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RESEARCH ARTICLE

# Formulation and *In vitro* Characterization of Metformin HCl *Hibiscus rosa sinensis* Mucilage Controlled Release Matrix Tablets

C. Soujanya[1], B. Lakshmi Satya[1], Nayudu Teja[2], Vemuri Akash[3]

*[1]Department of Pharmaceutics, Vishnu Institute of Pharmaceutical Education and Research, Narsapur, Medak, Telangana, India, [2]Department of Pharmaceutics, V.V Institute of Pharmaceutical Sciences, Gudlavalleru, Andhra Pradesh, India, [3]Department of Pharmaceutical Technology, Andhra University, Andhra Pradesh, India*

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## ABSTRACT

**Introduction:** Controlled release drug delivery systems have received much attention in the past two decades with numerous technologically sophisticated products on the market place. Such advancements have come about by convergence of many factors, including the discovery of novel polymers, formulation optimization, better understanding of physiological and pathological constraints, prohibitive cost of developing new drug entities, and the introduction of biotechnology and biopharmaceutical principles in drug product design. The major benefits of these products lie in the optimization of drug input rate into the systemic circulation to achieve an appropriate pharmacodynamic response. **Materials and Methods:** The drug metformin hydrochloride was selected taking into consideration of their physiochemical, biopharmaceutical properties, and rationale of clinical efficacy. It is an oral hypoglycemic agent; chemically it is 1, 1–dimethyl biguanide derivative, acts by suppressing hepatic gluconeogenesis. It is a white, crystalline powder, and hygroscopic in nature. It is freely soluble in water and slightly soluble in alcohol, practically insoluble in acetone and in dichloromethane. Metformin HCl is readily absorbed from the gastrointestinal tract, having oral bioavailability of 50–60%, peak plasma concentration (Cmax) is reached within 1–3 h with immediate release and 4–8 h with extended release. Plasma protein binding of Metformin HCl is negligible, as reflected by its very high apparent volume of distribution (300–1000 Lit after a single dose). Metformin HCl is not metabolized and excreted as unchanged form in urine, having elimination half-life of 2–6 h. **Results:** In the present work, the rate of dug release can be prolonged using polymer matrix system, which influences the intragel swelling dynamics and relative physical integrity of the swollen matrix structure. **Conclusion:** Furthermore, that may produce heterogeneous domains within the swollen gel boundary.

**Keywords:** Controlled release, *In vitro*, Metformin, Mucilage, Sustained release

## INTRODUCTION

An ideal drug delivery system (DDS) should be able to deliver an adequate amount of drug, preferably for an extended period of time for its optimum therapeutic activity. The most of the drugs are inherently not long lasting in the body and require multiple daily dosing to achieve the desired blood concentration to produce therapeutic activity. To overcome such a problem, controlled release (CR) and sustained release (SR) delivery systems are receiving considerable attention from the pharma industry world-wide. A CR-DDS not only prolongs the duration of action, but also results in predictable and reproducible drug-release kinetics. One important advantage of CR dosage forms is enhanced patient compliance.

CR technologies have been studied for a long time and many preparations have been supplied on the market. The drug release time is prolonged according to one of the following mechanisms:

***Corresponding Author:**
C. Soujanya,
E-mail: soujanya.c@viper.ac.in

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1. Changing the physical properties such as solubility and stability of the drug molecules.
2. Forming a complex of drug molecules with ion-exchanging resins.
3. Incorporating the drug molecules in slowly disintegrating or inert porous matrices.
4. Coating drug molecules with pharmaceutical polymers that have a barrier function for the diffusion of drug molecules.
5. Osmotic pumps.

In addition, new additives such as linear short-chains starches can be used to make sustained-release tablets. Delivery from these non-porous tablets is based on swelling-controlled solvent-activated mechanism. In oral DDS, this mechanism is used by itself or in combination with others.[1-10]

## Drug Used in the Present Investigation

***Metformin hydrochloride***

Metformin is an oral antidiabetic drug in the biguanide class. It acts by suppressing glucose production by the liver. It is primarily used for Type 2 diabetes, but is increasingly being used in gestational diabetes, polycystic ovary syndrome, non-alcoholic fatty liver disease, and premature puberty.

## Common Names

Hibiscus Rosa-sinensis, known colloquially as Chinese hibiscus, China rose, Hawaiian hibiscus, (The plant list, June 2015) rose mallow and shoeblack plant, is a species of tropical hibiscus, a flowering plant in the Hibisceae tribe of the family Malvaceae. It is widely cultivated as an ornamental plant in the tropics and subtropics, but its native range is Vanuatu.

## Taxonomic Classification

Kingdom: Plantae, Subkingdom: Tracheobionta, Superdivision: Spermatophyta, Division: Magnoliophyta, Class: Magnoliopsida, Subclass: Dilleniidae, Order: Malvales, Family: Malvaceae, Genus: Hibiscus, Species: Hibiscus rosa-sinensis.

## Extraction of Dry Water Soluble Mucilage

The method was followed from the literature. The matured leaves from hibiscus species were collected, washed, and dried at 37°C for 24 h. Then, crushed and soaked in warm water for 2–3 h and heated up to 80–90°C for 30–45 min. The leaves mixture was left for 24 h for complete release of the water soluble mucilage/polysaccharide into the solvent. The mucilage/polysaccharide was then be extracted by using a cheese cloth bag to remove the marc and get concentrate viscous solution. Acetone was added to the concentrate viscous solution with constant stirring. The gel like precipitate was formed and then separated by filtration. The precipitate was washed 2–3 times with Jayapirakasam *et al.* 30 Acetone. After complete washing of the precipitate, it was dried in oven (40°C ± 1°C) followed by air dry (overnight). The compact mass was collected, grounded, passed through a sieve (ASTM 50), and stored in a desiccator until further use.[11-20]

## Microcrystalline Cellulose

***Non-proprietary names***

Microcrystalline cellulose (BP) Microcrystalline cellulose (USPNF).

***Synonyms***

Avicel $p^H$, Cellulose gel.

***Description***

Microcrystalline cellulose is purified from partially polymerized cellulose. It occurs as white, odorless, tasteless, and crystalline powder composed of porous particles [Table 1].

# MATERIALS AND METHODS

Several methods have been reported for the estimation of metformin HCl by spectrophotometric and chromatographic methods. In the present investigation, a simple and sensitive more accurate spectrophotometric method was used for the estimation of metformin hydrochloride at a $\lambda_{max}$ of 233 nm [Tables 2 and 3].

## Preparation of Metformin HCL Matrix Tablets

Metformin HCl CR matrix tablets were prepared by wet granulation method. The CR matrix tablet formulations consisted of drug, polymer, and diluents. The ratio of drug and polymer concentration was varied. The weight of all the tablet formulations was maintained uniformly using MCC as diluents. The compositions of various tablet formulations were given in Tables 4 and 5.

The materials were individually weighed and prepared as damp mass using water as granulating fluid. The damp mass was passed through sieve no.18 and the granules obtained were dried. The prepared granules were evaluated for flow properties such as angle of repose and compressibility index. The dried granules were again passed through sieve no.40. The prepared granules were lubricated with 1% talc and magnesium stearate and were compressed as matrix tablets using clit-10 station mini press. To minimize the processing variables, all batches of tablets were compressed under identical conditions.

*Raw material → Weighing → Screening → Mixing → Damp mass → Granulation → Drying → Screening → Lubrication → Compression*

**Table 1:** Pharmacopoeial specifications of micro crystalline cellulose

| Test | USP NF 23 |
|---|---|
| $p^H$ | 5.0–7.5 |
| Loss of drying | ≤7.0% |
| Residue on ignition | ≤0.1% |
| Ether soluble substances | ≤0.05% |
| Water soluble substances | ≤0.25% |
| Heavy metals | ≤0.001% |

**Table 2:** List of materials used and their manufacturers

| Category | Name of the material | Manufacturer |
|---|---|---|
| Drug | Metformin HCl | Gift Sample from Yarrow Chem. Ltd., Mumbai |
| Polymer | Hibiscus Mucilage | Extracted in lab |
| Excipients | Avicel 102 $p^H$ | Commercially Procured from Colorcon Chemicals Asia Pvt., Ltd., and Mumbai |
| | Magnesium Stearate | Commercially Procured from S.D Fine Chem, Ltd., Mumbai |
| | Talc | Commercially Procured from S.D Fine Chem, Ltd., Mumbai |

The matrix tablets were further evaluated for their physical parameters such as weight uniformity, hardness, friability, and drug content.

## Evaluation of Powder Flow Characteristics

### *Angle of repose*

The internal angle between the surface of the pile of prepared granules and the horizontal surface is known as the angle of repose.

**Table 3:** List of instruments used and their manufacturers

| Instrument | Manufacturer and Model |
|---|---|
| Weighing Balance | SHIMADZU CORPORATION |
| Heating Mantle | KEMI |
| Bulk Density Apparatus | HEXATEC INSTRUMENTS PVT LTD |
| 16 Station Rotatory Tablet Punching Machine | KARNAVATI |
| Digital Dissolution Testing Apparatus | LAB INDIA DS8000 |
| U.V. Spectrophotometer | SHIMADZU U.V. 1800 |
| Friabilator | ROCHE |
| $P^H$ Meter | ELICO (LI120) |
| Digital Balance | SHIMADZU (ELB300) |
| Hot Air Oven | UNIVERSAL HOT AIR OVEN |
| Hardness Tester | MONSANTO HARDNESS TESTER |
| Fourier Transform Infra-red Spectrophotometer | BRUKER 8400S |
| Stability Chamber | UNIVERSAL THERMOSTAT OVEN |

**Table 4:** Specifications of angle of repose

| Angle of repose | Type of flow |
|---|---|
| <25 | Excellent |
| 25–30 | Good |
| 30–40 | Passable |
| >40 | Very Poor |

**Table 5:** Specifications of flow properties corresponding to Carr's index

| % compressibility | Flow description |
|---|---|
| <10 | Excellent |
| 11–15 | Good |
| 16–20 | Fair |
| 21–25 | Passable |
| 26–31 | Poor |
| 32–37 | Very poor |
| >38 | Extremely poor |

Angle of repose was calculated from the average radius using the following formula:

$\theta = \tan^{-1}(h/r)$

Where, θ=Angle of repose h

h=Height of the pile

r=Average radius of the circle

### Carr's Index

It is the propensity of prepared granules to be compressed.

Based on the apparent bulk density and tapped density, the percentage compressibility of the prepared granules was determined using the following formula*:*

Carr's index=Tapped density–Bulk density × 100

### Accelerated Stability Studies

***Accelerated study***

The product was subjected to accelerated stability studies at 40°C±2°C/75%±5% RH for 3 months.

***Long-term study***

The product was subjected to long-term studies at 25°C±2°C/60%±5% RH for 6 months.

The formulations which showed good *in vitro* performance were subjected to accelerated stability studies. These studies were carried out by investigating the effect of temperature on the physical properties of tablets and chemical stability of tablets containing drug.

The tablet formulations such as were subjected to accelerated stability studies. The above said formulations were kept in petri dishes after preparation and stored in thermo stated oven at a temperature and relative humidity of 25±2°C, 60±5% RH for 6 months and 40±2°C, 75±5% RH for 3 months. Then, the samples of each type of formulations were evaluated for the earlier mentioned physical parameters.

The tablets were evaluated for physical parameters and the drug was analyzed for drug content uniformity by a known spectrophotometric method as described earlier. Further, these were subjected to drug release studies as stated earlier. The data are given in Tables 6-11.

## RESULTS AND DISCUSSION

The formulations which showed good *in vitro* performance were subjected to accelerated stability studies. These studies were carried out by investigating the effect of temperature on the physical properties of the tablets and on drug release from the matrix tablets. F6 and F7 were subjected to accelerated stability studies. The results of these studies are given in Tables 12 and shown in Figures 1-3.

The results thus indicated that there was no visible and physical changes observed in the matrix tablets after storage. Weight uniformity, hardness, friability, and drug content were found to be uniform before and after storage at different conditions. It was also observed that there was no significant change in drug release from the matrix tablets. The slow and controlled drug release characteristics of the matrix tablets remained unaltered. Thus, the drug release characteristics of CR matrix tablets designed were found to be quite stable.

An ideal DDS should be able to deliver an adequate amount of drug, preferably for an extended period of time for its optimum therapeutic activity. The most of the drugs are inherently not long lasting in the body and require multiple daily dosing to achieve the desired blood concentration to produce therapeutic activity. To overcome such a problem, CR and SR delivery systems are receiving considerable attention from the pharma industry world-wide. A CR-DDS not only prolongs the duration of action, but also results in predictable and reproducible drug-release kinetics.

In the present investigation, metformin HCl was employed in the controlled DDS for extending the drug release for a prolonged period of time. It is an oral hypoglycemic agent, chemically, it is 1, 1–

**Table 6:** Calibration data for estimation of Metformin HCl in 6.8 $p^H$ Phosphate Buffer at 233 nm

| Concentration (μg/ml) | Absorbance* (x̄±SD) |
|---|---|
| 2 | 0.1692±0.003 |
| 4 | 0.3268±0.005 |
| 6 | 0.4989±0.008 |
| 8 | 0.6525±0.010 |
| 10 | 0.8222±0.007 |

*n=6

**Table 7:** Preformulation studies of Metformin HCl

| Description | Method Evaluated | 0th day | 1st month | 3rd month |
|---|---|---|---|---|
| Metformin HCl | Physical evaluation | White Crystalline | Complied | Complied |
| Metformin HCl+Polymer | Physical evaluation | Complied | Complied | Complied |
| Metformin HCl+Excipients | Assay (UV Spectrophotometri c) | Complied | Complied | Complied |
| Metformin HCl | FTIR Studies | 1625.33 $cm^{-1}$<br>1061.13 $cm^{-1}$ | Complied | Complied |
| Metformin HCl+Polymer | FTIR Studies | 1633.68 $cm^{-1}$<br>1062.58 $cm^{-1}$ | Complied | Complied |

**Table 8:** Composition of Metformin HCl Matrix tablets

| Ingredients (mg/tab) | Tablet formulations | | | | | | |
|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 |
| Metformin HCl | 800 | 800 | 800 | 800 | 800 | 800 | 800 |
| Hibiscus Dried Mucilage | __ | 50 | 60 | 70 | 80 | 90 | 100 |
| Water | Q.S | q.s | q.s | q.s | q.s | q.s | q.s |
| MCC | 190 | 140 | 130 | 120 | 110 | 100 | 90 |
| Talc | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Magnesium Stearate | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Total Tablet Weight (Mg) | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 |

**Table 9:** Pre-compressional parameters of Metformin HCl Matrix Tablets

| Formulation code | Angle of repose (°) | Compressibility index (%) |
|---|---|---|
| F1 | 23.90 | 13.23 |
| F2 | 22.34 | 12.17 |
| F3 | 24.54 | 11.87 |
| F4 | 23.18 | 11.41 |
| F5 | 22.77 | 12.61 |
| F6 | 21.32 | 12.27 |
| F7 | 22.54 | 12.37 |

dimethyl biguanide derivative, acts by suppressing hepatic gluconeogenesis. It is a white, crystalline powder, and hygroscopic in nature. It is freely soluble in water and 6.8 $p^H$ phosphate buffer and slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride. Metformin HCl is readily absorbed from the gastrointestinal tract, having oral bioavailability of 50–60%, Peak plasma concentration ($C_{max}$) is reached within 1–3 h with immediate release and 4–8 h with extended release. Plasma protein binding of metformin HCl is negligible, as reflected by its very high apparent volume of distribution (300–1000 L after a single dose). Metformin HCl is not metabolized and excreted as unchanged form in urine, having elimination half-life of 6.2 h.

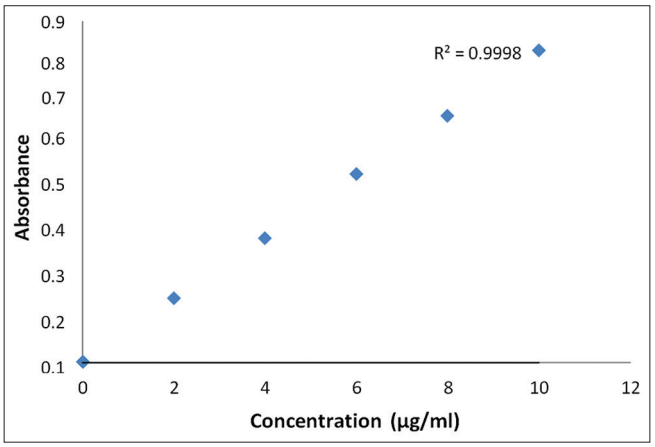


**Figure 1:** Calibration curve for estimation of Metformin HCl in 6.8 $p^H$ Phosphate Buffer at 233 nm

Basedonthesephysicochemicalandbiopharmaceutical properties, the drug metformin HCl was selected as a drug candidate for the formulation of CR matrix tablets. The present work was aimed to formulate the CR matrix tablets of metformin HCl with Hibiscus Gum for extending the drug release for a prolonged period of time.[21-30]

CR matrix tablets of metformin HCl were prepared by wet granulation method using water as granulating fluid. All the tablets were evaluated for physical parameters such as weight uniformity, hardness, friability, and drug content. The *in vitro*

**Table 10:** Physical parameters of Metformin HCl Matrix Tablets

| Formulation Code | Weight uniformity (mg) | Hardness (Kg/cm²) | Friability (% w/w) | Drug content* (mg/Tablet) |
|---|---|---|---|---|
| F1 | 998±2.0 | 4.0±0.3 | 0.12 | 800.3±0.5 |
| F2 | 997±3.0 | 4.5±0.3 | 0.12 | 798.2±0.5 |
| F3 | 998±3.0 | 4.5±0.3 | 0.18 | 796.4±0.5 |
| F4 | 997±2.0 | 4.5±0.3 | 0.17 | 800.2±0.2 |
| F5 | 998±4.0 | 4.5±0.3 | 0.15 | 799.2±0.3 |
| F6 | 1000±2.0 | 4.6±0.3 | 0.18 | 800.2±0.5 |
| F7 | 998±3.0 | 5.0±0.3 | 0.16 | 799.6±0.5 |

*n=6

**Table 11:** Dissolution parameters of various Matrix Tablets of Metformin HCl

| Formulation code | Zero order | | First order | | Higuchi | | Peppas | |
|---|---|---|---|---|---|---|---|---|
| | K0 (mg/hr) | R2 | K1 ($h^{-1}$) | R2 | KH ($mg/h^{1/2}$) | R2 | N | R2 |
| F1 | 15.33 | 0.600 | 0.742 | 0.984 | 272.89 | 0.918 | 0.454 | 0.943 |
| F2 | 11.47 | 0.641 | 0.554 | 0.974 | 265.66 | 0.947 | 0.508 | 0.960 |
| F3 | 9.14 | 0.630 | 0.451 | 0.982 | 243.85 | 0.949 | 0.524 | 0.960 |
| F4 | 7.41 | 0.630 | 0.319 | 0.984 | 218.81 | 0.964 | 0.523 | 0.966 |
| F5 | 6.78 | 0.244 | 0.384 | 0.995 | 180.51 | 0.902 | 0.477 | 0.941 |
| F6 | 6.81 | 0.452 | 0.187 | 0.992 | 206.71 | 0.989 | 0.549 | 0.980 |
| F7 | 7.06 | 0.722 | 0.208 | 0.997 | 212.99 | 0.985 | 0.730 | 0.983 |
| MP | 7.19 | 0.728 | 0.266 | 0.995 | 211.31 | 0.988 | 0.728 | 0.989 |

**Table 12:** Similarity factor (f2) For F7 and marketed formulations

| Time (hrs) | MP (a) | F7 (b) | (a-b) | $(a-b)^2$ | $\sum(a-b)^2$ | $\sum(a-b)^2/n$ | $f2 = 50 + log \frac{100}{\sqrt{1+\sum(a-b)2/n}}$ |
|---|---|---|---|---|---|---|---|
| 1 | 31.22 | 30.19 | 1.03 | 1.06 | 7.905 | 7.905 | 51.52 |
| 2 | 46.86 | 46.70 | .16 | 0.025 | 7.905 | 3.95 | 51.5 |
| 3 | 60.99 | 59.36 | 1.63 | 2.65 | 7.905 | 2.63 | 51.71 |
| 4 | 70.57 | 69.11 | 1.46 | 2.3 | 7.905 | 1.97 | 51.76 |
| 6 | 82.12 | 81.61 | 0.51 | 0.26 | 7.905 | 1.31 | 51.81 |
| 8 | 89.99 | 89.78 | 0.21 | 0.04 | 7.905 | 0.98 | 51.85 |
| 10 | 95.57 | 94.54 | 1.03 | 1.06 | 7.905 | 0.79 | 51.87 |
| 12 | 97.82 | 96.99 | 0.83 | 0.68 | 7.905 | 0.65 | 51.89 |

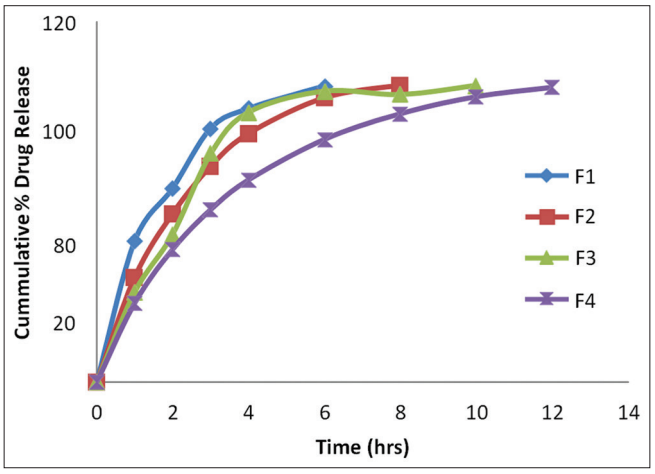


**Figure 2:** Drug release profiles of Metformin HCl Matrix Tablets

dissolution studies were carried out for all the matrix tablet formulations and the mechanism of drug release was elucidated.

## CONCLUSION

Metformin HCl is a water soluble drug, CR matrix tablets of Metformin HCl were prepared by wet granulation method using water as granulating fluid, with hibiscus gum as a rate retarding polymer. Preformulation studies were performed on the drug and excipients used in the formulations and were found to be compatible. No drug and excipient reactions were observed. The calibration curve for the estimation of metformin HCl in 6.8 $p^H$ phosphate buffer was found to be linear and obeyed Beer's law in the concentration range of 2–10 µg/ml. Flow properties such as angle of repose and Carr's index were evaluated for the

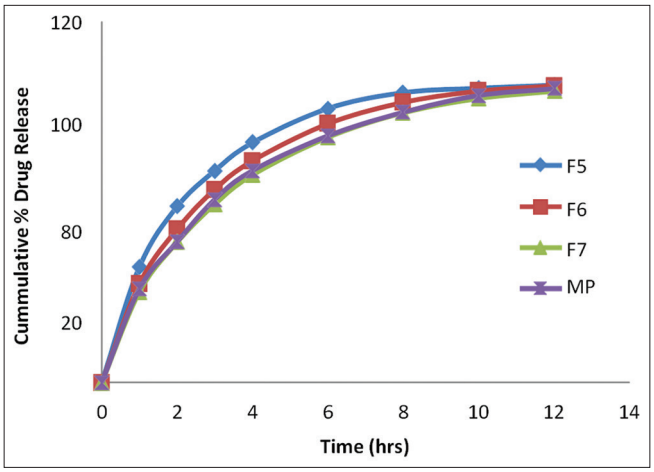


**Figure 3:** Drug release profiles of Metformin HCl Matrix Tablets

prepared granules and were found to exhibit good flow properties. The angle of repose values obtained for granules was in the range of 21.32–23.84° and the Carr's index values were in the range of 12.17–13.23%. Metformin HCl CR matrix tablets were prepared by wet granulation method using water as granulating fluid. All the tablets were prepared under identical conditions to minimize the processing variables. Wet granulation method was found suitable for drugs and polymers. Tablet formulations were further evaluated for physical parameters. It was revealed that all the tablet formulations were found to be stable and meeting I.P specified limits for weight uniformity, friability, and drug content. The hardness of all the tablet formulations was in the range of 4.0–5.0 kg/cm$^2$. Weight uniformity of all the tablet formulations was in the range of 1000±3 mg. Friability loss of the tablet formulations was found to be negligible and was in the range of 0.12–0.18% w/w. Drug content estimated for all the tablet formulations was highly uniform with <2.5% variation. The matrix tablet formulations prepared with drug and polymer with varied concentration in F6 and F7 could be suitable for extending the drug release more than 12 h. The matrix tablet formulations (with low concentration of gum) gave slow release of drugs up to 12 h. The first order $R^2$ values of tablet formulations were in the range of 0.974–0.995. Thus, all the formulations were found to be linear with first order rate constant. The zero order $R^2$ values of tablet formulations were in the range of 0.244–0.728. Thus, all the formulations were found to be non-linear with zero order rate constant. The drug release from the tablets depends on the concentration of polymer employed. Good linear relationships were observed between drug release and polymer concentration. Amount of drug released versus square root of time plots for all the matrix tablet formulations was found to be linear with $R^2$ values in the range of 0.887–0.989. The release exponent "n" values for all the matrix tablet formulations were in the range of 0.45–0.73 indicating that the drug release is by non-fickian diffusion. Thus, the drug release from the matrix tablet formulations was by diffusion of the drug from the polymer matrix followed by erosion of the polymer. Swelling index characteristics were performed on optimized matrix tablet formulations. The matrix tablet formulation with hibiscus gum as polymer tends to swell at a rapid rate. FTIR was performed for pure drug, polymer, F6, and F7 formulations. The results revealed that there were no major interaction between the drug, polymer, and electrolytes. Similarity factor (F2) between the optimized formulation and marketed formulation was found to be 51.52–51.89. Accelerated stability studies were performed for some selected matrix tablets. No significant change was observed in physical parameters such as weight uniformity, hardness, friability, and drug content. Drug release from the matrix tablets after storage at different conditions remained unaltered and found to be quite stable.

## REFERENCES

1. Al-Snafi AE. A review on chemical constituents, pharmacological effects and therapeutic importance of *Hibiscus rosa Sinensis*. IOSR J Pharm 2018;8:101-19.
2. Adams JF, Clark JS, Ireland JT, Kesson CM, Watson WS. Malabsorption of Vitamin B12 and intrinsic factor secretion during biguanide therapy. Diabetologia 1983;24:16-8.
3. Javaid A, Hasan R, Zaib A, Masroor S. A comparative study of the effects of hypoglycemic agents on serum electrolytes in the diabetic patients. Pak J Pharm Sci 2007;20:67-71.
4. Andres E, Noel E, Goichot B. Metformin-associated Vitamin B12 deficiency. Arch Intern Med 2002;104:490-2.
5. Anonymous. Metformin for non insulin-dependent diabetes mellitus. Drugs 1995;49:721-49.
6. Khan AR, Kumar P, Bhateja P, Shikha S, Nitika N,

Kritika D. Formulation, development and evaluation of metformin hydrochloride sustained release tablets. World J Pharm Res 2012;1:1424-50.
7. Aruna N, Babu MK. Formulation and evaluation of sustained release matrix tablets containing metformin HCl and *Syzygium cumini*. Int J Pharm Biol Arch 2011;2:900-5.
8. Asraful I, Halder S, Bachar SC. Formulation and *in vitro* evaluation of betahistine dihydrochloride twice daily controlled release matrix tablet. Dhaka Univ J Pharm Sci 2011;10:93-100.
9. Avilés-Santa L, Sinding J, Raskin P. Effects of metformin in patients with poorly controlled insulin-treated type diabetes mellitus: A randomized, double blinded, placebo-controlled trial. Ann Intern Med 1999;131:182-8.
10. Bailey CJ, Turner RC. Metformin. N Engl J Med 1996;334:574-9.
11. Bailey FE, Kolesky JV. Poly Ethylene Oxide. London: Academic Press; 1976.
12. Nanjwade BK, Mhase SR, Manvi FV. Formulation of extended-release metformin hydrochloride matrix tablets. Trop J Pharm Res 2011;10:375-83.
13. Bhoyar PK, Amgaonkar YM. Taste masking and molecular properties of metformin hydrochloride-indion 234 complexes. J Young Pharm 2011;3:112-8.
14. Bonderoni MC, Caramella C, Sangalli ME, Conte U, Hernadez RM, Pedraz JL. Reological behaviour of hydrophilic polymers and drug release from erodible matrices. J Controlled Release 1992;18:205-12.
15. Breimer DD, De Boer AG. Hydrophilic matrix sustained release systems based on polysaccharide carriers. Biopharm Drug Dispos 1981;2:131-6.
16. Squibb BM. U.S. Food and Drug Administration, Glucophage (Metformin Hydrochloride Tablets) Label Information. United States: Food and Drug Administration; 2008.
17. Callaghan TS, Hadden DR, Tomkin GH. Megaloblastic anaemia due to Vitamin B12 malabsorption associated with long term metformin treatment. BMJ 1980;280:1214-5.
18. Chan NN, Brain HP, Feher MD. Metformin-associated lactic acidosis: A rare or very rare clinical entity. Diabet Med 1999;16:273-8.
19. Chandira M, Venkateswarlu BS, Anup J, Debjit B. Formulation and evaluation of extended release tablets containing metformin HCl. Int J ChemTech Res 2010;2:1320-9.
20. Cheskin H, Briskin J, Engh K. Evaluation and comparison of dissolution data derived from different modified release dosage forms: An alternative method. J Controlled Release 1997;4:249-56.
21. Jadhav CM, Tekade BW, Thakare VM, Patil VR. Formulation and evaluation of sustained release matrix tablets of metformin hydrochloride. World J Pharm Pharm Sci 2012;1:717-30.
22. Collier CA, Bruce CR, Smith AC, Lopaschuk G, Dyck DJ. Metformin counters the insulin-induced suppression of fatty acid oxidation and stimulation of triacylglycerol storage in rodent skeletal muscle. Am J Physiol Endocrinol Metab 2006;291:E182-9.
23. Dharmendhra S, Jain SK, Sujatha M. Formulation and evaluation of sustained release metformin HCl matrix tablets using natural polysaccharide. Am J PharmTech Res 2021;4:493-500.
24. De Leede LG, De Boer AG, Breimer DD. Hydrophilic matrix sustained release systems based on polysaccharide carriers. Biopharm Drug Dispos 1981;2:131-6.
25. De Nesnera AP. Metformin dependence: A need for awareness. J Clin Psychiatry 1996;57:136-7.
26. Deasy PB. Sustained release of a water soluble drug from hydrophilic compressed dosage forms. Crit Rev Ther Drug Carr Syst 1991;8:39-89.
27. Deshpande AA, Rhodes CT, Shah NH, Malick AW. Formulation and evaluation of extended release dosage form of metformin hydrochloride using combined hydrophobic and hydrophilic matrix. Drug Dev Ind Pharm 1996;22:539-47.
28. Dinndorf PA. Risk of abuse of metformin in children and adolescents with chronic illnesses. J Pediatr 1998;13:293-5.
29. Dunn CJ, Peters DH. Metformin. A review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. Drugs 1996;49:721-49.
30. Eurich DT, Mcalister FA, Blackburn DF, Majumdar SR, Tsuyuki RT, Varney J, *et al*. Benefits and Harms of Antidiabetic Agents in Patients with Diabetes and Heart Failure": Systematic Review. BMJ 2007;335:497.