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Original Article

Preparation and Evaluation of Polymer Fused Metformin Hydrochloride Sustained Release Tablet

Mansi Butola[1], Vikas Bhatt[2], Nidhi Nainwal[1,*], Vikash Jakhmola[1], Kiran Dobhal[1], Yogita Ale[1]

[1]Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun, Uttarakhand, INDIA.
[2]GRD (PG) IMT, Dehradun, Uttarakhand, INDIA.

ABSTRACT

Introduction: Diabetes Mellitus (DM) is one of the most prevalent and chronic illnesses associated with an abnormally high level of glucose in the body which is hazardous to the body organs. Metformin Hydrochloride (HCl), a biguanide derivative is used for Type 2 DM. It has a relatively short plasma half-life and its regular administration is required to maintain a normal blood glucose level in diabetic patients. Therefore, sustained-release medications are a suitable approach to increase patient compliance and extend the duration of the effect of metformin for 8-12 hr. The main goal of this investigation was to prepare an oral sustained-release tablet of metformin HCl using natural polymers as release rate-controlling agents. **Materials and Methods:** Polymer fused metformin hydrochloride sustained-release tablet was formulated with sodium alginate, and pectin alone and in combinations at different ratios, by direct compression method. **Evaluations:** The formulation was evaluated for pre-compression parameters, like drug-excipient interaction (using Fourier-transform infrared spectroscopy), drug solubility, flow properties and density of powder blends. The compressed tablets were evaluated for diameter, friability, thickness, weight variation, hardness, content uniformity and *in vitro* drug release. **Results:** The drug release study showed that sodium alginate and pectin alone and in combination were able to sustain the drug release. It is also suggested that if the amount of polymer increased, the drug release decreased. Formulation (MA3) containing the highest amount of sodium alginate (250mg) gave 93.06% drug release after 12 hr and was therefore chosen as the best formulation. Diffusion and erosion may be the mechanism of drug release, according to the kinetic modelling of the *in vitro* drug release.

Keywords: Metformin HCl, Pectin, Sodium Alginate, Diabetes Mellitus.

Correspondence:
Dr. Nidhi Nainwal
Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun, Uttarakhand, INDIA.
Email: nidhi.nainwal87@gmail.com
ORCID ID: 0000-0003-0117-1701

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INTRODUCTION

Tablets are widely accepted solid dosage form used to treat various disorders and is mainly taken through the oral route. The bioavailability of drugs through oral administration depends on their *in vitro* dissolution and gastrointestinal permeability.[1-3] Conventional tablets require the delivery of therapeutic agents on a regular basis to maintain a desired drug plasma concentration. However sustained release tablets provide greater patient compliance due to sustained drug effects, easy and simple administration, less dosing frequency, and therefore fewer unwanted side effects.[4]

It is crucial to develop an economic, less time-consuming method for manufacturing sustained-release formulations on an industrial scale. Sustained release matrix formulation of hydrophilic rate-controlling polymer is the most frequently used method in oral drug delivery.

Matrix systems enable the manufacturers to produce a desired release profile, in a simple and cost-effective way.[5] In diabetes the drug must reach the systemic circulation on time and the blood glucose should be maintained at the normal level throughout the time.[6] The fundamental goal of antidiabetic sustained release formulation is to increase patient compliance by extending the duration of action of medications thus reducing the dosing frequency, and maintaining uniform plasma drug level.[7]

More than 400 million people worldwide are affected by Diabetes Mellitus (DM), a major public health issue. This metabolic condition develops into chronic, life-threatening microvascular, macrovascular, and neuropathic consequences over time.[8] DM is brought on either by lack of insulin production, pancreatic cell injury, or insulin resistance in relation to not using insulin. Inclination to sedentary living may be the main cause of the rising number of diabetes patients worldwide, which is predicted to reach 366 million in the elderly population (those over 65 years) by 2030.[9]

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Orally administered biguanides like metformin hydrochloride are frequently used to treat type-II diabetes, a major condition that includes abnormalities in insulin production and insulin action. Treatment for non-insulin dependent diabetes mellitus involves the use of metformin HCl either alone or in conjunction with other anti-diabetic drugs (NIDDM-Type II diabetes).[10]

Metformin HCl is referred to as an anti-hyperglycemic drug rather than a hypoglycemic drug because, in contrast to other antidiabetic medications, it does not cause hypoglycemia at any practicable dose. In individuals whose hyperglycemia cannot be adequately treated on diet alone, this medication is used in monotherapy as an adjuvant to diet to lower blood glucose levels. It is a hydrophilic drug with slow and incomplete gastrointestinal tract absorption.[11] The absolute bioavailability of metformin HCl is to be 50-60%. It has a very short plasma half-life of 1.5-4.5 hr. The daily dose of metformin HCl is 500 to 3000 mg taken every 12 hr and if necessary, the frequency may be raised to three times per day, gradually up to 2-3 g every day.[12]

Alginate has been extensively utilized as an effective polymer for the formulation of controlled-release drug delivery systems. It creates a gelatinous substance after hydration with media that acts as a barrier to the drug's dissolution and diffusion and slows down the permeation of media into the dosage form. Alginate has been shown in numerous studies as a promising agent for delaying the release of drugs.[13] Pectin, a plant polysaccharide, is a hydrophilic polymer that, has been used for emulsifying, gelating, thickening and suspending purposes. It has been demonstrated to be helpful in the formulation of targeted drug delivery systems.[14]

A matrix tablet made of hydrophilic polymers is one of the many drug delivery technologies for prolonging drug release over time in order to increase therapeutic efficacy, and better disease management.[15]

This study aimed to construct sustained release metformin HCl matrix tablets using hydrophilic polymers (sodium alginate and, pectin) alone or in combination to evaluate the *in vitro* release characteristic and predict and correlate the metformin HCl release behaviour from the matrices.[16]

MATERIALS AND METHODS

Materials

Metformin HCl was procured from Yarrow Chem, Mumbai, India. Sodium alginate, pectin, and Microcrystalline Cellulose (MCC) were procured from the Central Drug House (CDS), New Delhi, India.

Methods

Preformulation studies

Organoleptic Properties

Organoleptic properties of the drug samples like color, taste, odour, and physical form were determined using suitable methods.

Melting Point

The capillary technique was used to measure the melting point of the drug in triplicate, and the mean value was reported.[17]

Solubility

The aqueous solubility of the drug was measured in triplicate using the magnetic stirrer. An excess amount of the drug was added to a beaker containing solvent to make a saturated solution. The saturated solution was made with 24 hr stirring on a magnetic stirrer. The solutions were then filtered and diluted if needed and analyzed in an ultraviolet-visible (UV-visible) spectrophotometer.[18]

Drug excipients compatibility study

The drug excipients compatibility study was done by Fourier-Transform Infrared (FTIR) spectroscopy (Thermo electron scientific LITE iD1).[19]

Formulation of Matrix tablets of metformin HCl

Matrix-embedded metformin hydrochloride tablets were prepared using a direct compression approach with varied quantities of polymers, either alone or in combination as shown in Table 1. A weighed amount of drug, polymer (sodium alginate and/or pectin), and microcrystalline cellulose were all combined and blended properly for 30 min. Talc and sodium stearyl fumarate was added to the powder mixture after 30 min and stirred for 5 min. The powder blend was weighed, and the tablets were compressed using an eight-station rotary press (Cadmach rotary tablet machine).[20]

Evaluation of Matrix Tablets

Precompression evaluation

Before compression, the powder blend was evaluated for adequate flow properties using the angle of repose, Carr's compressibility index, and Hausner's ratio.[21]

Post compression evaluation

The metformin HCl compressed tablets were then assessed for appearance, thickness, diameter, weight variation, hardness, friability, drug content, and *in vitro* dissolution.[22]

Table 1: Formulation table of Metformin HCl Matrix tablet.

Formulation	MP1 (mg)	MP2 (mg)	MP3 (mg)	MA1 (mg)	MA2 (mg)	MA3 (mg)	MPA1 (mg)	MPA2 (mg)	MPA3 (mg)
Metformin HCl	500	500	500	500	500	500	500	500	500
Pectin	150	200	250	-	-	-	75	100	125
Sodium Alginate	-	-	-	150	200	250	75	100	125
MCC Grade 112	35	35	35	35	35	35	35	35	35
Sodium stearyl Fumarate	10	10	10	10	10	10	10	10	10
Purified talc	10	10	10	10	10	10	10	10	10
Total weight of one tablet	705	755	805	705	755	805	705	755	805

Thickness (t) and diameter of the tablets

Vernier calliper was used to determine the diameter and thickness (mm) of the tablets.

Tablet Hardness (h)

The tablet hardness was measured by using a Monsanto hardness tester. The hardness of a tablet determines its ability to withstand a mechanical shock while being handled.[23]

Friability (%F)

To determine friability, 20 tablets were tumbled for 4 min at 25 rpm in a friabilator (Electro lab, model EF1W, Mumbai). The weight loss resulting from fracture or abrasion was recorded as a percentage of weight loss after the tablets were dusted and weighed. % Friability of tablets <1% is considered acceptable.[24]

Weight variation (w) test

The test was performed using a Digital Electronic Balance and followed the procedure of Indian Pharmacopoeia. Twenty tablets were chosen from each batch randomly and weighed individually and then collectively. The weight variation was checked for individual tablets and deviation can be calculated by the given formula.[25]

$$\% \text{ Weight variation} = \frac{(\text{weight of single tablet} - \text{Average weight of 20 tablets}) \times 100\%}{\text{Average weight of 20 tablets}}$$

Drug content estimation

Twenty tablets were chosen at random and powdered in a mortar. Methanol was used to dissolve a quantity of powder equal to one drug dosage, which was then filtered using Whatman filter paper. The solution was appropriately diluted, and a UV-spectrophotometer was used to conduct a spectrophotometric analysis of the drug concentration (Shimadzu, model UV-19001). Each observation was performed three times, and the average amount of the drug was determined.

In vitro Dissolution Studies

The USP paddle type II Dissolution equipment (Electrolab (India) Pvt. Ltd., Mumbai) was used to examine the *in vitro* dissolution of a matrix tablet at a speed of 50 rpm. For the first two hours 900 mL of acid buffer (pH 1.2), was used, followed by phosphate buffer (pH 6.8) solution for the next 12 hr. The temperature of the dissolution medium was kept constant at 37.5°C throughout the study. At regular intervals, a sufficient volume of samples was collected and promptly filtered using a membrane filter. After each sampling, a volume of dissolving medium equal to the volume of the samples removed was added to the vessel. The UV-visible spectrophotometer was used to determine the concentration of the drug in the samples at 233 nm.[26]

Kinetics of drug release

By fitting the *in vitro* release data to the zero-order, first-order, Higuchi, Hixson-Crowell cube root, and Korsmeyer-Peppas equations in Microsoft Excel 2007, the drug release kinetics for all formulations were determined. A model with regression coefficients R^2 approaching unity provided the greatest match for the system under investigation.[27]

RESULTS AND DISCUSSION

Pre-formulation studies

Metformin HCl was evaluated for various pre-formulation parameters like organoleptic properties, melting point, solubility, and drug excipients compatibility studies. The drug was found white or almost white crystalline powder with no taste and odour. The Melting point of the drug was found between 233-235°C. The drug is freely soluble in water. The observed solubility of metformin HCl in water was found to be 1.5mg/mL.

Drug-excipients compatibility study

To evaluate the compatibility between the drug and polymers, FTIR-spectra was used. The FTIR spectrum of metformin HCl, sodium alginate, pectin and, their physical combinations are shown in Figures 1, 2, 3, and 4, respectively. The FTIR-spectrum

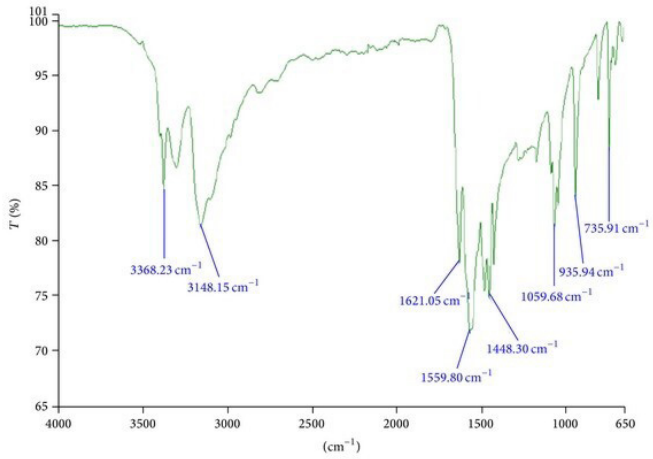

Figure 1: FTIR-spectra of Metformin HCl.

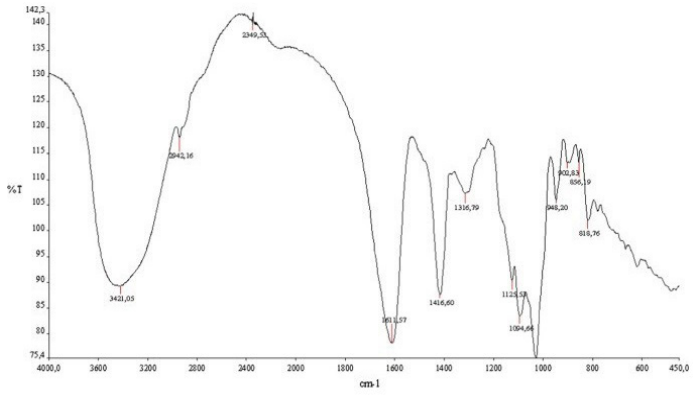

Figure 2: FTIR spectrum of Sodium alginate.

test results showed that there was no interaction between the drug and the polymer.

Evaluation of Matrix Tablets

Precompression evaluation

Flow property is an essential parameter to ensure dose uniformity in the tablets. The powder blend of all formulations was evaluated for assuring good flow properties and the selection of lubricants/ anti-adherents. Carr's compressibility index, Hausner's ratio and Angle of repose were calculated for flow characterization. The results showed good to excellent flow properties which are desirable for the compression of the tablets as given in Table 2.

Post compression evaluation of matrix tablet

The compressed tablets of all batches were prepared successfully using the direct compression method. The tablets were characterized for thickness, diameter, weight variation, hardness, and % friability. The formulation showed satisfactory results for all parameters which were within the desired limits and ranges of the acceptance criteria. The average diameter and thickness of tablets were 12mm, and 6.0+0.5 mm respectively. The average hardness of the tablets was 5.2+0.5 Kp. The tablets passed the

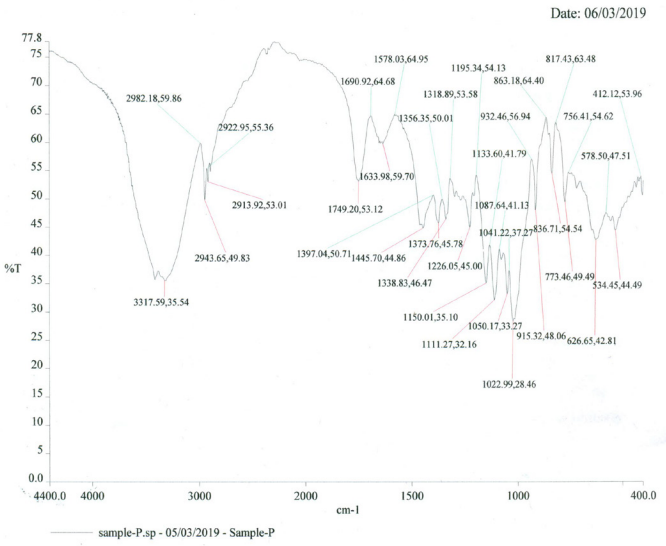

Figure 3: FTIR spectrum of Pectin.

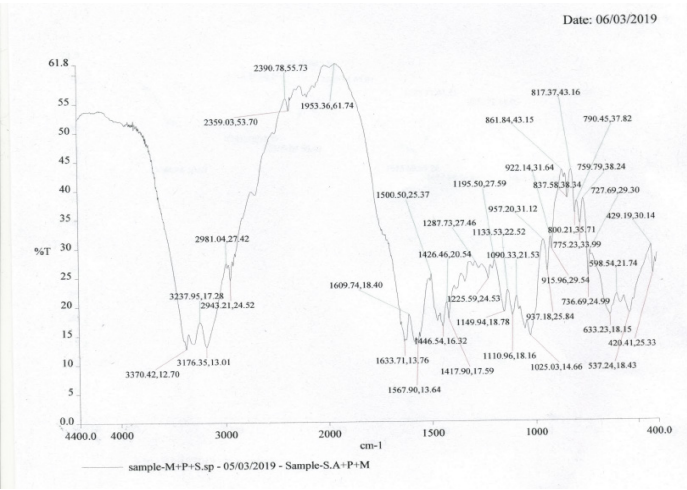

Figure 4: FTIR-spectra of drug, pectin, and sodium alginate mixture.

friability test and the % friability for all tables was less than 1%. The weight variation of all formulation batches was within the acceptable limit of +5%.

Drug Content

The values of the % drug content of various batches of tablets were given in Table 3. The drug content of all formulations was found to be within the USP limit (85-115%).

In vitro Drug Release Study

The data of *in vitro* drug release studies are shown in Figure 5. A bi-phasic release pattern showing initial burst release was evident from release data. Drug release in the first hour for formulations MP1, MP2, MP3, MA1, MA2, MA3, MPA1, MPA2 and MPA3 was 34.99%, 31.72%, 26.41%, 29.97%, 29.42%, 23.52%, 30.24%, 30.19% and 26.18% respectively. It is attributed that wetting of the polymers initially can cause swelling of the outer layer of the tablets that causes initial burst release. It is also suggested that as

Table 2: Flow characteristics of formulations.

Formulations	Carr's index	Hausner's ratio	Angle of repose	Flow property
MP1	12.34±0.51	1.12±0.006	23.74±0.11	Good
MP2	11.51±0.86	1.14±0.008	21.10±0.60	Good
MP3	11.36±0.49	1.12±0.007	25.76±0.32	Good
MA1	13.49±0.45	1.14±0.012	20.44±0.34	Good
MA2	13.85±0.34	1.15±0.009	20.48±0.31	Good
MA3	14.45±0.22	1.13±0.007	24.28±0.53	Good
MPA1	12.33±0.67	1.12±0.010	23.10±0.67	Good
MPA2	10.21±0.56	1.10±0.008	25.93±0.83	Good
MPA3	10.62±0.67	1.11±0.007	24.54±0.91	Good

Table 3: % Drug Content of the formulations.

Formulations	% Drug Content
MP1	99.24±1.15
MP2	98.97±0.96
MP3	98.24±0.46
MA1	98.97±0.76
MA2	99.25±0.79
MA3	98.89±1.23
MPA1	98.68±0.78
MPA2	99.32±0.97
MPA3	99.15±1.23

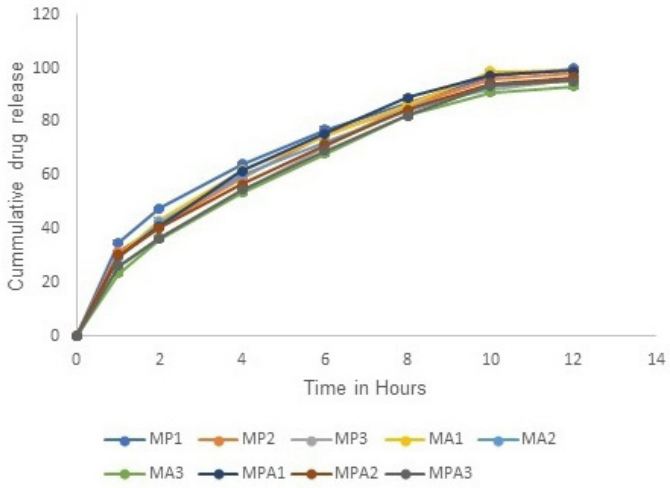

Figure 5: *In vitro* drug release of different formulations.

Table 4: *In vitro* release kinetic of Metformin HCl matrix tablets.

Formulations	Zero order	First order	Higuchi	Hixon crowell	Korsmeyer-Peppas	
	R^2	R^2	R^2	R^2	R^2	N
MP1	0.874	0.790	0.993	0.972	0.998	0.431
MP2	0.901	0.962	0.995	0.991	0.994	0.480
MP3	0.921	0.985	0.992	0.993	0.993	0.545
MA1	0.900	0.907	0.994	0.973	0.995	0.495
MA2	0.897	0.980	0.996	0.992	0.997	0.486
MA3	0.925	0.987	0.993	0.990	0.995	0.570
MPA1	0.900	0.950	0.993	0.992	0.994	0.503
MPA2	0.911	0.972	0.996	0.990	0.995	0.490
MPA3	0.927	0.972	0.994	0.988	0.996	0.543

the quantity of polymer increased, the drug release decreased. As the tablet came into contact with the medium, the matrix tablets swell initially and its erosion increased when swelling proceed with time. Cumulative % drug release data showed that all formulations showed sustained release. The formulation (MA3) containing the highest amount of sodium alginate (250mg) gave 93.06% drug release after the 12th hr and was therefore chosen as the best formulation.

Kinetic Analysis of Release Data

Release data were evaluated using several kinetic equations to characterize the kinetics of drug release from matrix tablets. The data were examined using the regression coefficient technique. Table 4, displayed regression coefficient (R^2) values, which were computed using the least-squares approach with a 95% confidence level. Analysis of the regression coefficient values of all formulations revealed that MP1, MP3, MA1, MA2, MA3, MPA1 and MPA3 matched the Korsmeyer-Peppas model with the greatest regression (R^2) values close to 0.99. Data that fit into the Korsmeyer-Peppas equation revealed that the drug release occurred via a diffusion process that followed non-Fickian behavior. A further extrapolation of the release data reveals that, out of the nine formulations investigated, seven were well-fitted into the Korsmeyer-Peppas model while the other two were well-fitted into the Higuchi matrix model. For the Higuchi model, MP2 and MPA2 had the greatest R^2 values of 0.995 and 0.996, respectively, showing that the release is through diffusion. Hixon Crowell's cube root rule is likewise followed by the formulations MP3, MP2, MA2, and MPA1, which all had R^2 values of 0.993, 0.993, and 0.992, respectively. This suggests that drug release occurred through erosion.

CONCLUSION

In this study, sodium alginate and/or pectin were used to manufacture metformin HCl sustained-release matrix tablets. Studies on *in vitro* drug release have shown that the drug release decreases with an increase in the quantity of polymer. Studies have also shown that swelling and erosion of matrix tablets affect drug release. The results data clearly shows a bi-phasic release with an initial burst effect in the matrix tablets. Studies on the swelling and erosion of Metformin tablets revealed that the swelling and erosion of matrix tablets increase with time. Cumulative drug release in percentage was found to be sustained for all formulations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

DM: Diabetes Mellitus; **PCOS:** Polycystic ovarian syndrome; **MCC:** Microcrystalline cellulose; **FTIR:** Fourier Transform infrared spectroscopy.

SUMMARY

Metformin HCl sustained-release dosage forms are created to achieve a desired pharmaceutical concentration in the blood or at the intended site for a certain period. The only oral anti-hypoglycemic/diabetic drug in the market that blocks hepatic glucose release is metformin. Metformin is also helpful in reducing glycosylated hemoglobin (HbA_{1c}) by 1-2 percentage points, whether provided alone or in combination with other blood glucose-decreasing drugs or insulin since persons with type 2 diabetes often have increased hepatic glucose production. The direct compression approach was used to develop a variety of matrix-embedded formulations of metformin hydrochloride using various quantities of polymers, either alone or in combination. All the formulations were able to give the sustained drug release for more than 12 hr, and thus able to maintain the blood glucose level at optimum level.

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