Physicochemical and Pharmacokinetic Studies of Metformin for Development of Controlled Release Matrix Tablet: Formulation Optimization Using *in silico* Tools

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ABSTRACT: Metformin, taken by nearly 120 million people across the world as a treatment for type 2 diabetes, has a relatively short plasma half-life and low absolute bioavailability. In this study, physicochemical and pharmacokinetics properties of metformin have been thoroughly assayed using ADMETLab, SwissADME, SmartCYP, LigandScout web-servers and software to evaluate the effectiveness of its formulation as controlled-release matrix tablets. The objective of the present work was to develop a formulation of an oral controlled-release (CR) metformin tablet, using hydrophilic hydroxylpropylmethylcellulose (HPMC) grades K4M and K100M polymers at different concentrations utilizing computational simulatory tools. Intestinal membrane permeability of the drug has been assayed using 2 hours simulation run with MembranePlus Software. Simulated environment generated for *in silico* dissolution study, using DDDPlus software, of the prepared formulations used USP Apparatus Type 2 rotating at 100 rpm. The simulation run was for 2 hours using 0.1N HCl phase followed by 8 hours with 6.8 USP Phosphate buffer phase. The results showed that drug release from the higher viscosity grade, K100M was slower as compared to the lower viscosity grade K4M at a fixed polymer concentration level. Furthermore, plasma concentration-time curves for the formulations have been generated using GastroPlus software.

Key words: Metformin, physicochemical properties, pharmacokinetics, bioavailability, computational simulation, formulation, HPMC.

INTRODUCTION

About 7.5 million people suffer from diabetes in Bangladesh. The diabetic centres extend a lot of services including some regulations and lifestyle to be followed as a diabetic person. However, the doctors also suggest antidiabetic drugs as a therapy. Metformin is one of the most popular medication for type II diabetes mellitus (DM) patients. It is used as an orally administered biguanide that is commonly used to treat type 2 diabetes, a prevalent illness characterized by both insulin secretion and insulin action defects.[1] Its primary mode of action is decreasing hepatic glucose output and increasing insulin mediated glucose usage in peripheral tissues such as muscle and liver. It also decreases glucose absorption in small intestine and decrease free fatty acid levels in the plasma, ultimately reducing substrate availability for gluconeogenesis. Because metformin HCl, unlike other antidiabetic medicines, does not cause hypoglycemia at any tolerable dose, it is referred to as an anti-hyperglycaemic rather than a hypoglycemic drug.[2] It is a hydrophilic drug that is absorbed slowly and incompletely from the gastrointestinal tract, with a bioavailability of 50-

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60%.[3,4] The high occurrence of accompanying gastrointestinal symptoms, such as nausea, stomach discomfort and diarrhoea, which occur primarily during the early term of medication, is a barrier to more successful therapy.

The extensive use of metformin HCl tablets apparently keeps the patients well. But in reality, they are exposed to threats of severe side effects on different organs due to excessive dosage and limited bioavailability. The chemical has a short plasma half-life of 1.5-4.5 hours and a low absolute bioavailability of 50-60%.[5] According to this information, to reach steady-state, dosing 2–3 times per day is recommended.[4] At usual clinical doses and schedules, metformin steady-state plasma concentrations are generally < 1.5 μg/ml, and the maximum drug plasma levels during controlled clinical trials do not generally exceed 5 μg/ml.[5]

Patient compliance can be hampered by short half-lives, limited bioavailability, side effects, and the requirement to administer greater dosages two to three times a day. Metformin requires sustained release medications to extend its duration of action and increase patient compliance. Controlled release drug delivery improves patient compliance by reducing drug administration frequency and lowering steady-state drug levels. It also increases the utility of a drug by optimizing its biopharmaceutical, pharmacokinetic, and pharmacodynamic properties in order to maximize efficiency, reduce adverse effects, and lowering healthcare costs through improved therapy. Matrix tablets are a useful tool for administering oral extended-release medication. By dispersing solid particles within a porous matrix made of hydrophilic and hydrophobic polymers, matrix tablets can be made using wet granulation or direct compression processes. The availability of various kinds of polymers for managing drug release has become the most essential aspect of matrix tablet composition.

Due to their cost effectiveness, low influence of physiological factors on release behaviour, flexibility, and broad regulatory approval, matrix systems are widely utilized in oral controlled drug delivery.[6,7] Several natural, semi-synthetic and synthetic polymeric materials were examined by a number of researchers. Hydroxypropylmethylcellulose, sodium carboxymethylcellulose, eudragit (polymethacrylate) polymer[8,9] and ethyl cellulose[10,11] are examples of cellulose ethers that may be employed.

Computational modeling techniques are becoming increasingly popular in designing formulation development of a drug because they can decrease time and save investments before experimental studies are done. Formulation development of drug can be a labor and time-consuming task if varying ratio of polymer development needs to be employed in case of CR tablet formulation. Thus, by applying computational models, prediction and optimization of better formulation profiles can be made possible. This way, resource and time management efficiency can be improved markedly. With this aim, formulation optimization of metformin HCl controlled release tablets has been carried out in the present study after a detailed analysis on the drug's pharmacokinetic and physicochemical parameters.

MATERIALS AND METHODS

Web-servers and software. Computational software and web-servers were utilized to study the physicochemical and pharmacokinetic properties of metformin. SwissADME, ADMETLab, SMARTCyp are publicly accessible web servers that suggest various properties of the active chemical entity by using accurate algorithms. The academic versions of MembranePlus, DDDPlus and GastroPlus software are developed and provided by SimulationsPlus Company. LigandScout software has been used for pharmacophore generation.

The workflow for methodology adopted is represented in figure 1.

Assessment of physicochemical properties of metformin. The physicochemical properties of metformin, such as canonical SMILES, formula, molecular weight, number of heavy atoms, aromatic heavy atoms, rotatable bonds, H-bond acceptors, H-bond donors, etc. were collected from web-based

online servers such as SwissADME[12] and ADMETLab.[13] At first, the PubChem ID of metformin was retrieved from PubChem database. The structure data file (SDF) of PubChem ID 4091 was incorporated into the web-servers' designated search engines.

Analysis of oral bioavailability radar. The bioavailability radar gives graphical interpretation of properties such as lipophilicity, compound size, insolubility, polarity, insaturation and flexibility in its six hexagonal vertices which help to evaluate scopes of improvement of bioavailability score. The radar images for metformin were collected from SwissADME and ADMETLab web-servers. At first, the SDF files of metformin was collected from PubChem by searching the molecule in the search box. The collected file was uploaded in the designated section of SwissADME and ADMETLab to generate the radar images.

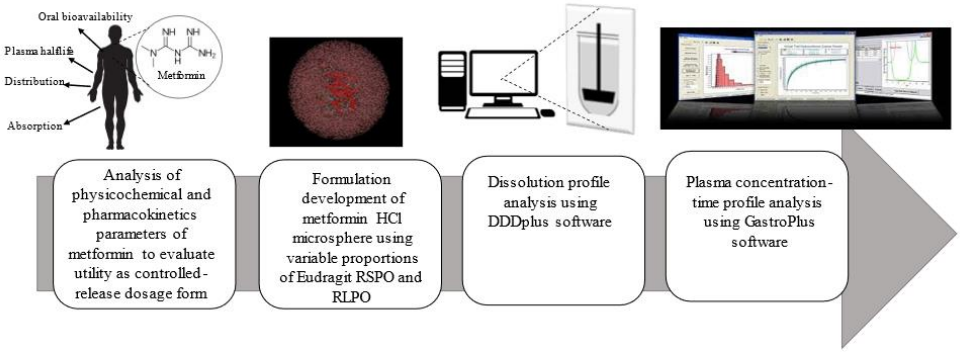


Figure 1. Workflow followed in the present study.

Pharmacophore generation of metformin molecule. A pharmacophore is the collection of steric and electronic properties required for the best supramolecular interactions with a certain biological target and for inducing (or inhibiting) the target's biological response. The pharmacophore of metformin molecule was generated using LigandScout software. The structure data file of metformin collected from PubChem was opened as a separate project in the software. The structure was then copied to ligand perspective. The pharmacophore was generated using default settings in the software.

Distribution study of metformin. Distribution profile analysis was carried out using data from ADMETLab. Initially, the SDF file for metformin was obtained by searching the chemical in PubChem's search box. To generate the distribution profile, the gathered file was uploaded to the designated sections of ADMETLab. The web-server suggested the properties relating to distribution of the drug inside human body. The information was collected and tabulated.

Analysis of metabolism profile of metformin. SMARTCyp predicts the sites in molecules that are most liable to Cytochrome P450 mediated metabolism. The analysis of metabolism profile was done using SMARTCyp web-server.[14] The structure data file of metformin, collected from PubChem was incorporated in the search engine. The data were generated under different sub-sections for different isoform of cytochrome P450 enzyme in liver.

Assessment of absorption profile of metformin. The SDF file format of metformin was uploaded in the designated section of GastroPlus software for generation of the absorption profile of the drug. The absorption profile of metformin HCl into the blood stream in human model was generated for 12 hours. The time window was set in the parameter selection area of the search dialogue.

Intestinal permeability of metformin using MembranePlus software. MembranePlus software

version 3.0 can be used to predict *in vitro* permeability & hepatocyte modelling of active moiety.[17] The mdb file format of the drug was entered into the database. Permeability across intestinal membrane of metformin HCl was predicted via simulation run conducted for 2 hours. For the simulation, the following parameters were set: shaking rate of 100 rpm, cell culture time of 21 days, filter area of 1.2 cm^2, filter pore size of 0.4 micron, filter pore density of 1.0E+8, filter membrane depth of 10 microns and diffusion layer thickness of 638.74 microns.

***In silico* dissolution profile of metformin with polymer blend using DDDPlus.** *In silico* dissolution profile of metformin with polymer blend using DDDPlus was carried out. The following parameters were incorporated in the software: USP dissolving apparatus-2, paddle type, rotational speed of 100 rpm and temperature 37.5°. For the first two hours, 900 ml of 0.1 mol/l HCL was employed, followed by 8 hours of pH 6.8 phosphate buffer solution. Throughout the experiment, the sink condition was maintained. At regular intervals, samples (10 ml) were extracted and replaced with the same volume of pre-warmed (37.5°) fresh dissolving media to keep the volume constant. All these parameters were set into the software before simulation run.

Plasma-concentration curve retrieval for the proposed drug-polymer combination using GastroPlus software. The dissolution profiles (percent dissolved vs. dissolution time data) for the prepared formulations were retrieved from DDDPlus software as the file format of file.dsd. The dsd. files of the required dissolution data were incorporated into the GastroPlus software. Then *in vivo* absorption behavior of the entered dissolution profiles for the prepared formulations were found out after running simulation in the gastro-intestinal tract of human model under fasted condition.

RESULTS AND DISCUSSION

Assessment of physicochemical properties of metformin. The physicochemical qualities of an active pharmaceutical ingredient (API) as well as an excipient can influence the creation and performance of a dosage form. The physicochemical factors such as solubility, partition coefficient, crystalline and amorphous molecular solid properties, dissolution diffusion rates and release mechanisms all play major roles in determining the characteristics of the solid dosage form. Poor solubility and low dissolution rates frequently result in poor bioavailability in solid oral dosage forms.

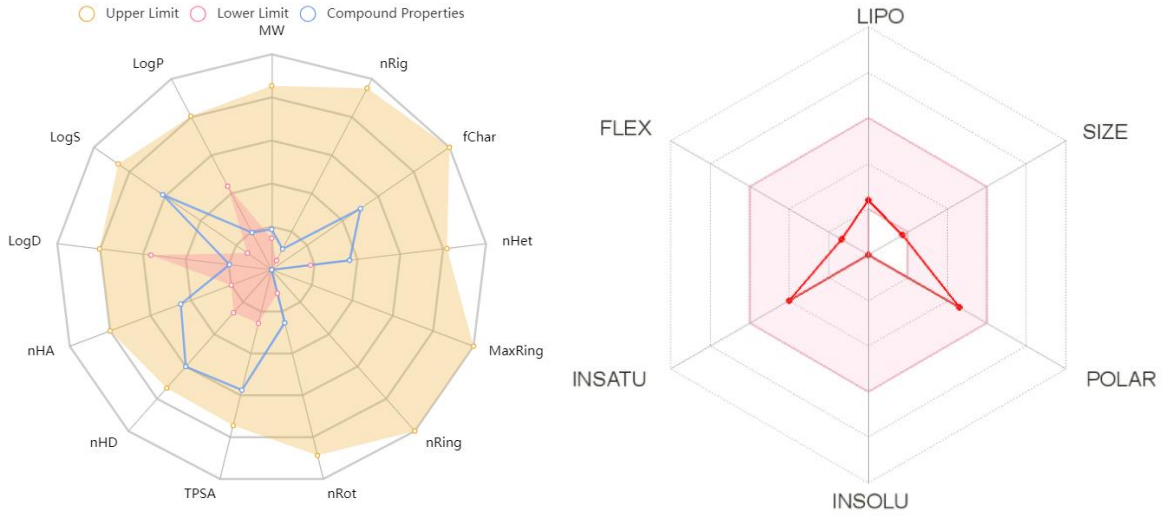
Physicochemical properties obtained from SwissADME revealed that metformin is highly soluble in aqueous media according to total polar surface area (TPSA), ESOL (estimated solubility) class, Ali Class, Silicos-IT class GI absorption, Lipinski violations and bioavailability score (Table 2). Thus, it can be said that metformin is a hydrophilic drug. Metformin follows Lipinski's rule of five as the number of hydrogen bond donor is not greater than 5, number of hydrogen bond acceptor is less than 10. It has a molecular weight of 129.16 Daltons which is less than 500 Daltons. It also has an octanol-water partition coefficient (log P) that does not exceed 5. Thus, it can be assumed that metformin has proper drug likeness characteristics.

Table 2. Physicochemical properties of metformin from SwissADME.

Physicochemical parameter	Metformin
Formula	C4H11N5
MW	129.16
TPSA	91.49
#H-bond acceptors	2
#H-bond donors	3
LogP	0.34
Ali class	Very soluble
ESOL class	Highly soluble
Silicos-IT class	Soluble
GI absorption	High
Lipinski violations	0
Bioavailability score	0.55

*MW = Molecular weight, TPSA = Total polar surface area, ESOL = Estimated solubility

Bioavailability score and oral radar interpretation. Bioavailability, manufacturability and stability are critical characteristics for achieving an effective solid dosage form in terms of pharmacokinetics and pharmaceutics. These parameters are impacted by and/or reliant on a variety of essential solid-state features. An effective drug molecule must reach its target site inside the body in appropriate concentration and remain there in a bioactive form long enough for the anticipated biologic activities to occur for it to be successful as a medication. Metformin is only partially absorbed from the gastrointestinal system after oral administration to humans, with a 40–60 % absolute bioavailability and a short elimination half-life (1.5–1.6 h).[7] Some animal species, such as cats, horses and dogs have incomplete absorption and limited bioavailability.[4,5,8] Metformin must be taken at large doses (2.5 g/day) frequently to maintain an effective plasma concentration, which causes substantial gastrointestinal adverse effects.[9]



A B

Figure 2. Bioavailability radar images of metformin as retrieved from (A) ADMETLab and (B) SwissADME.

The bioavailability score as indicated by SwissADME is 0.55. The absorption profile retrieved from GastroPlus software shows that metformin HCl is 35% absorbed into the blood stream in human model. The bioavailability radar images as shown in figure 2 indicates that the compound properties are within the upper limit range of physicochemical properties that govern bioavailability of a drug. In figure 2, the pink area in the radar collected from SwissADME represents the optimal range for each property. For optimal size, the molecular weight of the drug candidate should be between 150 and 500 g/mol; for optimal lipophilicity, XLOGP3 value should be between −0.7 and +5.0; for optimal saturation, fraction of carbons in the sp^3 hybridization should be not less than 0.25; for optimal solubility, log S should not be higher than 6; for optimal polarity, TPSA should be between 20 and 130 $Å^2$; and for optimal flexibility, there should be no more than 9 rotatable bonds. From figure 2, we can see that the value for metformin falls within the optimal range of each property.

Pharmacophore generation of metformin molecule. Understanding the interaction between the receptor and ligand depends on the pharmacophore of a molecule. The few features that make up a pharmacophore model are arranged in a particular 3D manner in LigandScout software. Although there are variations, each feature is normally depicted as a sphere, with the tolerance for deviation from the

exact position being determined by the radius. To aggregate many interaction patterns under a single label, the features can be labeled as a single feature or any logic combination made up of "AND," "OR," and "NOT." Interactions between restricted volumes can have additional properties (typically to represent the receptor boundary).

The pharmacophore of metformin consists of three hydrogen bond donor areas, two hydrogen bond acceptor areas, two positive ionizable areas and a single hydrophobic area. One of the positive ionizable area is positioned in the coordinates -0.05, 0.58 and -0.35. The other positive ionizable area is positioned in the coordinates 1,68, -0.08 and -0.09. The hydrophobic area is situated at coordinates -1.91, -0.76 and 0.07.

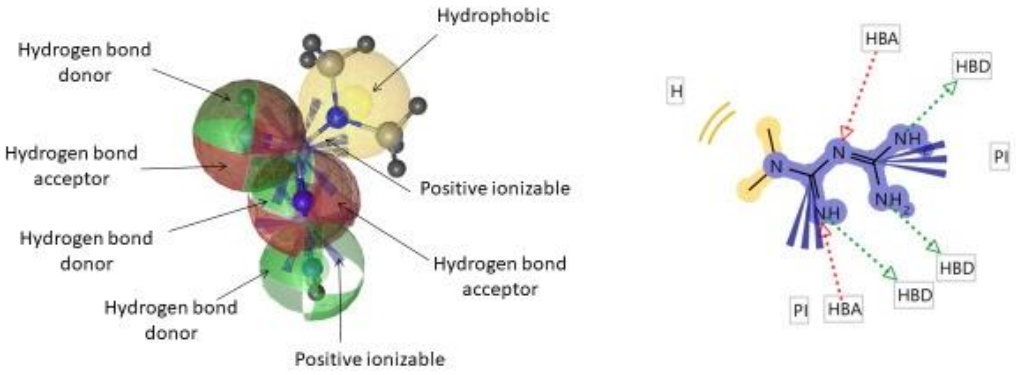


Figure 3. Generated pharmacophore of metformin molecule.

Pharmacokinetics profile analysis of metformin using ADMETLab and GastroPlus. Controlled-release drug product should showcase a pharmacokinetic profile that provides the desired therapeutic efficacy and minimizes undesired adverse events. The maintenance dose is released at a rate that ensures that the amount of medicine lost through elimination is replenished on a regular basis. A consistent plasma drug concentration is maintained with minimal changes using the sustained-release product. Pharmacokinetic properties of metformin indicate successful portfolio for controlled-release tablet formulation. Table 3 reveals that the plasma half-life of metformin is in the category score of 0.47 as indicated by ADMETLab. The range of score for plasma half-life is between 0-1 and lower the score, shorter is the half-life. Metformin has a relatively short plasma half-life score indicating that it can be formulated as controlled-release tablet. Long half-life is not desirable for formulating controlled-release tablet. The drug has a plasma-protein binding of 5.83%. The clearance rate can be said to be low as it has a predictive value of 3.504 ml/min/kg. The percentage amount of metformin HCl absorbed from gastro-intestinal tract into the bloodstream after a 12-hour simulation run in GastroPlus software is shown to be 38% (Figure 4). This percentage can be considered as low bioavailability.[18]

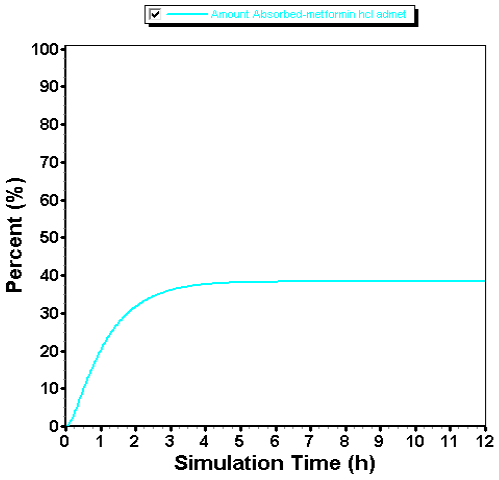


Figure 4. Absorption profile of metformin HCl (API) into blood plasma in human models simulated by GastroPlus software.

Table 3. Distribution and excretion profile analysis using data from ADMETLab.

Property	Value	Comment
Blood brain permeant	0.175	*Category 1*: BBB+; *Category 0*: BBB-; The output value is the probability of being BBB+
Plasma protein binding	5.83%	*Optimal*: < 90%. Drugs with high protein-bound may have a low therapeutic index
Volume of distribution	1.16	*Optimal*: 0.04-20L/kg
Fu	74.15%	*Low*: <5%; *Middle*: 5~20%; *High*: > 20%
Clearance	3.504	*High*: >15ml/min/kg; *Moderate*: 5-15 ml/min/kg; *Low*: <5ml/min/kg
$T_{1/2}$	0.47	*Category 1*: long half-life; *Category 0*: short half-life; *Long half-life*: >3h; *Short half-life:* <3h; The output value is the probability of having long half-life.

Intestinal permeability studies of metformin using MembranePlus software. Figure 4 represents the regional concentration of the metformin API in the form of a bar chart. According to the 2-hour simulation run in MembranePlus software, 60.2% of the drug reaches basolateral region of the intestinal membrane and about 39.7% remains in the apical region. The red curve in figure 5 is indicating that metformin concentration in apical side of intestinal membrane was initially at 1 micromole. As time passed, the concentration gradually decreased as the drug transited from apical side to basolateral side as indicated by a rise in the blue curve in figure 6. At the end of 2 hours, the concentration of metformin remaining in apical side is about 0.5 micromole. This indicates that at the end of the 2-hour simulation, the transit of metformin from apical side to basolateral side was still incomplete. This can be explained by the low intestinal permeability of metformin.

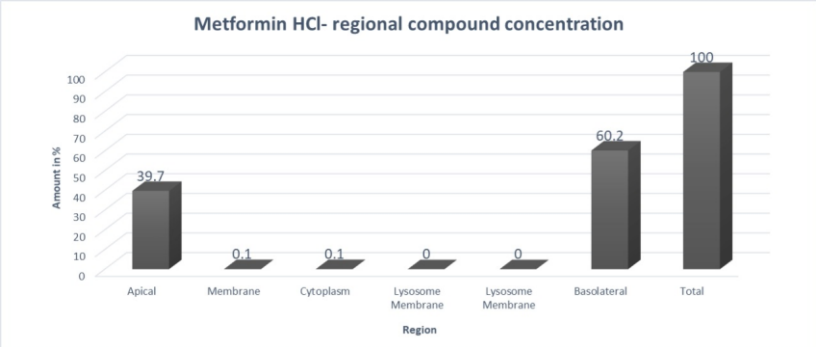


Figure 5. The percentage end amounts (regional compound concentrations) of metformin HCl in various regions of intestinal membrane as generated by MembranePlus software

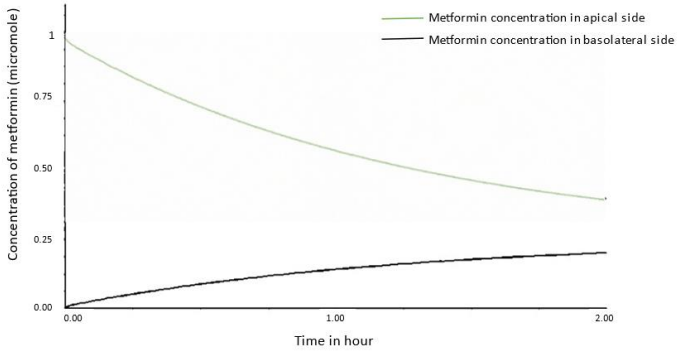
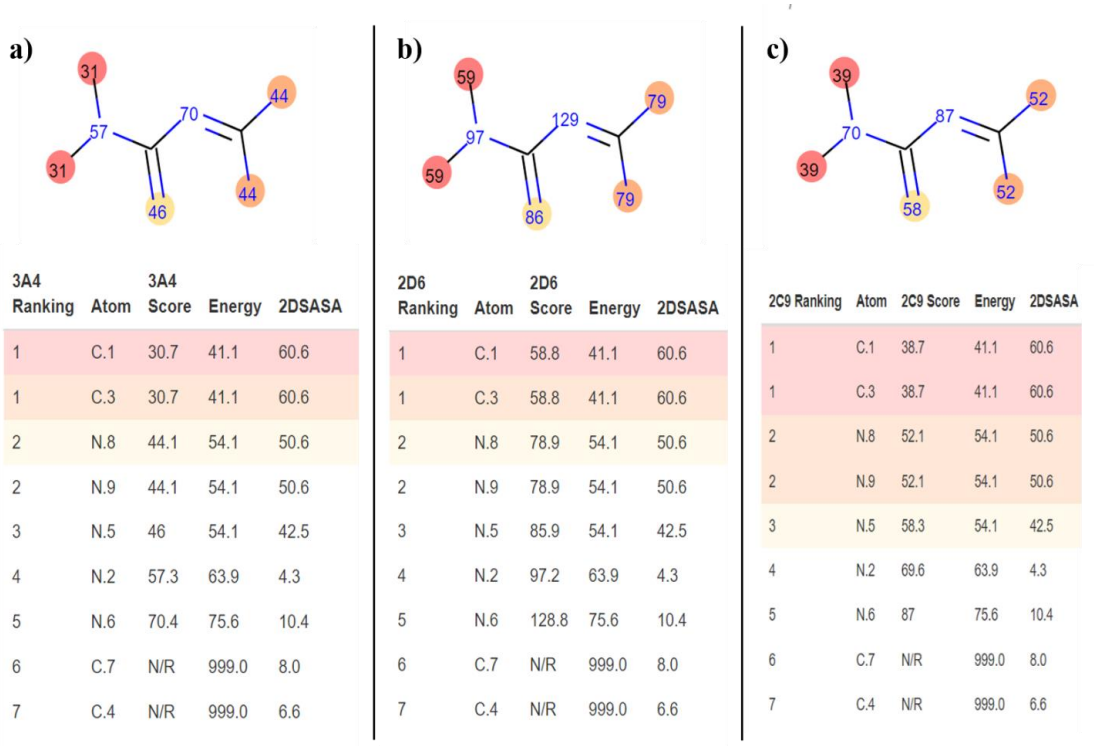


Figure 6. Concentration of metformin HCl versus simulation time graph for the analysis of change in concentration of the drug from apical side to the basolateral side of intestinal membrane as generated by MembranePlus software.

Evaluation of metabolism pattern of metformin. Metabolism pattern of metformin was analysed to get insight into its pharmacokinetic behaviour using SMARTCyp, which gives prediction on the sites in chemical entities that are most liable to cytochrome P450 mediated metabolism. It gives insights on sites that are metabolized by the cytochrome P450 3A4, 2D6 and 2C9 isoforms. The web-server shows probability score of the atoms within query molecule that interacts with the particular isoform of cytochrome P450. The metabolism profile of metformin by the various isoforms (3A4, 2D6 and 2C9) of cytochrome P450 are summarized in figure 6. In figure 7, the structure of metformin is shown whereby the probability score of interaction of each atom with liver cytochrome P450 isoforms are indicated in place of the atoms. The energy of each interaction, isoform score and 2DSASA are summarized beside each structure. From the table, it can be inferred that 2D6 isoform is more prone to metabolize metformin.



3A4 Ranking	Atom	3A4 Score	Energy	2DSASA
1	C.1	30.7	41.1	60.6
1	C.3	30.7	41.1	60.6
2	N.8	44.1	54.1	50.6
2	N.9	44.1	54.1	50.6
3	N.5	46	54.1	42.5
4	N.2	57.3	63.9	4.3
5	N.6	70.4	75.6	10.4
6	C.7	N/R	999.0	8.0
7	C.4	N/R	999.0	6.6

2D6 Ranking	Atom	2D6 Score	Energy	2DSASA
1	C.1	58.8	41.1	60.6
1	C.3	58.8	41.1	60.6
2	N.8	78.9	54.1	50.6
2	N.9	78.9	54.1	50.6
3	N.5	85.9	54.1	42.5
4	N.2	97.2	63.9	4.3
5	N.6	128.8	75.6	10.4
6	C.7	N/R	999.0	8.0
7	C.4	N/R	999.0	6.6

2C9 Ranking	Atom	2C9 Score	Energy	2DSASA
1	C.1	38.7	41.1	60.6
1	C.3	38.7	41.1	60.6
2	N.8	52.1	54.1	50.6
2	N.9	52.1	54.1	50.6
3	N.5	58.3	54.1	42.5
4	N.2	69.6	63.9	4.3
5	N.6	87	75.6	10.4
6	C.7	N/R	999.0	8.0
7	C.4	N/R	999.0	6.6

Figure 7. Metabolism profile of metformin analyzed using SmartCYP. Probability score of interaction of each atom of metformin with liver cytochrome P450 isoforms **a)** 3A4, **b)** 2D6 and **c)** 2C9.

Formulation of metformin hydrochloride matrix tablet. Swellable hydrophilic or non-swellable hydrophobic polymers are frequently used as matrix materials. The drug entity must be dissolved at first before it can be released. Thus, the ability of the API to dissolve and diffuse out of the matrix and come in contact with the bulk solution is directly related to the speed at which water penetrates the tablet matrix. As a result, the length of the diffusional path out of the tablet will affect the rate of drug release and absorption.[15,16] Polymers are good matrix materials for controlling diffusion rates. Hydrophilic and hydrophobic polymers are two types of matrix tablet polymers.

Dissolution of the polymer matrix and diffusion of the drug molecules are both engaged in dissolution and diffusion-controlled release kinds of drug delivery systems. The polymeric membrane around

drug particles is partially dissolved when introduced in biological fluids (dissolution media). As a result, pores form, allowing the dissolving media to have access to the core, which contains the medication molecules. The dissolution media subsequently dissolves the drug particles, allowing diffusion to begin the release process. Polymer swelling takes place due to the osmotic stress exerted at the slowly increasing glassy core and rubbery gel. As the solubility of drug or excipient increases, the increasing osmotic stress causes more water penetration into the matrix resulting in a greater degree of polymer swelling. Thus, matrices that show higher swelling for an increased period of time followed by erosion, are better choices for preparation of controlled-release formulations in case of highly soluble drugs.[17]

HPMC is one of the most widely used hydrophilic matrix polymers in modified-release delivery systems. The molecular weight of the HPMC used can affect the growth and thickness of the advancing gel layer.[18] The HPMC employed must quickly hydrate to generate a gelatinous coating that surrounds the tablet for proper medication release. If the polymer hydrates too slowly, moisture can seep into the tablet core, causing disintegration and unintended fast medication release. The percentage of hydroxypropyl and methoxyl substitution on the polymer chains affects hydration rates in HPMC.[16] HPMC grades with higher hydroxypropyl replacements and lower methoxyl substitutions hydrate faster and release drugs more slowly than those with lower hydroxypropyl substitutions.[17]

Microcrystalline cellulose is a water-swellable polymer that swells with hydroxy propyl methyl cellulose, as a result increasing the diffusion path length and reducing the drug release rate. Researchers conducted an experiment on the effects of microcrystalline cellulose, dicalcium phosphate and lactose on swelling and erosion of compressed HPMC matrix tablets.[19] The study found that lactose, microcrystalline cellulose, and dicalcium phosphate were all able to absorb water in contact with the dissolving media, according to gravimetric experiments (dynamic technique), with percent weight growth in the sequence lactose > MCC > DCP. Because of the more elastic and swellable character of MCC, which encouraged better water absorption over a longer length of time compared to lactose and DCP, the order of percent remaining weights changed to MCC > DCP > lactose, resulting in a slower erosion rate within the same amount of time. Due to the reported rate retardant effects of MCC, the excipient was included in the formulations of the present study in order to evaluate its effectiveness and increase the success rate of controlled-release drug profile of the proposed formulations. Lactose has been incorporated as a tablet filler and the varying proportions are used to keep the tablet mass constant at 800 mg (Table 4).

Table 4. Formulation of controlled-release tablets of metformin HCl.

Formulation	Ingredients(mg)						
Code	Metformin (HCl)	HPMC K100M	HPMC K4M	MCC	Lactose	Magnesium stearate	Total
F1a	500	100	--	40	150	10	800
F1b	500	150	--	40	100	10	800
F1c	500	200	--	40	50	10	800
F1d	500	250	--	40	--	10	800
F2a	500	--	100	40	150	10	800
F2b	500	--	150	40	100	10	800
F2c	500	--	200	40	50	10	800
F2d	500	--	250	40	--	10	800

***In silico* dissolution profile of metformin with polymer blend using DDDPlus.** Dissolution studies are the most widely used tools in the development, characterization, and utilization process of pharmaceutical dosage forms.[20] With DDDPlus, the dissolution of drug component and excipients in dosage unit under various experimental conditions can be modelled and simulated computationally to help improve chances for success.[21]

Drug release from formulation 1d was shown to be the slowest among other formulations. The total percentage of drug dissolved in formulations 1a, 1b, 1c and 1d are found to be 99.91%, 99.78%, 98.31% and 98.30% respectively (Figure 8). The total percentage of drug dissolved in formulations 2a, 2b, 2c and 2d are found to be 99.78%, 99.58%, 98.91% and 98.43% respectively (Figure 9). The individual dissolution curves have also been generated using DDDPlus as indicated in figure 10.

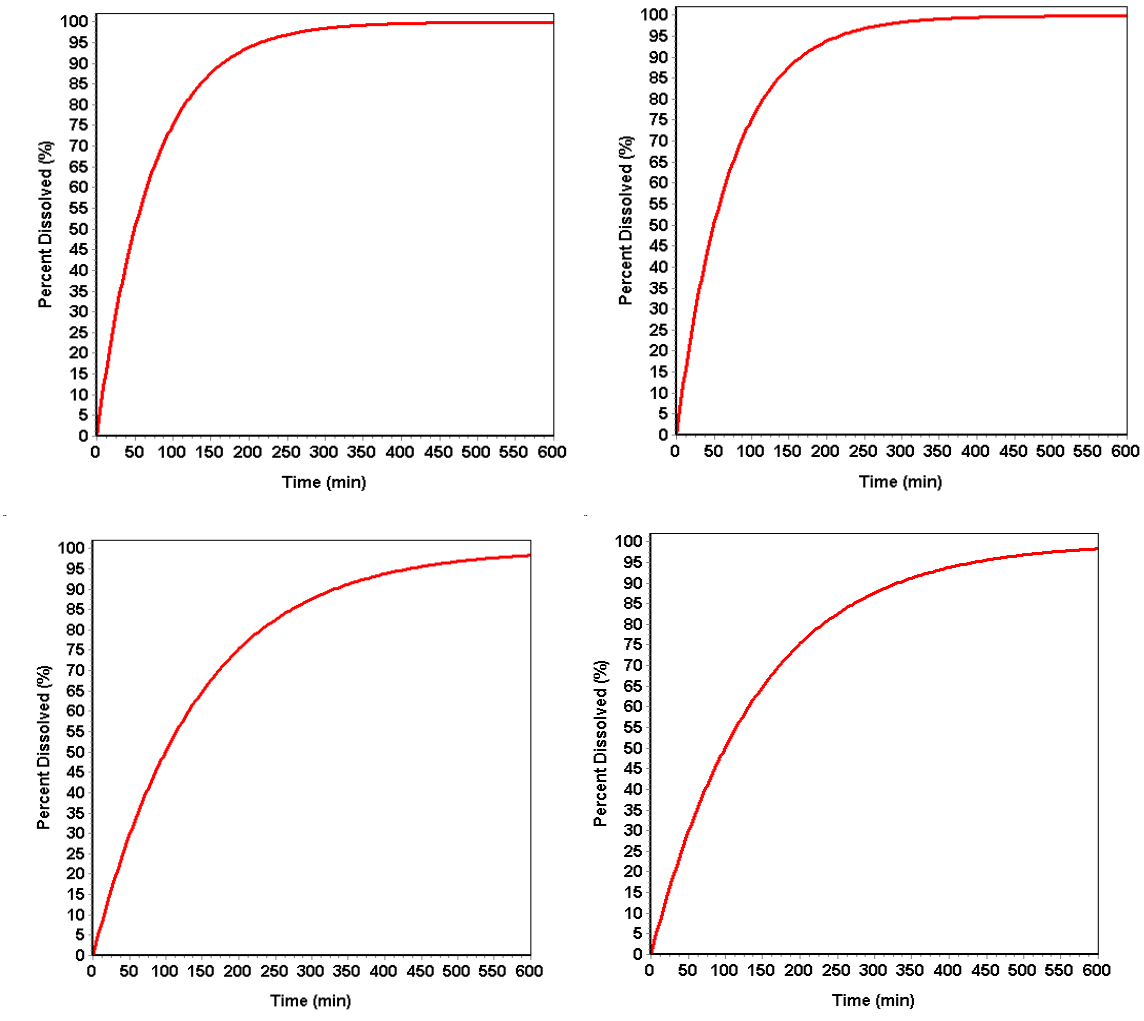


Figure 8. Percent dissolved of metformin HCl versus simulation time curves for formulation F1a (top left corner), F1b (top right corner), F1c (bottom left corner) and F1d (bottom right corner) as retrieved from DDDPlus software. Conditions incorporated into the software for *in silico* dissolution simulation- USP apparatus Type 2, Rotation speed-100 rpm, 2 hours 0.1N HCL phase followed by 8 hours 6.8 USP phosphate buffer phase.

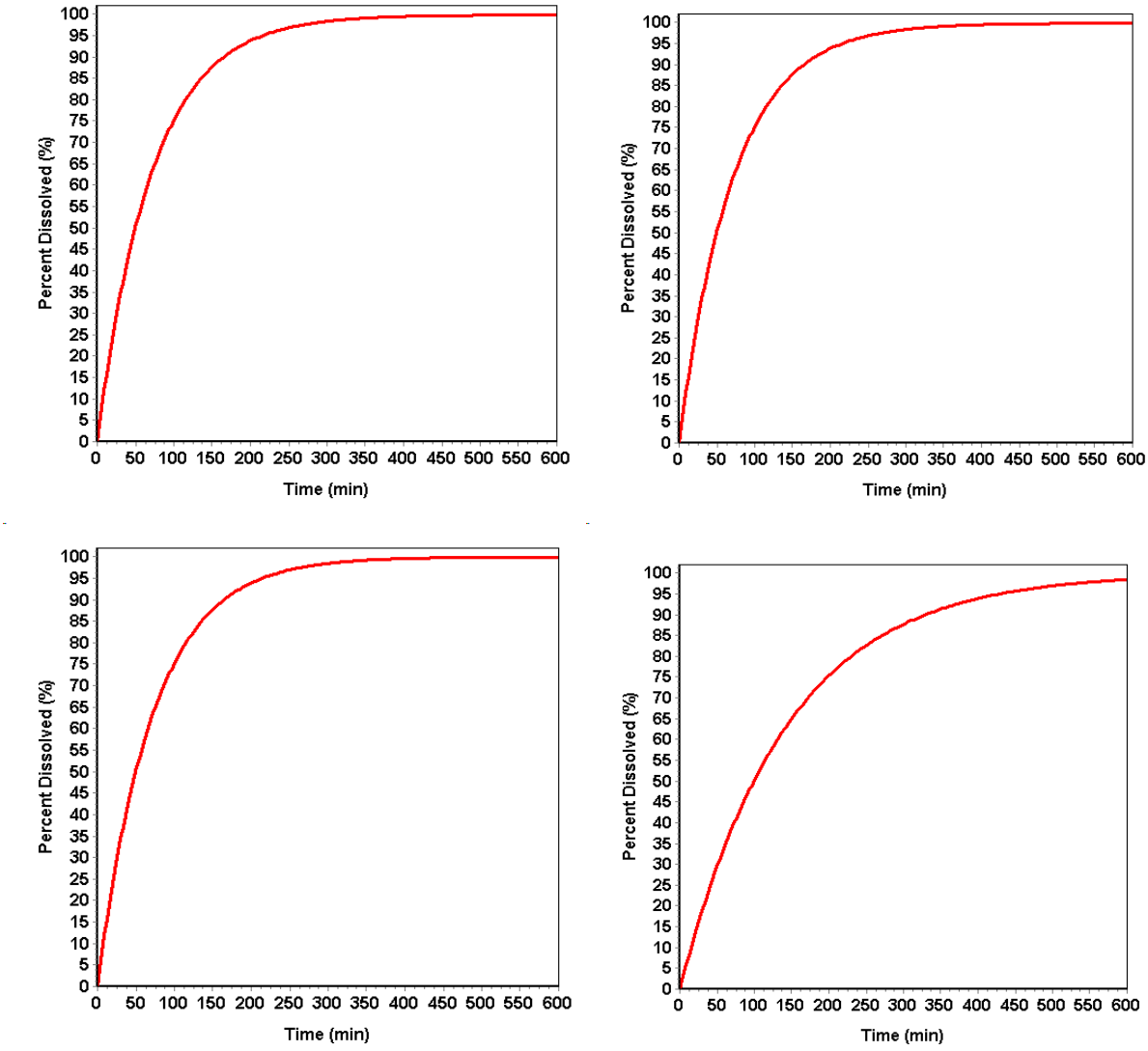


Figure 9. Percent dissolved of metformin HCl versus simulation time curves for formulation F2a (top left corner), F2b (top right corner), F2c (bottom left corner) and F2d (bottom right corner) as retrieved from DDDPlus software. Conditions incorporated into the software for *in silico* dissolution simulation- USP apparatus Type 2, Rotation speed-100 rpm, 2 hours 0.1N HCl phase followed by 8 hours 6.8 USP phosphate buffer phase.

Plasma-concentration curve retrieval for the proposed drug-polymer combination using GastroPlus. A crucial step in the drug development process is the generation of a pharmacokinetic curve, which depicts the plasma concentration of an administered medication as a function of time and contains data on the drug's bioavailability, elimination half-life and clearance. Preclinical research is carried out to establish medication safety and dose metrics from data gathered from the pharmacokinetic investigations prior to a drug of interest receiving clearance for usage in human clinical trials. Due to species differences and related simplifications, both *in vitro* platforms and *in vivo* animal models have constraints in predicting the human response to a medicine. In order to precisely anticipate pharmacokinetic parameters in human investigations, *in silico* experiments employing computer simulation have been put into practice.[20] The plasma-time concentration curves for the proposed formulations were retrieved and analysed using GastroPlus software. Under normal clinical

doses, metformin steady-state plasma concentrations are generally less than 1.5 µg/ml. Plasma-time concentration curve for controlled-release tablet (F1d) of metformin HCl as simulated in GastroPlus software is represented in figure 10. The plasma concentrations were maintained over 0.8 microgram/ml for 4.42 hours (Figure 11).

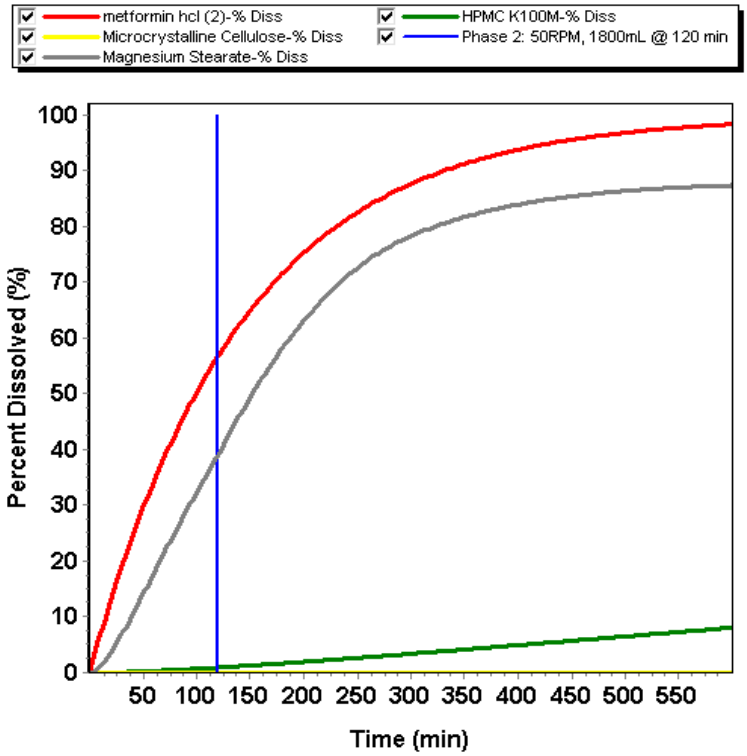


Figure 10. Percent dissolved of metformin HCl and other ingredients versus simulation time curves for formulation F1d as retrieved from DDDPlus software. Conditions incorporated into the software for *in silico* dissolution simulation- USP apparatus Type 2, Rotation speed-100 rpm, 2 hours 0.1N HCl phase followed by 8 hours 6.8 USP phosphate buffer phase.

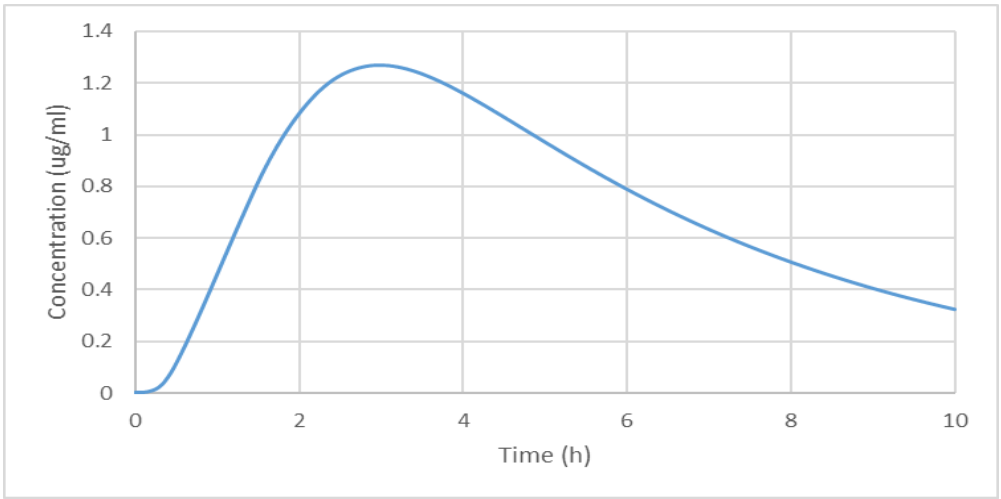


Figure 11. Plasma-time concentration curve for controlled-release tablet (F1d) of metformin HCl.

CONCLUSION

The main goals of a controlled-release drug delivery system are to increase the utility of a drug by optimizing its biopharmaceutical, pharmacokinetic and pharmacodynamic properties in order to maximize efficiency, reduce adverse effects and cure the condition. The uniform medication plasma concentration and hence uniform therapeutic impact are the key advantages of a controlled release dosage form over a traditional dosage form. Matrix devices have gained continuous appeal for controlling drug release due to their chemical inertness, drug embedding ability, and drug release character. Metformin has pharmacokinetic and physicochemical properties that supports the formulation of the drug as controlled-release matrix tablets. *In silico* dissolution profiles indicate a slower drug release from HPMC K100M compared to HPMC K4M polymer matrix in presence of water-insoluble excipient microcrystalline cellulose and hydrophilic filler lactose. The *in silico* plasma concentration time graph of optimized formulation indicate a controlled release of drug into bloodstream in human models. Thus, the results of this study can be used to formulate controlled release matrix tablets of Metformin for anti-diabetic treatment.

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