Evaluation of Metformin Hydrochloride Floating Drug Delivery System: In vitro Study and In vivo Prediction

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Authors’ contributions

This work was carried out in collaboration between both authors. Author RP run experiments, data collection, literature survey and performed the statistical analysis, wrote the first draft of the manuscript. Author SJ designed the study and guided. Both managed the analyses of the study, managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Aim: This research work was aimed to evaluate Metformin hydrochloride (MH) floating dosage form by In vitro evaluation/In vivo prediction and to evaluate it’s predictability through it’s application during the R&D using Insilico technique in WINONLIN Software. MH was examined as a model drug, which is a biguanide and is an hypoglycemic agent administered orally. The study was aimed to determine the the systemic concentrations of MH using In-vivo prediction.

Study Design: Fabrication and assessment of Metformin hydrochloride floating drug delivery system: In Vitro evaluation /In Vivo prediction. Biorelevant media was selected for dissolution profile of 12 units of dosage form. Software assisted program used for data feeding and results output.

Methodology: The absorption window for MH is the upper portion of the small gut in which the GI absorption is complete after 6 h. Hence gastroretentive formulation was developed and validity of...
dissolution study was extended by In vivo pharmacokinetic prediction using WinNonlin Software. A mechanistic oral absorption model was built in Phoenix WinNonlin® software. In the presented work, significant yet crucial, gastrointestinal (GI) variables are considered for biopredictive dissolution testing to account for a valuable input for physiologically-based pharmacokinetic (PBPK) platform programs. While simulations are performed and mechanistic insights are gained from such simulations from the WinNonlin program. 

Results: These floating tablets were observed for In vitro release and studied for In vivo pharmacokinetic prediction. From the obtained values, a meaningful In vivo prediction was done. interestingly from the results attained floating tablets showed sustained drug release and extended drug absorbed in 24h. Fascinatingly, from the data it was proved that drug formulation resides for desired time. The absorption of MH from the developed CR tablet was 1.4 fold higher than its marketed tablet and it had higher AUC0–t values than the marketed product which indicates superior bioavailability of test product compared to marketed tablet with similar dose in Invivo pharmacokinetic prediction. The mean value of biological half-life (T1/2) and Tmax of MH from test formulation is two times more, Test product has shown higher MRT, showing that the drug is maintained longer in the body in comparison to marketed product indicates controlled absorption.

Conclusion: Here we concluded that, a comparative prediction pharmacokinetic evaluation of the fabricated controlled release tablets and the marketed formulation indicates that the fabricated controlled release tablets are well absorbed and the degree of absorption is greater than that of the marketed ER formulation with larger gastric residence time.

Keywords: Metformin HCl; pharmacokinetics; bioavailability; AUC, Cmax, GRDS.

ABBREVIATIONS

MH : Metformin HCl
GRDS : Gastroretentive drug delivery system
ER : Extended release
SR : Sustained release
Cmax : Maximum plasma concentration
Tmax : Time to reach maximum plasma concentration
AUC : Area under curve
GIT : Gastrointestinal tract
RLD : Reference listed drug
T1/2 : Half life
MRT : Mean residence time
GR : Gastroretentive
Hr : hours
GRT : Gastric residence time
FLT : Floating lag time
TFT : Total floating time

1. INTRODUCTION

Absorption by oral route is a dynamic and complex process that allows you to accurately predict the future. However, it is possible to estimate the likely human uptake based on a combination of a number of physicochemical properties, in vitro permeability, and animal/human in vivo data. Its intake improves absorption due to increased solubility in water and tends to correlate well with in vitro permeability when there are no certified restrictions. In the case of oral administration, the absorption process and the underlying bioavailability problems are more complex, because the rate of drug delivery to the systemic circulation changes over time when long-release oral products have been used, and this problem becomes even more complex [1]. The constantly changing climate of GI pH and motility patterns can alter drug behavior along the GI tract in such a way that it is necessary to investigate these mechanisms and, in a next step, to take these variables into account in in vitro and in silico predictive models to facilitate oral drug development. GI motility is defined by the different contractile phases of the migrating motor complex (MMC). Existing Knowledge and methods are incapable of predicting Invivo absorption. Nowadays, it is feasible to analyse and predict pharmacokinetic properties of drugs using Insilico simulations [2 ].

Metformin HCl (MH) is an antidiabetic drug which has a short half-life, possess a small absorption window in the upper gastrointestinal tract, and low gastrointestinal permeability [3]. It is fabricated as matrix floating drug delivery system which increases the gastric residence time (GRT) and give extended-release profile in comparison to marketed product and utilized for In vivo prediction using Phoenix® WinNonLin® 8.2 software [4]. Hence motive of the study is to predict Invivo performance of the developed formulation based on software assisted mechanistic model. The presented study was
conducted to develop the model with the help of software using established pharmacokinetic data.

All this work refers to the fact that important, yet crucial, gastrointestinal (GI) variables should be integrated into biopredictive dissolution testing (low buffer capacity media, considering phosphate versus bicarbonate buffer, hydrodynamics) and it signifies to account for a valuable input for physiologically-based pharmacokinetic platform programs. This PBPK software tool is capable of consistently predicting the in vivo performance of formulations and rationalize product development [5]. In silico mathematical modeling and simulation represents a substantial part of the research and development in pharmaceutical industry aiming to optimize the design of dosage forms. Computer simulations have been used in many ways such as physiologically based pharmacokinetic (PBPK) models, clinical trial simulations, software tools that predict the systemic pharmacokinetics of certain drugs and mathematical models to predict bioequivalence. In case of PBPK modeling, certain software platforms are widely used in pharmaceutical industry to simulate drug absorption through a variety of administration routes and predict pharmacokinetics and pharmacodynamics in animals and humans [6].

Commerciably available software packages such as the Simcyp® simulator, GastroPlus™, and PK-Sim® are just a few programs that are frequently used in the non-clinical stage of drug product development to get an idea about the in vivo performance of the drug product when administered to patients. The underlying syntax/algorithm of these packages describes the mass transport of the drug throughout the different built-in compartments and should be adequately reflecting the physiological processes of human body. While simulations can be performed and mechanistic insights can be gained from such simulations from current WinNonlin software. The novelty of the study is indicated by the development of a mechanistic oral absorption model in the software package that could only explain the observed luminal data [7].

For this study, we aimed to reflect the luminal and systemic concentrations of MH under fasting state conditions starting with the simplest model, assuming a first-order kinetic process for dissolution, gastric emptying and absorption. The In-vivo prediction of MH gastroretentive formulation based on the software assisted model differentiates the presented study in comparison to established results of earlier studies. Hence the current knowledge of gastroretentive drug delivery system Invivo prediction gets new exploration with the presented approach [8,9,10].

2. METHODOLOGY

2.1 Chemicals and Reagents

MH (gifted from Lupin, Pune) served as the model drug and hydroxypropyl methylcellulose (Methocel K100 M), Microcrystalline cellulose, stearyl alcohol (gift sample from Lupin, Pune), NE (Novel excipient) and citric acid (gifted from Ipca Labs, Mumbai, India), PEO (Polyox™ WSR 303, The Dow chemical company, Midland, Michigan), Isopropyl alcohol (Avantor, India) were used. Marketed tablets purchased from local market.

2.2 Methods

MH needs the input of twice or thrice daily doses in order to maintain desired beneficial concentrations since it has less oral bioavailability and it’s plasma half-life is small. In the light of contrary relation between medication adherence and dosing frequency, a GRDS (SR) formulation designed for once-daily dosing was considered suitable for MH for improving the compliance and reducing side effects. To enhance the bioavailability of MH, floating tablet with extended GRT and slow drug release at the site of absorption was developed. It was prepared by wet granulation method using release retarding polymers like HPMC K100M and Polyethylene oxide (Polyox-WSR 303) along with novel excipient and citric acid as gas forming agents. The critical quality attributes like FLT was less than 3 minutes and TFT was more than 24 hrs for developed formulation. [4,5,8]

Marketed tablets of MH ER formulation viz Carbophage XR tablets 500mg, Lot No. N22AE19032, Mfg by Merck Specialities, Pvt Ltd, India was used for the study. The dissolution of MH from the Floating tablets was studied using the USP dissolution apparatus I (Rotating basket). The evaluation was done using 900 ml of 6.8 phosphate buffer at temperature 37±0.5°C. The 100 RPM was rotation speed. 5 ml was withdrawn at preset time intervals of 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 h from each basket and the medium was refilled using 5 ml of fresh dissolution medium every interval. Samples were...
examined with the help of 233 nm wavelength of UV/visible spectroscopy [11,12,13].

The drug dissolution, as well as the fraction that is absorbed from the gastro-intestinal tract, can be predicted by means of physical, chemical, and well-established pharmacokinetic properties of the approximation (reported in the literature) and harmonization of the selected drugs, by using WinNonLin. The First-pass metabolism and the systemic availability is not taken into account in this work. These factors are important for the optimal development of the product and the systemic availability of the prediction. The Oral absorption of the reference drug can be predicted with the help of using WinNonLin and online tests. The mean Cmax, AUC0-inf, and the standard deviation (SD) were retrieved with n = 12 and a virtual exercise for ER dosage form [14].

The performance of prediction was evaluated by comparing predicted plasma concentration–time profiles of the marketed product and test product of Metformin HCl ER floating tablet using software Phoenix® WinNonLin® 8.2 (Certara, Princeton, NJ, USA). Some generalizations about dissolution and permeation characteristics In vivo can be made based on relative solubilities, as well as on permeability along the intestine, characteristics of drug substances, which can be used as a resuming point for development of an In vivo bipredictive dissolution methodology (IPD) and IVIVC technique. These predictions are obtained using software which involves physiologically based pharmacokinetic models describing drug concentration in tissues using physicochemical data of the drugs as well as other data [15,16].

## Table 1. Physicochemical properties of Metformin hydrochloride

| Sr. No. | Title                  | Details                        |
|---------|------------------------|--------------------------------|
| 1       | API name               | Metformin hydrochloride (MH)   |
| 2       | API info               |                                |
| A       | pH of solution         | 6.68 (1% aqueous solution)     |
| B       | PKa                    | 12.4                           |
| C       | Log P                  | -1.43 (Low lipophilic)         |
| D       | Solubility data        |                                |
| E       | Dose                   | 500mg                          |
| 3       | Formulation information| Brand and Test Batch: Sustained release product |

The below parameters mentioned in tabl 2 were cited from the literature [11]

| Sr. No. | Solution pH | Solubility (mg/ml) | Solubility (mg/250ml) |
|---------|-------------|--------------------|-----------------------|
| 1       | Buffer pH 1.2 | 143.99             | 35997.5               |
| 2       | Buffer pH 4.5 | 165.12             | 41280.0               |
| 3       | Buffer pH 6.8 | 170.20             | 42550.0               |
3. RESULTS AND DISCUSSION

In this study, a new in vitro–in vivo simulation approach has been developed which utilizes in vitro dissolution data in order to make predictions for the probability of Pharmacokinetic parameters acceptance. It is a systematic procedure that contains in vitro dissolution fitting, establishment of a pharmacokinetic model, and lastly the application of joint in vitro–in vivo simulations. In order to evaluate the predictive ability, the IVP approach was applied to the development process of a new anti-diabetic product containing active Metformin Hydrochloride [19,20].

Due to the challenge of simulating the In vivo dissolution profile at particular absorption window using in vitro release tests, differences between the $f_2$ value and absorption profiles may arise from the region specific absorption nature of MH. Infact, it has been noted after oral administration that the absorption of MH occurs chiefly from the proximal part of the gastrointestinal tract and is well linked with gastric emptying. Therefore, extending the residence of the ER tablet in the stomach might be a right ploy for enhancing MH absorption by barring it from overshooting the absorption window by trapping within the matrix [21].

An In vivo prediction (IVP) is a mathematical model which is predictive and illustrates a key role in the evolution, growth, assessment and maximization of sustained release, modified release and immediate release compositions. A IVP design can be time saving, effort and expenditure saving during pharmaceutical product development. It is well known that variations in drug release and release pattern impacts the systemic availability of drug and subsequent remedial failure or victory of a produc [22,23].

Prospective human PK projections are very challenging. This quantitative prediction arrange a compartmental GI absorption and passage model also as other parameters describing penetrability, release rate, micelles partitioning. In this evaluation we demonstrates the MH oral absorption profiles using the simulation software. The maximum concentration in oral drug absorption ($C_{\text{max}}$), the time taken to reach the maximum concentration ($T_{\text{max}}$) after administration of a drug, area under the concentration curve (AUC0-inf) are predicted in silico. It is based on comprising the effects of presumed In vivo release kinetics. Additional important elements muddling systemic circulation availability prediction ($F_{\text{sys}}$), such as nonlinear, carrier mediated intestinal or hepatic absorption, secretion; intestinal and hepatic metabolism are not taken into consideration. Also, elements impacting the total release processes, In vitro and In vivo e.g. solubilization, buffer and buffer strength are not appraised in detail. In current study, we stressed on absorption and empirical (simulated) In vivo release, and the outcome desired release and absorption outlines based on this input data [24,25].

A brief elaboration on the physicochemical properties (octanol–water partition coefficient (logP), acid dissociation constant (pKa), and molecular weight (MW)) of the active is made in order to relate them with the IVP methodology. MH is a soluble in water base (logP = -1.43, MW = 165.62, pKa = 12.4) which means that basic media the dissolution will be fast and in a greater extent, which is in accordance with the experimental dissolution data utilized in this study. Thus, in the IVIVS setting a longer residence in stomach, would result in a greater dissolution and more MH to be absorbed in the small intestine. Additionally, the IVP can assist the Formulator on the proper design of the release characteristics (i.e., as they are reflected on the dissolution profiles), since the IVP translates the in vitro data into the anticipated in vivo performance [26,27].

Final optimized formulation batch (F-10) was selected based on formulation optimization study with desired TFT, FLT and multimedia dissolution. Since the Metformin is absorbed from proximal region of small gut, pH 6.8 Buffer was selected as Biorelevant media for deconvolution of the data. Coupling the IVP procedure with biopredictive dissolution media can increase its predictive ability. [27] The test and marketed product release profile data is displayed in below table.

Table 2. Pharmacokinetic information of MH

| Parameters                  | Values/Constant |
|-----------------------------|-----------------|
| Volume of distribution      | 63-276L         |
| Kel (Terminal rate constant)| 0.15 /hr        |
| Bioavailability             | 60%             |
| Strength of drug            | 500 mg          |

In this study, we stressed on absorption and empirical (simulated) In vivo release, and the outcome desired release and absorption outlines based on this input data [24,25].
Table 3. In-vitro dissolution profile comparison

| Time (h) | Marketed product | Test (F-10) |
|----------|------------------|-------------|
|          | Dissolution condition: pH 6.8 Buffer, 900ml, Basket, 100 rpm | % drug release |
| 0        | 0                | 0           |
| 1        | 30               | 28          |
| 2        | 45               | 42          |
| 3        | 57               | 50          |
| 4        | 62               | 58          |
| 6        | 77               | 69          |
| 8        | 85               | 74          |
| 10       | 96               | 79          |
| 12       | 99               | 86          |
| 16       | 100              | 90          |
| 20       | 100              | 98          |
| 24       | 100              | 101         |

Table 4. In-vivo data summary for Test product

| Time (hr) | Summary | 0.00 | 1.00 | 2.00 | 3.00 | 4.00 | 4.50 | 5.00 | 5.50 | 6.00 | 6.50 | 7.00 | 7.50 | 8.00 | 8.50 |
|-----------|---------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| N         | 12      | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   |
| Mean (ng/mL) | 112.941 | 189.185 | 256.574 | 343.860 | 436.889 | 580.518 | 760.627 | 947.152 | 1142.207 | 1412.536 | 1587.187 | 1793.904 | 1942.659 |
| SD       | 48.989  | 71.250 | 174.131 | 235.885 | 271.982 | 256.940 | 197.736 | 270.295 | 318.006 | 375.496 | 298.171 | 211.442 | 108.255 |
| CV%      | 43.38   | 37.66 | 67.87 | 68.60 | 62.25 | 44.26 | 26.00 | 28.54 | 27.84 | 26.58 | 18.79 | 11.79 | 5.57 |
| Min      | 53.01   | 110.65 | 135.65 | 190.17 | 223.53 | 404.17 | 586.07 | 602.78 | 899.32 | 1215.76 | 1489.93 | 1746.07 |
| Median   | 105.26  | 157.65 | 189.72 | 309.87 | 397.18 | 515.92 | 748.64 | 939.90 | 1175.57 | 1312.83 | 1530.16 | 1803.66 | 1931.18 |
| Max      | 249.17  | 287.79 | 773.53 | 1065.39 | 1239.91 | 1377.68 | 1248.24 | 1296.94 | 1492.21 | 1933.52 | 1984.52 | 2042.42 | 2124.42 |

| Time (hr) | Summary | 9.00 | 9.50 | 10.00 | 10.50 | 11.00 | 11.50 | 12.00 | 13.00 | 14.00 | 16.00 | 20.00 | 24.00 | 30.00 | 36.00 | 48.00 |
|-----------|---------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| N         | 12      | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   |
| Mean (ng/mL) | 2116.603 | 2208.128 | 2176.710 | 2046.286 | 1798.450 | 1652.675 | 1490.910 | 1306.404 | 1142.089 | 821.871 | 604.088 | 402.929 | 269.711 | 129.830 | 44.623 |
| SD       | 138.510 | 138.832 | 186.997 | 221.414 | 220.438 | 200.490 | 171.840 | 171.818 | 176.802 | 258.969 | 245.077 | 199.366 | 161.372 | 79.127 | 49.242 |
| CV%      | 6.54    | 6.29 | 8.59 | 10.82 | 12.26 | 12.13 | 11.53 | 13.15 | 15.48 | 31.51 | 40.57 | 49.48 | 59.83 | 60.95 | 110.35 |
| Summary | Time (hr) | 0.00 | 1.00 | 2.00 | 3.00 | 4.00 | 4.50 | 5.00 | 5.50 | 6.00 | 6.50 | 7.00 | 7.50 | 8.00 | 8.50 |
|---------|-----------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| N       | 12        | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   | 12   |
| Mean (ng/mL) | 0.000 | 644.533 | 971.154 | 1159.621 | 1361.731 | 1571.718 | 1707.853 | 1777.238 | 1816.386 | 1872.899 | 1662.812 | 1569.618 | 1475.391 | 1361.720 |
| SD      | 0.000 | 462.329 | 523.815 | 682.232 | 736.526 | 546.200 | 449.867 | 279.615 | 213.752 | 189.825 | 194.985 | 202.763 | 190.309 | 139.819 | 139.819 |
| Min     | 0.000 | 95.65  | 127.69 | 156.17 | 165.17 | 165.17 | 165.17 | 165.17 | 165.17 | 165.17 | 165.17 | 165.17 | 165.17 | 165.17 | 165.17 |
| Median  | 0.000 | 578.66 | 951.37 | 1136.78 | 1322.19 | 1663.40 | 1864.85 | 1811.69 | 1787.13 | 1760.29 | 1629.42 | 1531.81 | 1435.59 | 1344.34 | 1344.34 |
| Max     | 0.000 | 1447.12 | 1764.06 | 2159.05 | 2359.05 | 2259.05 | 2230.41 | 2165.44 | 2294.97 | 2334.91 | 1961.26 | 1865.17 | 1791.99 | 1672.98 | 1672.98 |

Table 5. In-vivo data summary for RLD (Marketed product)
Table 6. Summary of PK parameters for Test product (F-10)

| Treatment | Subject | Cmax (ng/mL) | AUClast (hr*ng/mL) | AUCINF_obs (hr*ng/mL) | Tmax (hr) | T1/2 (hr) | Kel (1/hr) | MRT (hr) |
|-----------|---------|--------------|---------------------|-----------------------|-----------|----------|------------|----------|
| F-10      | 1       | 2349.457     | 37168.83            | 39350.044             | 10.00     | 9.94     | 0.07       | 16.96    |
|           | (Test Product) | 2373.807     | 29020.066           | 29545.016             | 10.00     | 7.22     | 0.096      | 16.16    |
|           | 3       | 2078.555     | 21806.845           | 22157.109             | 9.00      | 6.6      | 0.105      | 15.18    |
|           | 4       | 2527.459     | 26922.954           | 27576.122             | 9.50      | 8.09     | 0.086      | 15.33    |
|           | 5       | 2236.456     | 23483.867           | 23694.502             | 9.50      | 7.22     | 0.096      | 16.95    |
|           | 6       | 2262.418     | 20556.998           | 20584.628             | 10.00     | 4.6      | 0.151      | 11.91    |
|           | 7       | 2219.105     | 20716.428           | 20810.188             | 9.50      | 5.35     | 0.13       | 12.53    |
|           | 8       | 1786.064     | 25841.096           | 26126.485             | 11.00     | 6.15     | 0.113      | 15.89    |
|           | 9       | 2264.418     | 20464.018           | 20628.5               | 10.00     | 4.53     | 0.153      | 11.73    |
|           | 10      | 2068.555     | 21331.845           | 21553.202             | 9.00      | 5.73     | 0.121      | 14.97    |
|           | 11      | 2266.456     | 24083.034           | 24365.107             | 9.50      | 5.41     | 0.128      | 16.28    |
|           | 12      | 2306.418     | 23175.572           | 23195.09              | 10.50     | 4.27     | 0.162      | 12.95    |
|           | N       | 12           | 12                   | 12                    | 12        | 12       | 12         | 12       |
|           | Mean    | 2228.264     | 23547.63             | 24965.5               | 9.875     | 6.259    | 0.117      | 14.737   |
|           | SD      | 185.629      | 4814.513             | 5359.441              | 8.01      | 1.662    | 0.029      | 1.937    |
|           | CV%     | 8.33         | 19.61                | 21.47                 | 8.11      | 26.55    | 24.39      | 13.14    |
|           | Min     | 1786.06      | 20464.02             | 20584.63              | 9         | 4.27     | 0.07       | 11.73    |
|           | Median  | 2263.42      | 23329.72             | 23444.8               | 9.75      | 5.94     | 0.12       | 15.25    |
|           | Max     | 2527.46      | 37168.83             | 39350.04              | 12        | 9.94     | 0.16       | 16.96    |
Table 7. Summary of PK parameters for Reference product (RLD)

| Treatment     | Subject | Cmax (ng/mL) | AUClast (hr*ng/mL) | AUCL INF_obs (hr*ng/mL) | Tmax (hr) | T1/2 (hr) | Kel (1/hr) | MRT (hr) |
|---------------|---------|--------------|--------------------|-------------------------|-----------|----------|------------|----------|
| RLD           | 1       | 2359.051     | 22761.265          | 22976.477               | 4         | 4.32     | 0.16       | 7.98     |
|               | 2       | 2256.023     | 20976.274          | 21476.001               | 4         | 4        | 0.173      | 7.14     |
| (Marketed     | 3       | 1675.501     | 11427.576          | 11517.761               | 4.5       | 1.3      | 0.535      | 6.68     |
| Product)      | 4       | 1953.678     | 15863.694          | 16046.258               | 5         | 4.27     | 0.162      | 9.25     |
|               | 5       | 2145.146     | 16362.94           | 16366.124               | 4.5       | 1.93     | 0.36       | 6.6      |
|               | 6       | 2165.438     | 15238.632          | 15353.991               | 5.5       | 1.79     | 0.347      | 6.45     |
|               | 7       | 2294.97      | 17390.423          | 17782.037               | 6         | 4.11     | 0.169      | 9.56     |
|               | 8       | 1988.103     | 16646.667          | 17162.377               | 5         | 4.05     | 0.171      | 8.1      |
|               | 9       | 1839.656     | 16240.933          | 16329.423               | 6         | 2.77     | 0.25       | 10.05    |
|               | 10      | 2207.949     | 18722.592          | 19416.791               | 4         | 4.15     | 0.167      | 6.5      |
|               | 11      | 1976.172     | 15205.735          | 15272.225               | 6.5       | 3.25     | 0.213      | 9.27     |
|               | 12      | 2230.41      | 15304.08           | 15340.075               | 5         | 0.83     | 0.832      | 6.21     |
| N             | 12      | 12           | 12                 | 12                       | 12        | 12       | 12         | 12       |
|               | Mean    | 2091.008     | 16845.07           | 17086.63                | 5         | 3.064    | 0.298      | 7.817    |
| SD            | 204.654 | 2930.755     | 3051.193           | 1.29                     | 2091 ± 204.65 | 2228.26 ± 185.63 | 2228.26 ± 185.63 | 2228.26 ± 185.63 |
| CV%           | 9.79    | 17.4         | 17.86              | 42.09                    | 17.4 ± 17.4 | 6.259 ± 1.662 | 14.74 ± 1.94 | 14.74 ± 1.94 |
| Min           | 1675.5  | 11427.576    | 11517.76           | 0.853                    | 2091 ± 204.65 | 2228.26 ± 185.63 | 2228.26 ± 185.63 | 2228.26 ± 185.63 |
| Median        | 2155.29 | 16301.94     | 16347.77           | 3.63                     | 16845.07 ± 2930.76 | 23547.63 ± 4814.51 | 23547.63 ± 4814.51 | 23547.63 ± 4814.51 |
| Max           | 2359.051| 22761.265    | 22976.477          | 4.32                     | 17086.63 ± 3051.19 | 24965.5 ± 5359.44 | 24965.5 ± 5359.44 | 24965.5 ± 5359.44 |
|               |         |              |                    |                         | Mean ± SD (n=3) | Mean ± SD (n=3) | Mean ± SD (n=3) | Mean ± SD (n=3) |

Table 8. Summary of Pharmacokinetic parameters for GR Metformin ER tablets

| Pharmacokinetic Parameters* | Marketed Tablet | Metformin ER GRDS Tablet |
|-----------------------------|-----------------|--------------------------|
| Cmax (ng/mL)                | 2091 ± 204.65   | 2228.26 ± 185.63         |
| tmax (h)                    | 5.0 ± 0.853     | 9.88 ± 0.80             |
| Kt(h⁻¹)                     | 0.298 ± 0.206   | 0.117 ± 0.029           |
| ke(h⁻¹)                     | 3.06 ± 1.29     | 6.259 ± 1.662           |
| AUC (ng. h /ml)             | 16845.07 ± 2930.76 | 23547.63 ± 4814.51      |
| AUC 0–∞(ng. h /ml)          | 17086.63 ± 3051.19 | 24965.5 ± 5359.44       |
| MRT (h)                     | 7.82 ± 1.41     | 14.74 ± 1.94            |

*All values are Mean ± SD (n=3)
The dissolution profile of test product was found to be slower in the later time points than Marketed product in the biorelevant media pH 6.8 phosphate buffer.

Pharmacokinetic parameters that mark oral profiles, such as the maximum concentration (Cmax), time to reach the Cmax i.e (tmax) and AUC, were assessed by applying non-compartmental analysis by loading the data obtained from the marketed product and test product into the Win Nonlin.

- **In-Vivo data:** The summary statistics/predicted In-vivo data concentration obtained from the software based on the input data is displayed in above Table 4.

The predicted Invivo concentration of MH against time after the orally administered test formulation as compared to marketed tablets is shown in above Fig. 1.

Various predicted pharmacokinetic frameworks are enumerated in above Table 6 and 7.

- **In-Vivo data:** The summary statistics for In-vivo data as below:

4. **CALCULATED IN-VIVO DATASUMMARY**

In vitro studies showed less difference for gastroretentive test tablet in dissolution profile with marketed tablet. However, As portrayed in above table, test tablet had higher AUC_{0-1} values (23547.63 ng.h/ml) than the marketed product (16845.07 ng.h/ml) which indicates approximately 40% improvement. The inference was drawn that MH is released out of the test batch with a gradual and controlled, prolonged fashion and eventually got absorbed *In vivo*. Peroral dosing of Carbophage® XR reach to the peak plasma concentration about the 5th hour, then after by active concentration lowers as time passes, while the active was not found in the systemic circulation beyond 48 h. While in case of test formulation the peak plasma concentration occurs at around 10th hour indicating slow absorption and correlating the dissolution profile of later time points. Since the technology is developed in such a way that the Invitro minor performance difference coverts into significant Invivo performance [28,29].

The time for gastro-retention of a conventional composition is normally not more than 2 h, though MH was chiefly absorbed in the proximal GIT, mainly in the duodenum. The regular extended release tablets are discharged to the bottom GIT after 2 h, thereby hampering its absorption. In the opposite manner, the gastroretentive tablets that may not be transferred to the inferior GIT endlessly releasing the active in the actual absorption window (duodenum and jejunum), increasing the absorption that shown a higher plasma concentration after 2h of administration [30,31].

In case of marketed tablets there exists a faster absorption and an intense elimination phase, as 30% of drug gets absorbed in stomach as revealed by the predicted absorption data. In case of developed MH GRDS pills, the
absorption pattern was gradual and extended since only 10% drug is absorbed in stomach in earlier absorption phase of 2h. The Tmax for the drug was 9.88h, the predicted peak concentration of the active (Cmax) was 2091.69 ng/mL, and the AUC was 23547.63ng·h/mL which indicates superior bioavailability. Thus, the altogether absorption of MH from the developed slow release tablet was 1.4 fold higher than its marketed tablet which depicts improvement of bioavailability of test product compared to marketed pill with similar dose in pharmacokinetic prediction. The mean value of biological half-life (t½) of MH from marketed tablet and test formulation was 3 and 6h, respectively, which is about two times more. The predicted variation seen here is assigned to extended absorption of the controlled release composition (F-10); there is controlled non stop input of MH into the blood circulation which is due to mean residence time of 15hr for test formulation as compared to 8h for marketed tablets. Mean residence time has shown significant difference for test and marketed product. Test product has shown higher MRT, showing that the drug is maintained longer in the body in comparison to marketed product. Hence, the Slow release test formulation indicates to possess longer plasma half-life, i.e., the active resides in the plasma for a higher time compared to the marketed tablet of MH. The rate of elimination (Kel) of formulated GRDS slow release tablet (0.117 h⁻¹) was smaller than that of marketed tablet of MH (0.298 h⁻¹), which denotes that the active was released in slow fashion and absorbed slowly from the slow release tablets compared to the marketed tablets. In discrete, the GRDS of the swelling and expanding system aims swelling up the tablet volume to facilitate it to bigger than the dimension of the pylorus in the stomach. Thereby, the movement of the active to the small gut is avoided though the sphincter muscle is relaxed. With due consideration, the systemic concentration of MH in the floating pills within the 2–24 h period was greater than regular extended release marketed tablets. This stressfully endorses that the floating pills stayed within stomach for a extended time by floating on the gastric fluid In vivo [31,32].

5. CONCLUSION

The defined objective of this study was to present an in vitro–in vivo simulation approach that allows predictions of the probability of success of a pharmacokinetic study. This IVP tool can assist pharmaceutical development by providing guidance to the scientists on the possibility of BE acceptance of a developed formulation. Based on software assisted predicted outcomes, it is inferred that the enhanced bioavailability obtained from the GRDS is assigned to its prolonged gastric stay time. The orally administered test formulation was resided in the proximal region of small gut for a extended period than Marketed product, because of the unique composition for GRDS. Thus, Tmax was extended to 10 h, Nevertheless, by increasing the retention time of the active in the stomach by the outline of the GRDS. The GRDS will have the capacity to deliver the active to the small gut where the drug gets rightly assimilated. Therefore, the studied formulation not only prolonged MH release In vivo but also got improved absorption. The sustained release of MH from the GRDS would be anticipated to slowly release all of the MH content into the intestines, thus leading to enhancement of its oral bioavailability. So, the worthier plasma concentration of MH GRDS could extend the anti-diabetic action of MH in comparison to Carbophage® XR, due to the superior relative bioavailability. This is differing from the other conditions, where major oral compositions including the marketed product utilized in the study stays only ~ 5 h in the stomach. In addition to the extended gastric residence time (GRT), the sustained release of the MH is also vital element to explain the improved bioavailability. GRDS could reside in the stomach and facilitate the drug release in the prolonged fashion and hence it depicted that the aim of this investigations are achieved in successful manner.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable
ETHICAL APPROVAL

It is not applicable

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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