PHS Scientific House

International Journal of Pharma Research and Health Sciences

Available online at **www.pharmahealthsciences.net**

Original Article

Formulation of Sustained Release Matrix Tablets of Metformin hydrochloride by Polyacrylate Polymer

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A R T I C L E   I N F O

A B S T R A C T

The current paper was an attempt to design a sustained release dosage form using various grades of hydrophilic polymers, Hypromellose (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. *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 hr using Phosphate buffer of pH 6.8 at 37±0.5°C. The *in-vitro* release mechanism was evaluated by kinetic modelling. *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 hours and followed Higuchi pattern quasi Fickian diffusion. With that combined effect of HPMC K15M as extragranular section and Eudragit RS100 displayed a significant role in drug release. 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 FT-IR and DSC study. *Conclusion*: Hence combinely HPMC K200M and Eudragit RS100 at a suitable concentration can effectively be used to sustain drug release.

Keywords: Hydrophilic polymer, Metformin Hydrochloride, Sustained release tablet matrix, Micromeritic properties.

1. INTRODUCTION

Oral drug delivery is the most widely utilized routes for administration of drugs, which have been explored for systemic delivery via various pharmaceutical products as different dosage form. 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

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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. They often produces better patient compliance, maintain uniform drug therapeutic level, cost effectiveness, broad regulatory acceptance, reduce dose as well as side effects and increase safety margin for high potency therapeutic agents. [1, 2]

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 the body does not produce enough insulin, or cells do not respond to the insulin that is produced by pancreatic cells. In developing countries, the majority of people suffering from diabetes are in the 45 to 64 year age range. As per the WHO report, the total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030.[3, 4]

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. Metformin helps to improve hyperglycaemia primarily by suppressing glucose production of the liver (hepatic gluconeogenesis). It does activate AMP-activated protein kinase (AMPK), an enzyme that plays an important role in insulin signalling, 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 found to have many associated drawbacks such as gastrointestinal upset, including diarrhea, cramps, nausea, vomiting and increased flatulence. So as to reduce the above mentioned side effect and to enhance patient compliances, sustained release formulation of Metformin was developed. Numerous studies have been reported in literature investigating the HPMC matrices to control the release of variety of drug from

matrices. 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 hydroxyl-propyl methylcellulose (HPMC), methylcellulose, sodium carboxymethylcellulose, 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. [5-7]

Thus, an attempt has been made to formulate the extended-release matrix tablets of Metformin HCl and tested for controlled delivery of drug using hydrophilic matrix polymer, Hypromellose or Hydroxy-propyl methyl cellulose (HPMC K15M, HPMC K100M) 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 dose of Metformin HCl and there by its dose related side effects.

2. MATERIALS AND METHODS

Materials

Metformin HCl was procured from Tocris bioscience (USA). Hypromellose or Hydroxy-propyl methyl cellulose (HPMC K15M, HPMC K100M) and Ethyl cellulose (Aqualon T10 Pharm EC) were purchased from Ashland Aqualon Functional Ingredients (Wilmington, DE, United states). MCC and Eudragit RS 100/ RL 100 were purchased from Emzor exports Pvt. Ltd (Ahmedabad, India). Polyvinyl pyrolidone (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 were used are of high analytical grade. [8]

Method for preparation of tablets

Metformin HCl, HPMC K100M, HPMC K200M, MCC, Eudragit RS 100, Eudragit RL 100 and kollidon CL-SF were passed through #40 mesh and collected separately in polyethylene bag. Wet granulation technique was applied for the batch preparation of matrix tablets. All the materials were sifted to rapid mixing granulator (Ganson Ltd, India) and mixed for 20 minute at optimized speed. Kollidon-30 was dissolved in the mixture of Iso propyl alcohol (IPA) and Water (1:0.5) by the help of mechanical stirrer. The above binder solution was added to dry mix and mixed for 15 minute to get wet mass. Then the resulted wet mass was dried at inlet temperature of 45°C to 65°C for 45 minutes and passed through multi mill (Propack Techno Pvt Ltd, India). The resulted 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 minutes, further lubricated with glyceryl behenate (sifted through #60 mesh) for 5 minutes in Octagonal Blender (Mevish engineering, India). [9, 10] Finally, the lubricated granules were compressed to formulate tablets using tablet compression machine (Cadmach Machinery Pvt. Ltd, India) with 18.5 x 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. 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 [11, 12]

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

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

$$HR=TD/BD \text{.. (2)}$$

Table 1: Composition of tablet formulation(mg)

Sl no.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
	Intragranular preparation(mg)									
1	Metformin Hydrochloride	500	500	500	500	500	500	500	500	500
2	MCC	90	90	90	90	90	90	90	90	90
3	HPMCK100M	210	5	-	-	-	-	-	-	-
4	HPMCK200M	-	5	160	165	210	265	225	245	280
5	Aqualon T10 Pharm EC	-	165	-	-	-	-	-	-	-
6	Eudragit RL 100	10	10	10	10	10	-	-	-	-
7	Eudragit RS 100	-	-	-	-	-	10	10	10	10
8	Kollidon CL-SF	10	10	10	10	10	10	10	10	10
	Granulating solution									
9	Kollidon 30	50	50	50	50	50	50	50	50	50
10	Isopropyl Alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
11	Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
	Extra granular prepartion(mg)									
12	HPMC K15M	110	145	160	155	110	55	95	75	40
13	Aerosil R 972	10	10	10	10	10	10	10	10	10
14	Glyceryl behenate	10	10	10	10	10	10	10	10	10
	Total weight(mg)	1000	1000	1000	1000	1000	1000	1000	1000	990

Physical Characterization of Matrix Tablets

The physical properties such as crushing strength, friability, weight variation thickness and assay of compressed matrix tablet for each formulation were determined. 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 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 USP30 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

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Instruments CA 224, India). The thicknesses of tablets were measured by Vernier callipers (Mitatoyo, Japan). The drug content in terms of assay of each batch was determined in triplicate. For each batch a number of 20 tablets were weighed and crushed to fine powder using mortar and pestle. An accurately weighed of 500 mg of the powder was taken and suitably dissolved in water and analyzed by HPLC after making appropriate dilutions. The procedure was carried out on Shimadzu LC-10AT (Phenomenex C_{18}; 250 × 4.60 mm) with flow rate of 1.0 ml/minute at ambient temperature.

Table 2: Micromeritic properties of prepared granules

Sl. No	Formulation code	Bulk Density (X±SD)	Tapped Density (X±SD)	Hausner's Ratio	Compressibility Index(Carr's index)	Angle of Repose (X±SD)
1	F1	0.613 ±0.12	0.712±0.13	1.16	13.9	38 ± 0.65
2	F2	0.624±0.01	0.772±0.43	1.23	19.1	40 ± 0.12
3	F3	0.622±0.04	0.721±0.25	1.15	13.7	39 ± 0.77
4	F4	0.63±0.22	0.769±0.32	1.22	18	30 ± 0.29
5	F5	0.613±0.24	0.753±0.27	1.22	18.5	34± 0.81
6	F6	0.618±0.25	0.749±0.36	1.21	17.4	31 ± 0.72
7	F7	0.612±0.18	0.781±0.12	1.27	21.6	39 ±0.65
8	F8	0.615±0.62	0.767±0.26	1.24	19.8	37 ±0.23
9	F9	0.609±0.27	0.737±0.15	1.16	17.3	40 ±0.05

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

In-vitro dissolution studies

Release rate of all designed formulations were studied up to 12 hours. The procedure was determined using United States Pharmacopoeia (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 hour interval with the replacement of fresh dissolution medium for 12 hours. 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 UV-1601 UV/Vis double beam spectrophotometer.[13-15]

3. 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 micromeritic properties of the designed formulations. The angle of repose ranged from 30 ± 0.29 to 40 ± 0.12 which indicates optimal flow ability. In addition to that the tapped density and bulk density for all formulation granules ranged between 0.712 to 0.781 and 0.609 to 0.624 respectively whereas Hausner's ratio was obtained as 1.15 to 1.27.

Table 3: Physical characterization of the designed formulations

Sl. No	Formulation code	Average Weight (mg) (X±Sd)	Thickness (mm) (X±Sd)	Crushing strength (Newton) (X±Sd)	Drug content (%) (X±Sd)	Friability (%)
1	F1	990.6± 1.53	6.49±0.05	190.22± 1.45	99.21±1.06	0.10%
2	F2	991.2± 1.31	6.5±0.04	164.21± 2.03	101.74± 0.49	0.13%
3	F3	990.6± 0.56	6.46±0.07	170.44± 1.51	98.63±1.03	0.15%
4	F4	989.2± 1.43	6.49±0.02	163.95± 2.65	99.38±1.25	0.11%
5	F5	991.9± 1.57	6.5±0.06	177.04± 1.53	100.17± 0.98	0.16%
6	F6	989.1± 0.45	6.49±0.09	181.84± 2.35	99.49±0.06	0.14%
7	F7	989.6± 2.12	6.42±0.07	195.57± 1.50	100.01± 0.52	0.19%
8	F8	990.7± 1.43	6.5±0.13	185.77± 2.13	99.21±1.71	0.13%
9	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

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 formulation containing HPMC K100M as intragranular polymer

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showed highest hardness, this could be due to higher binding capacity of HPMC K100M than HPMC K200M. 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 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 pharmacopoeial 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. Average weight of each formulation tablets ranged from 990.6±1.53 mg to 991.9±1.57 mg. Satisfactory uniformity in drug content were found among different batches of the tablets, and the percentage of drug content was more than 96%.

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 to 28% of HPMC K200M was choosen in intragranular preparation except formulation F1. Whereas HPMC K100M was considered in F1, meanwhile 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. Result

showed that approximately 17 % of the drug was released within 30 minute for all formulation and 80% of the drug was found to release at the end of 12 hrs. While comparing the drug release pattern between F1 and F2, the formulation F2 released 38.36±2.54% at the end of initial 30 mimute, whereas F1 released only18.59±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 Figures 1. [17]
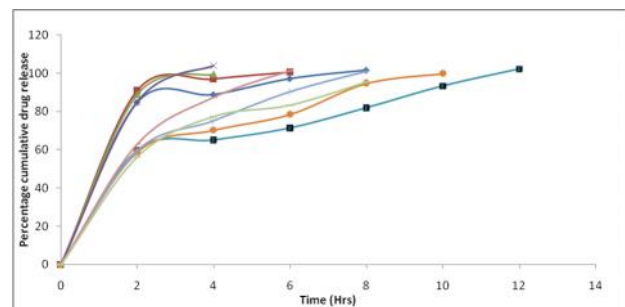

Fig 1: Percentage cumulative drug release of all formulation

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 Korsemeyer-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. On the basis of the above results, F6 was selected as a promising formulation for further studies.

Drug polymer interaction study

FT-IR Study

Pure Metformin hydrochloride, mixed with the polymer HPMC K200M, HPMC K100M, Kollidon 30 and MCC separately with IR grade 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 to 4,500 cm^{-1} using an FTIR 8400S, Schimazu. There was no chemical interaction between Metformin hydrochloride and the polymers used which is obtained by employing I.R. spectral study 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 were appeared in the region of 3180, 3300, 3325 and 3368 cm^{-1} respectively because of N-H asymmetric and symmetric stretching vibrations.
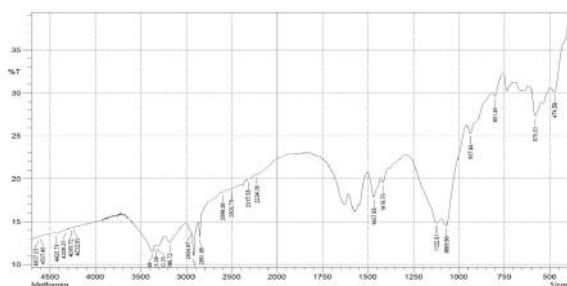

Fig 2: FTIR of Optimized Tablet

DSC Study

Differential scanning calorimetry (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 study was performed using Universal V4.2E TA instruments to determine the drug excepient compatibility study. During study a sharp endothermic peak for Metformin hydrochloride was obtained at 231^{0}C corresponding to melting point. But in the formulation there was a slight change in peak temperature and peak shape, which might be due to reduction of the purity level of component and interaction with excipients.

Stability study of best batch

Long term, intermediate and accelerated stability testing study was carried out according to ICH guidelines considering 25±2°C/60±5% 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 aluminium blister and placed in humidity chamber. 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. Thus, F6 formulation batch confirmed its stability.

4. CONCLUSION

The present investigation shows that various grades of Hypromellose at suitable concentration combinely with Polyacrylate polymers can effectively be used to modify the release rates in hydrophilic matrix tablets 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 drug release pattern. Furthermore the *in-vivo* and pharmacokinetic study have to carry out.

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