	0.721±0.25	1.15	13.7	39±0.77
F4	0.63±0.22	0.769±0.32	1.22	18.0	30±0.29
F5	0.613±0.24	0.753±0.27	1.22	18.5	34±0.81
F6	0.618±0.25	0.749±0.36	1.21	17.4	31±0.72
F7	0.612±0.18	0.781±0.12	1.27	21.6	39±0.65
F8	0.615±0.62	0.767±0.26	1.24	19.8	37±0.23
F9	0.609±0.27	0.737±0.15	1.16	17.3	40±0.05

Data is presented as mean±standard deviation; For: Formulation; Carr's index: Compressibility index; *n*=3

In-vitro dissolution studies

Different grades of HPMC like HPMC K15M, HPMC K100M, and HPMC K200M were used to formulate various Metformin HCl matrix tablets and those formulations were subjected to *in-vitro* drug dissolution studies. The dissolution studies were performed in Phosphate Buffer of pH 6.8. A range of 16-28% of HPMC K200M was chosen in intragranular preparation except formulation F1. Whereas HPMC K100M was considered in F1, Aqualon T10 Pharm EC was taken as intragranular section in F2 with a trace amount of HPMC K100 and 200M. HPMC K15M was considered in extra granular section for all formulations. The result showed that approximately 17% of the drug was released within 30 min for all formulations and 80% of the drug was found to release at the end of 12 h. While comparing the drug release pattern between F1 and F2, the formulation F2 released 38.36 ± 2.54% at the end of initial 30 min, whereas F1 released only 18.59 ± 1.22% of drug. This could be due to the immediate formation of channels in ethyl cellulose-based matrix tablet formulation. From the release profile, it was observed that the concentration of polymer influences the *in-vitro* drug release pattern of different formulations as shown in Figure 1.

The result showed that the formulations having Eudragit RS100 prolonged drug release as compared to formulations

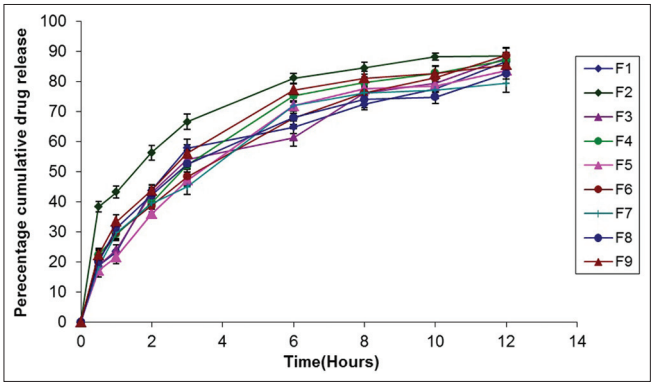

Figure 1: *In-vitro* release profile of all formulations

Table 3: Physical characterization of the designed formulations

Formulation code	Average weight (mg) (X±Sd)	Thickness (mm) (X±Sd)	Crushing strength (newton) (X±Sd)	Drug content (%) (X±Sd)	Friability (%)
F1	990.6±1.53	6.49±0.05	190.22±1.45	99.21±1.06	0.10
F2	991.2±1.31	6.5±0.04	164.21±2.03	101.74±0.49	0.13
F3	990.6±0.56	6.46±0.07	170.44±1.51	98.63±1.03	0.15
F4	989.2±1.43	6.49±0.02	163.95±2.65	99.38±1.25	0.11
F5	991.9±1.57	6.5±0.06	177.04±1.53	100.17±0.98	0.16
F6	989.1±0.45	6.49±0.09	181.84±2.35	99.49±0.06	0.14
F7	989.6±2.12	6.42±0.07	195.57±1.50	100.01±0.52	0.19
F8	990.7±1.43	6.5±0.13	185.77±2.13	99.21±1.71	0.13
F9	991.8±0.77	6.49±0.08	186.59±1.26	100.09±1.08	0.18

Data are represented as mean±standard deviation (SD); *n*=3

based on Eudragit RL 100. The percentage of drug release from formulations F3 to F6 were 54.11 ± 0.18%, 52.18 ± 1.72%, 47.14 ± 1.34%, and 48.35 ± 2.37%, respectively, at the end of 3 h, as they contained proportionately higher concentration of HPMC K200M. The release pattern is the same for the next 9 h. As stated above, it was supposed to obey the release pattern for next three formulations as they contained 22%, 24%, and 28% of HPMC K200M in formulations F007 to F009. But on the contrary, the percentage of release was found to progressively increase such as 79.41 ± 1.52%, 82.6 ± 1.72%, and 85.58 ± 2.72%, respectively, at the end of 12 h. Hence, a relationship was tried to be established between release profile and polymer. It was found out that F7, F8, and F9 contained progressive decrease in extragranular polymer, i.e., HPMC K15M ranging 9%, 7%, and 4% respectively. It was also noticed that formulations (F6-F9) based on Eudragit RS100 sustained for longer period than Eudragit RL100-based formulae. Hence, it can be concluded that the combined effect of polyacrylate polymer, i.e., Eudragit RS100 and extragranular polymer, i.e., HPMC K15M at a suitable concentration produced significant effect on drug release.

The data obtained from *in-vitro* dissolution studies were fitted to zero-order, first-order, and Higuchi release kinetics. The best fit with higher correlation coefficient ($r^2 > 0.98$) was found with Higuchi's equation for F6. To confirm the exact mechanism of drug release, the data were fitted by Korsmeyer–Peppas equation. Regression analysis was performed and values of regression coefficient (R^2) were ranged from 0.955 to 0.990 for different formulations and slope of $0.43 < n < 0.54$. Hence, it can be inferred that the release was based on diffusion and quasi Fickian.[23] On the basis of the above results, F6 was selected as a promising formulation for further studies.

Comparison of dissolution profile

The comparative results of the selected formulation batch F6 was compared with the theoretical dissolution profile (Innovator) using the similarity factor *f*2 test and dissimilarity factor *f1* test to assure the best batch. The results of the similarity tests showed that formulation F6 containing 265 mg HPMC K200M in intragranular and 55 mg HPMC K15M in extragranular had an *f*2 value > 50, i.e., 70, indicating the closest fit to the dissolution profile of innovator.[24]

Drug-polymer interaction study

Fourier transform infrared spectroscopy study

Pure Metformin hydrochloride, mixed with the polymer HPMC K200M, HPMC K100M, Kollidon 30, and anhydrous dicalcium phosphate separately with IR grade Potasium Bromide (KBr) and pellets were prepared by applying a pressure of 15 tons in a hydraulic press. The pellets were scanned over a wavelength range of 450-4,500 cm^{-1} using an FT-IR 8400S, Schimazu.[25] There was no chemical interaction between Metformin hydrochloride and the polymers used which is obtained by employing I.R. spectral studies [Figures 2 and 3]. Metformin being a biguanide, has strong absorption band at 1634, 1573, and 1562 cm^{-1} due to presence of C = N stretching vibrations. It has been reported that C-N stretching of aliphatic diamine is generally weak and occurs in the region of 1220-1020 cm^{-1}. Hence, weak intensity bands were found at 1069 and 1122 cm^{-1}. N-H stretching of C = N-H groups occurs in the region of 3400-3100 cm^{-1}. So medium intensity peaks appeared in the region of 3180, 3300, 3325, and 3368 cm^{-1}, respectively because of N-H asymmetric and symmetric stretching vibrations.

Differential scanning calorimetry study

DSC has shown to be an important tool to quickly obtain information about possible interactions between the active and the excipients, according to the appearance, shift, or disappearance of endothermic or exothermic peaks. DSC

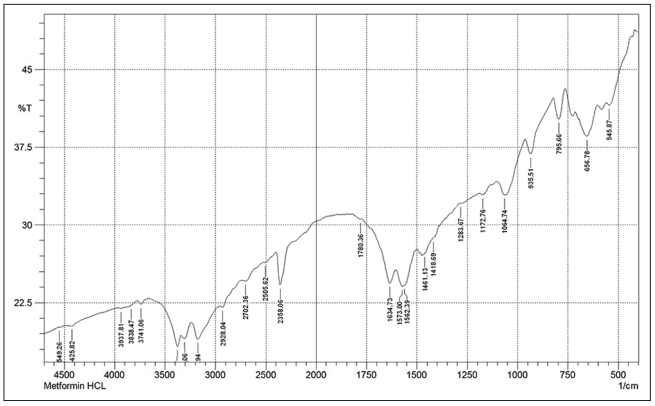

Figure 2: Infrared spectra of Metformin hydrochloride

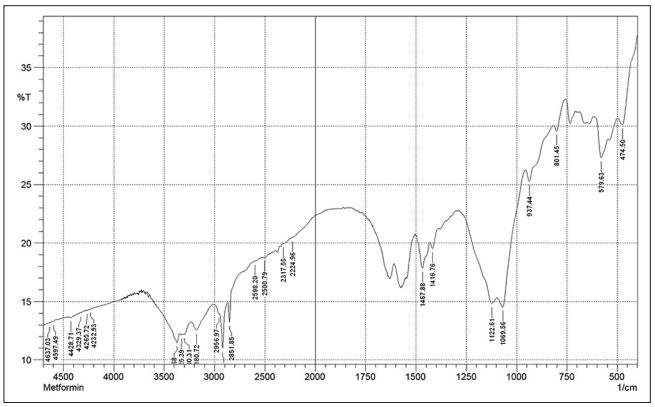

Figure 3: Infrared spectra of optimized batch F6

study was performed using universal V4.2ETA instruments to determine the drug excipient compatibility study. During the study, a sharp endothermic peak for Metformin hydrochloride was obtained at 231°C corresponding to the melting point. But, in the formulation, there was a slight change in peak temperature and peak shape [Figure 4], which might be due to reduction of the purity level of component and interaction with excipients.[26]

Stability study of best batch

Long-term, intermediate, and accelerated stability testing study was carried out according to International Conference on Harmonisation (ICH) guidelines considering 25 ± 2°C/60 ± 5% Relative Humidity (RH), 30 ± 2°C/65 ± 5% RH, and 40 ± 2°C/75 ± 5% RH respectively. One hundred tablets of batch F6 were securely packed in aluminum blister and placed in humidity chamber.[27,28] There was no significance change in crushing strength and drug assay at a regular interval of 3 months during the study of 24 month as shown in Table 4. Thus, F6 formulation batch confirmed its stability.

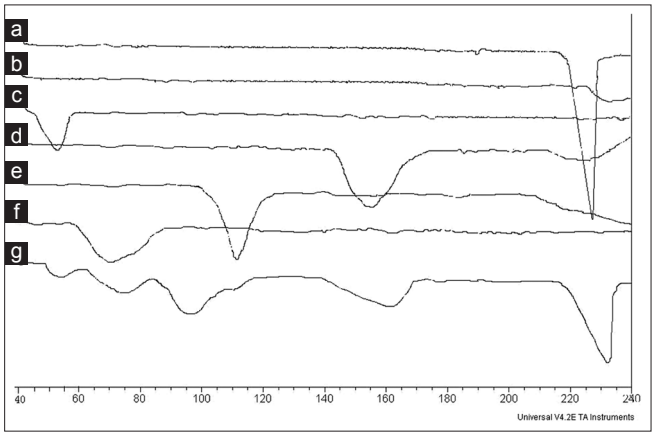

Figure 4: Differential scanning calorimetry study of (a) Pure Metformin hydrochloride (b) Anhydrous dicalcium phosphate (c) (HPMC) K200M (d) Eudragit RS100 (e) Kollidon 30 (f) HPMC K15M (g) Formulation F6

Stability study of production batch

From the studies like *in-vitro* dissolution, comparison of dissolution profile, drug polymer interaction and accelerated stability study, the batch no. F6 was selected as optimized laboratory scale which was subjected for reproducible production batches namely F10, F11, and F12 containing each of 1000. The tablets were packed in Polyvinyl chloride/Polyvinylidene chloride and charged for stability testing according to ICH guidelines. The parameters and results are explained in Tables 5, 6 and 7.

Dissolution was carried out in 1000 mL phosphate buffer of pH 6.8 using USP-II (paddle apparatus) at 75 rpm with temperature of 37 ± 0.5°C. The dissolution profiles of F10, F11, and F12 were found to be similar with that of dissolution profile of optimized initial samples, which releases not more than 45% at 1st h, 35-65% at 2nd h, and 65-85% at end of 6th h respectively. Moreover, the impurity profile was observed to be well within the specification limit of less than 0.02% for known impurity and 0.1% for unknown maximum single impurity and 0.3% for total impurity. The tests for salmonella were negative as well as the colony forming units were within the specified limit. Hence, the results of the stability studies confirm that the designed F6 is a stable formulation and can be produced in large scale as an antidiabetic drug. Thus, the formulation development in this direction leads to designing promising oral sustain release matrix tablet containing Metformin hydrochloride intended to be used clinically for the treatment of diabetes.

Conclusion

The present investigation shows that various grades of Hypromellose at suitable concentration combinedly with Polyacrylate polymers can be used effectively to modify the release rates in hydrophilic matrix tablets

Table 4: Stability study of best batch

Long term stability study (25±2°C and 60±5% RH)						
Days (month)	3	6	9	12	18	24
Drug assay (%)	99.39±0.21	99.19±0.43	100.46±0.62	99.32±0.07	99.17±0.41	99.09±0.26
Crushing strength (newton)	183.35±1.25	181.06±1.08	183.62±1.37	180.33±1.53	179.80±1.16	179.91±1.09
Intermediate stability (30±2°C and 65±5% RH)						
Days (month)	3	6	9	12	18	24
Drug assay (%)	99.47±0.35	99.01±0.12	99.38±0.06	98.27±0.72	98.37±0.52	97.24±0.09
Crushing strength (newton)	181.39±1.05	181.88±1.42	181.07±1.03	180.11±1.17	180.02±1.02	179.09±0.29
Accelerated stability (40±2°C and 75±5% RH)						
Days (month)	1	2	3	6	-	-
Drug assay (%)	99.45±0.47	99.38±0.72	99.52±0.05	99.03±0.15	-	-
Crushing strength (newton)	183.56±1.27	182.88±1.03	182.69±1.08	180.11±1.13	-	-

Data are represented as mean±standard deviation (SD); *n*=3; RH: Relative humidity

prepared by wet granulation technique.The physiochemical characterizations of all prepared formulations were found to be satisfactory. Result shows Eudragit RS100 produced better sustained release pattern compared to Eudragit RL100 based formulae. During the study, higher binding capacity of HPMC K100M, as compared to HPMC K200M was also found out. Moreover, concentration of extra granular polymer HPMC K15M had significant influence on the drug release pattern. From dissolution study and similarity factor (*f2*) value, formulation F6 was selected as best laboratory scale grade batch. Hence, reproducible production scale batches of 1000 tablets were designed

Table 5: Stability study of reproducible batch formulation 10

Batch no.	F10	Reason for study	Stability		
Pack details	10's clear blisters PVC/PVDC	Condition	40°C±2°C and 75%±5% RH		
Name of test	Limit	Initial	1st month	2nd month	3rd month
Description: White to off white, biconvex, uncoated tablets	*	Complies	Complies	Complies	Complies
Hardness (newton)	179-246	187±3	188±4	184±3	183±5
Dissolution					
Highly soluble drug %		98.5-101.5			
1st h	NMT 45	32	30	30	29
2nd h	35.0-65.0	39	38	37	36
6th h	65.0-85.0	68	67	68	66
Loss on drying	For information only	2.78%	2.70%	3.12%	3.70%
Related substances					
Impurity A (cyanoguanidine)	NMT 0.02%	ND	ND	ND	ND
Max. individual unknown impurity	NMT 0.1%	0.025	0.028	0.032	0.034
Total impurities	NMT 0.3%	0.142	0.148	0.169	0.182
Assay					
Highly soluble drug (%)	100±05	99.83	99.72	99.70	99.53
Microbial limit test					
Total aerobic microbial count (CFU/g)	NMT 10^3	11	11	11	12
Total yeast and mould count (CFU/g)	NMT 10^2	<8	<8	<8	<9
Bile tolerant gram negative bacteria (CFU/g)	NMT 10^2	<10	<10	<10	<10
Salmonella	Should be absent/10 g	Absent	Absent	Absent	Absent

RH: Relative Humidity; PVC: Polyvinyl chloride; PVDC: Polyvinylidene chloride; NLT: Not less than; NMT: Not more than; ND: Not detected; CFU: Colony forming unit

Table 6: Stability study of reproducible batch formulation 11

Batch no.	F11	Reason for study	Stability		
Pack details	10's clear blisters PVC/PVDC	Condition	40°C+2°C and 75%+5% RH		
Name of test	Limit	Initial	1st month	2nd month	3rd month
Description:White to off white, biconvex, uncoated tablets	*	Complies	Complies	Complies	Complies
Hardness (newton)	179-246	188±7	186±6	184±5	183±3
Dissolution					
Highly soluble drug		98.5-101.7			
1st h	NMT 45%	34	32	30	29
2nd h	35.0-65.0%	40	40	39	39
6th h	65.0-85.0%	68	67	67	66
Loss on drying	For information only	3.08%	3.11%	3.23%	3.32%
Related substances					
Impurity A (cyanoguanidine)	NMT 0.02%	ND	ND	ND	0.002
Max. individual unknown impurity	NMT 0.1%	0.02	0.022	0.026	0.032
Total impurities	NMT 0.3%	0.122	0.182	0.183	0.198
Assay (mg)					
Highly soluble drug (%)	100±05%	101.1%	99.81%	99.79 mg	99.61%
Microbial limit test					
Total aerobic microbial count (CFU/g)	NMT 10^3	12	12	12	12
Total yeast and mould count (CFU/g)	NMT 10^2	<5	<5	<5	<5
Bile tolerant gram negative bacteria (CFU/g)	NMT 10^2	<8	<8	<8	<8
Salmonella	Should be absent/10 g	Absent	Absent	Absent	Absent

RH: Relative humidity; PVC: Polyvinyl chloride; PVDC: Polyvinylidene chloride; NLT: Not less than; NMT: Not more than; ND: Not detected; CFU: Colony forming unit

Table 7: Stability study of reproducible batch formulation 12

Batch no.	F12	Reason for study	Stability		
Pack details	10's clear blisters PVC/PVDC	Condition	40°C+2°C and 75%+5% RH		
Name of test	Limit	Initial	1st month	2nd month	3rd month
Description: White to off white, biconvex, uncoated tablets	*	Complies	Complies	Complies	Complies
Hardness (newton)	179-246	185±3	184±4	183±2	183±4
Dissolution					
Highly soluble drug		98.0-101.5			
1st h	NMT 45%	32	30	29	29
2nd h	35.0-65.0%	40	39	39	38
6th h	65.0-85.0%	69	69	68	67
Loss on drying					
Related substances	For information only	3.07%	3.10%	3.19%	3.28%
Impurity A (cyanoguanidine)	NMT 0.02%	ND	ND	ND	0.001
Max. individual unknown impurity	NMT 0.1%	0.024	0.025	0.028	0.031
Total impurities	NMT 0.3%	0.147	0.158	0.163	0.179
Assay					
Highly soluble drug (%)	100±05%	101.12%	99.97%	99.96%	99.96%
Microbial limit test					
Total aerobic microbial count (CFU/g)	NMT 10^3	12	12	12	12
Total yeast and mould count (CFU/g)	NMT 10^2	<5	<5	<5	<5
Bile tolerant gram negative bacteria (CFU/g)	NMT 10^2	<8	<8	<8	<8
Salmonella	Should be absent/10 g	Absent	Absent	Absent	Absent

RH: Relative humidity; PVC: Polyvinyl chloride; PVDC: Polyvinylidene chloride; NLT: Not less than; NMT: Not more than; ND: Not detected; CFU: Colony forming unit

and charged for stability studies which were found to be within the specified limit. Furthermore, the *in-vivo* and pharmacokinetic study have to be carried out.

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