PREPARATION AND EVALUATION OF ACTIVE FILM COATING TABLET OF TENELIGLIPTIN HYDROBROMIDE HYDRATE WITH METFORMIN HYDROCHLORIDE FIXED DOSE COMBINATION

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ABSTRACT

The aim of the present study was to formulate fixed-dose combination tablets of metformin hydrochloride and teneligliptin hydrobromide hydrate. The extended-release core tablet consisted of a seal coating over metformin and outer layer coated by teneligliptin for immediate release using perforated film coating equipment. The seal coating is necessary to prevent the contact between metformin and teneligliptin. 2^3 Full factorial design was planned to determine critical processing parameters like the effect of hydroxypropyl methyl cellulose and ethyl cellulose in seal coating, ratio of drug and polymer in the coating solution, and spray rate as variables with lower and higher level. Optimized (F9) batch prepared from the design space from experimental variable as seal coat ratio of 0.33, drug coat ratio of 2 with rate of spray 3 g mL^{-1}, gave desired release pattern. The optimized formulation was subjected to *in vivo* kinetic studies using Wistar rats. Metformin 100 mg kg^{-1} was administered orally and blood was withdrawn at various time intervals to assess the kinetic parameters. The observed AUC and C_{max} were found to be 260 ng*h mL^{-1}, and 58.0 ng mL^{-1}, respectively, and the time needed to reach T_{max} was 6 h for metformin tablets.

Keywords: Teneligliptin, metformin, fixed dose combination, design space. QbD, factorial design

INTRODUCTION

Type 2 diabetes mellitus (T2DM), which is more common in the elderly age group is caused by insulin resistance because of failure of the pancreatic beta cells[1]. The prevalence of diabetes has been increasing exponentially over the last few years. In 2015, 415 million people had diabetes all over the world and three quarters (75 %) of these patients were living in low- and middle-income countries[2,3]. India is poised to become the diabetic capital of the world, with a patient population of 69.2 million in 2015, which is projected to increase to 123.5 million in 2040[4,5]. Teneligliptin hydrobromide hydrate (teneligliptin) is a novel dipeptidyl peptidase-4(DPP-4) inhibitor for use in management of type 2 diabetes mellitus. In multiple dose studies, teneligliptin was rapidly absorbed in patients with type 2 diabetes mellitus, with peak concentrations being achieved 0.5 to 1.6 h after once a day dosing[6]. Metformin hydrochloride (metformin) has been used for the treatment of type 2 diabetes mellitus for more than 40 years and is recommended as first line treatment, particularly in overweight or obese patients. When used alone, metformin does not produce hypoglycaemia[7,8]. The fixed drug combination therapies (FCTs) carry the benefits of improved patient compliance, reduced pill burden, and thus increased potential of attaining glycaemic targets. Teneligliptin is currently registered in Japan, South Korea and India[9]. Teneligliptin phase II clinical trials are underway in several European countries and phase I trials are being conducted in the US[10]. Therefore, there have been medicinal needs of FCTs consisting of an immediate-release (IR) part of teneligliptin and an extended-release (ER) part of metformin for better clinical efficacy and patient compliance. A few pharmaceutical technologies could be employed to prepare combined oral dosage forms consisting of an immediate release part and an extended-release part[11]. For example, multi-layer tablets can be designed for such a purpose, but expensive and specialized tableting machine is necessary[12]. A few pharmaceutical technologies could be employed to prepare combined oral dosage forms consisting of an immediate release part and an extended-release part. For example, multi-layer tablets can be designed for such a purpose, but expensive and specialized tableting machine

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is necessary[13,14]. Multi-unit dosage forms which have different release rates (e.g., coated pellets or mini-tablets) are studied as well[15-17]. However, there have been some limitations such as a time-consuming process to prepare these pellets/mini-tablets. Furthermore, preparation of the pellets requires expensive and specialized equipment (e.g., a fluid bed processor). Active film coating method is a favoured oral dosage form and can be prepared with a smaller tablet diameter than multi-layer coated tablets. Further, a film coating machine and tableting machine can simply be used without other specialized equipment, making this process more advantageous[11].

Quality-by-design(QbD) is a concept introduced by the International Conference on Harmonization (ICH) Q8 guideline, as a systematic approach to development, with the emphasis to shift pharmaceutical product development from the empirical, trial- and-error approach, to the scientifically based process of design space appointment[18]. Therefore, implementation of the QbD concept is important for all products, including generics and biotechnological products[19,20]. The aim of the present study was to formulate fixed-dose combination tablets (FCTs) by metformin extended-release (ER) core tablet, a seal coating over metformin and outer coated by teneligliptin- immediate release (IR) using perforated film coating equipment. The 2^3 full factorial design was planned to study the effect of HPMC, EC in seal coating, ratio of drug and polymer in the coating solution, and spray rate with lower and higher level. Optimized batch prepared from the design space and *in vitro* dissolution and other characterization were carried out. *In vivo* animal study was performed for optimized batch.

MATERIALS AND METHODS

Metformin hydrochloride and teneligliptin hydrobromide hydrate, were purchased, respectively, from Amri India Pvt. Ltd., and Prajna Generics Pvt. Ltd., India. Hydroxypropyl methylcellulose (HPMC) 5 cps, and K100 were obtained from Qualikems Fine Chem. Pvt. Ltd., India. Hydroxypropyl methylcellulose (HPMC) 15 cps was purchased from Colorcon Asia. Pvt. Ltd., Singapore. Povidone was purchased from Nanhang Indl. Co., China. Microcrystalline cellulose (MCC) pH 101 was procured from S.D Fine Chemicals Ltd., India. Ethyl cellulose was purchased from Feicheng Ruitai Fine Chemicals, China. Other ingredients used for manufacturing and analysis were of analytical grade.

Determination of drug interaction

The FTIR spectra of metformin (pure drug), teneligliptin (pure drug) HPMC 15 cps, ethyl cellulose and tablet formulation were recorded using Perkin Elmer Spectrum Two with IR resolution software[21]. The physical mixtures of the drug and excipients were placed in contact with diamond crystal. Samples were analyzed in a FTIR spectrophotometer, scanned over the range of 4000 to 400^{-1} cm.

Experimental design

Experimental runs were designed by Design Expert 11.1.2 [Stat Ease][22]. 2^3 full factorial design was applied for examining three variables (factors) at two levels with a minimum of 8 runs, as shown in Table I. These are the two levels of factor X1 HPMC and EC in seal coating at a ratio of 1:3 and 3:1, two level of factor X2 drug and polymer in drug coating at a ratio of 1:1 and 1:2 , and two level of factor X3 spray rate (mL min^{-1}) of 3 and 6. Totally eight fixed dose combination tablet formulations were prepared employing selected combinations of the three factors i.e. X1, X2 and X3 as per 2^3 factorial and evaluated to find out the significance of combined effects of X1, X2 and X3 to select the best combination and the ratio required to achieve the desired prolonged/ sustained release and immediate release of drug from the dosage form.

Table I: Coded value for independent variable

Sr. No	Factor	Low level	High level
1	Ratio of hydroxy propyl methylcellulose: ethylcellulose *	0.33	3
2	Ratio drug: polymer**	1	2
3	Spray rate***	3	6

** Seal Coat ** Drug coat ***g mL^{-1}*

Preparation of metformin core tablet

The core tablets were prepared by slugging method[23,24]. Ingredients of tablets are shown in Table II. The required quantity of ingredients were weighed separately and sifted through sieve 40. All materials were transferred to blender, and mixed for 15 min., magnesium stearate was sieved through 60 and added to blender and lubricated for 3 min. The lubricated blend was used for slugging. Slugs were made using punches by 16/32 ″. The above prepared slugs were milled by using multi mill equipment with 4.00 mm screen and products were passed through sieve 20. Granules were mixed in a blender for 5 min. To the mixed blend, magnesium stearate and aerosil were added, and then lubricated for 3 min. The

Table II: Preparation of metformin HCl core tablet

Ingredient	Quantity (mg tablet^{-1})
Metformin HCl	500.00
Microcrystalline cellulose pH 101	59.00
Hydroxy propyl methyl cellulose K 100M*	170.00
Povidone	35
Aerosil	4.5
Magnesium stearate	2.5
Hydroxy propyl methyl cellulose K 100M*	120.00
Aerosil	1.5
Magnesium stearate	7.5
Formula for preparation of seal coating	
Hydroxy propyl methyl cellulose E 15 cps*	13.8
PEG 6000	1.55
Ethyl cellulose-N7**	4.65
Isopropyl alcohol	q. s
Methylene chloride	q. s
Formula for preparation of teneligliptin drug coating	
Teneligliptin hydrobromide hydrate	31.40
Hydroxypropyl Methyl cellulose 5 cps	46.60
PEG 400	3.5
Ferric Oxide Red	0.5

above lubricated blend was compressed using punch no. 19 mm. Total weight of tablet was kept 900 mg for all the batches.

Seal coating

A seal coating layer was introduced to separate the core from the drug coating according to Table II. This inert mid layer consisted of a blend of ethyl cellulose and HPMC 15 cps according to 2^3 factorial design as reported. HPMC 15 cps was dissolved in isopropyl alcohol (solution 1) and ethyl cellulose was dissolved in methylene chloride separately and PEG 6000 (solution 2) was added under mechanical stirrer at 1000 rpm for 10 min to get a clear solution. Solution 2 was added to solution 1. The solution was sprayed onto the core tablet in a conventional coating pan (SS316 Size 18"X12", rpm12, temp 30 °C–65 °C). Seal coat imparted 20 mg to the core tablet.

Teneligliptin (drug) coating

Seal-coating of core tablets were coated using teneligliptin. Coating solution was prepared based on 2^3 factorial design as reported. Teneligliptin (20 g) were added to distilled water and homogenized using a mechanical stirrer at 2000 rpm for 10 min to prepare drug solution. Excipients such as HPMC (5 cps), PEG 400 and ferric oxide red were added to the teneligliptin solution. The solution was sprayed onto the seal coated tablet in a conventional coating pan (SS316 Size 18" X 12", rpm15, Temp 30 °C- 45 °C). Teneligliptin layer imparts additional 82 mg to the seal coated core tablet. Thus, the total weight of the tablet was 1.002 g.

In vitro release study[25]

Dissolution studies of the teneligliptin coated metformin tablets were carried out in USP type-II apparatus (USP XXIII Dissolution test apparatus) following the required conditions that simulate gastrointestinal tract. 0.1 M HCl (pH 1.2) for teneligliptin and phosphate buffer of pH 6.8 for metformin were used as a dissolution medium. The temperature of the dissolution medium was maintained at 37 ± 0.5 °C with a stirring speed of 50 rpm. Metformin content and release was detected by UV spectroscopy at 233 nm and teneligliptin content and release was detected by HPLC. Sampling was carried out for metformin after 1, 3, 5, 7, and 10 h and for teneligliptin after 5, 15, 30, 45, and 60 min. For HPLC analysis buffer: 2.16 g of octane-1-sulfonic acid sodium salt was weighed, dissolved and diluted to 1000 mL of water. pH of solution was adjusted to 3.5 ± 0.05 by adding dilute ortho phosphoric acid. Solution was mixed well and filtered through 0.45 µm membrane filter. Mobile phase: 600 mL of buffer and 400 mL of acetonitrile.

Comparison of dissolution profile

The drug release profiles of formulations were compared with mathematical models like Zero order, First order, Higuchi, and Korsemeyer-Peppas and release exponent determined to prove mechanism of drug release from the dosage form[26,27].

In vivo studies[28]

Male Wistar rats (230-250 g) were acclimatized for 2 days prior to the study. Animals were separated into 2 groups (n=6). Both groups (all animals) were administered an oral solution (granules of metformin equivalent to administered dose were dispersed in water) of optimized

metformin formulation (F9) and metformin controlled release (CR) tablets from the market as standard (100 mg kg^{-1}) based on the individual rat weight. All the animals in four groups were fasted prior to the experiment. Blood samples were taken via tail vein bleed at predefined time intervals of 2, 4, 6, and 8 h with the maximum of 0.5 mL collected at each sampling point into heparinized tube. The samples were analysed for pharmacokinetic parameters using PK Solutions 2.0®software. Curve fitting procedure was used to determine the kinetic parameter of T_{max} (the time taken to reach the maximum concentration) and C_{max} (the maximal plasma concentration). The area under curve (AUC) and area under moment curve (AUMC) were calculated by trapezoidal rule. Approval for animal experiments was obtained from committee for the purpose of control and supervision of Experiments on animal (CPCSEA)/ Institutional Animal Ethical Committee (IAEC) Proposal No: 03/321/PO/Re/S/01/CPCSEA.

Deproteinization of plasma

Metformin was extracted by deproteinization of plasma. Acetonitrile (1.0 mL) was added to plasma (0.5 mL) and mixture was vortexed for 30 s and centrifuged at 5000 rpm for 3 min. The upper layer (about 100 µL) was separated and filtered through cellulose nitrate membrane filter (0.22 µm). 100 µL of the solution was used to estimate metformin by HPLC method.

Analytical method

The plasma concentration of metformin was determined by HPLC method. A reverse-phase column (Zorbax ODS,4 ± 6 mm i.d.; DuPont de Nemours, Wilmington, DE, USA.) was used. The column was warmed to 55.8 °C. The mobile phase consisted of 0.01 M disodium hydrogen phosphate buffer (pH 6.1): methanol (50:50V/V). The flow rate was 0.1 mL min^{-1} and the detection wavelength of metformin was 233 nm.

RESULTS AND DISCUSSION

Formulation development of active film coated tablet

Traditional tablet formulations are developed using direct compression, wet granulation, or dry granulation technology, API is weighed and mixed with other excipients as a part of the manufacturing process. In the active coating approach, API is sprayed on the tablet cores. An active film-coating technology is often used to prepare FDC tablet formulations[29]. In this research, FDCs were comprised of the following 3 layers: (a) a metformin-ER core tablet, (b) an inert mid layer (seal coating) and (c) an outer teneligliptin-IR layer. Inert mid-layer was necessary to prevent contact between metformin-ER core tablet and teneligliptin-IR layer. Teneligliptin is the better choice to add on drug to metformin in type 2 diabetes patients for its safety, efficacy and many other benefits.

Interaction study

The characteristic absorption of the metformin was the band at 1563.02 cm^{-1}, which is assigned to the asymmetric N-H deformation vibration. Another band[30] at 1061.36 cm^{-1}, is due to C-N stretching vibration. The characteristic absorption of the teneligliptin was the band at 1623.14 cm^{-1}, which is assigned to the C=O stretching vibration[31]. The peaks 1624.68 cm^{-1}, 1062.72 cm^{-1} and 1566.00 cm^{-1} of metformin with teneligliptin coated tablet (Fig.1) were

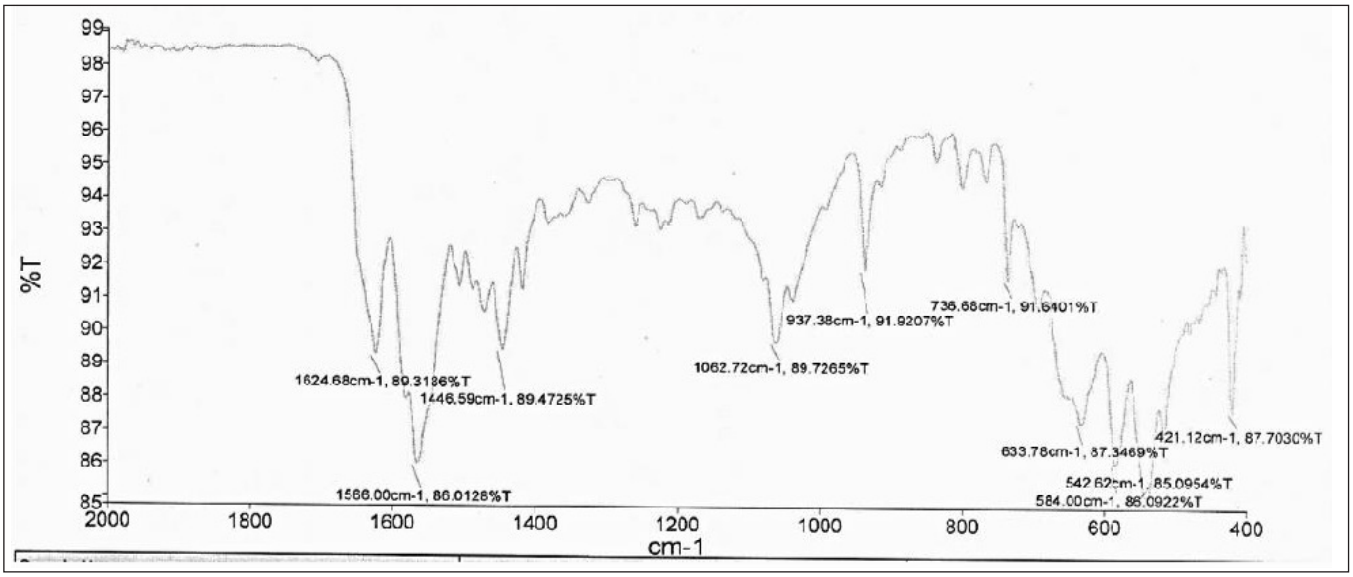

Fig. 1: FT-IR spectrum of metformin and teneligliptin granules

similar to the spectrum of metformin and teneligliptin. The peaks of various functional groups as described in the infrared spectrum of metformin and teneligliptin were also present in the metformin with teneligliptin coated tablet without any shift or change. These observations revealed the intact nature of the metformin and teneligliptin present in the tablet. From these results, the absence of drug–drug interaction and the stability of the drug in the tablet were confirmed.

Tablet characteristics

All the tablets of different formulations showed acceptable results with respect to drug content uniformity. Earlier, flow property of granules also found to be satisfactory including, bulk density, angle of repose, Carr's index and compressibility ratio. Friability of the tablet was well within the acceptable range of 1 %, and indicated that tablet surfaces were strong enough to withstand mechanical shock or attrition during storage and transportation and until they were consumed[32]. The manufactured tablets showed less weight variations and a high degree of drug content uniformity among different batches of the tablets, and drug content was more than 95 %.

Effect of seal coat and drug coat (metformin layer) on dissolution of metformin and teneligliptin

All formulation showed prolonged drug release over 10 h (Fig. 2). The cumulative drug release for formulations was found within the range of 53-100 %. The drug release directly depends on the seal coat and drug coat of formulation. For seal coating Factor X1 HPMC and EC with different ratio of 1:3 (low level, 0.33) and

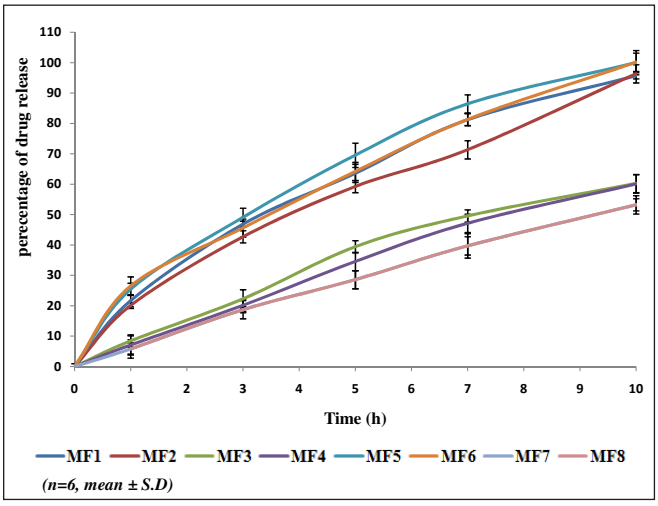

Fig. 2: *In vitro* dissolution profile of metformin from formulations MF1-MF8 (pH 6.8)

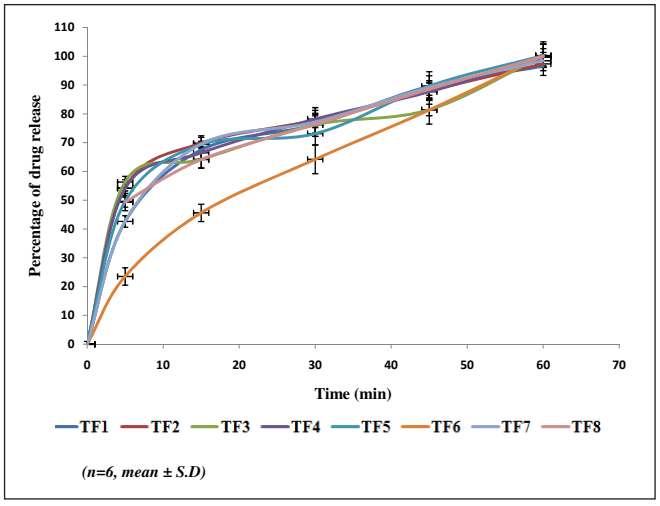

Fig. 3: *In vitro* dissolution profile of teneligliptin from formulations MF1-MF8 (pH 1.2)

3:1 (high level, 3) and for drug coat factor X2 drug and polymer with different ratio of 1:1 (low level, 1) and 1:2 (high level, 2) were studied. The effects of independent variables on cumulative drug release were investigated as per optimized response parameters. While comparing percentage drug release of low-level F1 and F5 (1:3) of seal coat and (1:1) of drug coat 100.01 and 100.14 the release of these formulation was found higher than other formulations, due to the higher concentration of HPMC in the seal coating and lower concentration of HPMC in drug coat[33]. Higher initial drug release was achieved with F5 (26.54 %). The release rate was found to be moderate in Formulations F3 and F7, which gave 96.33 % and 95.66 %, respectively, due to the lower concentration of ethyl cellulose in seal coat and higher concentration of HPMC in drug coat. Whereas, while comparing the high level (3:1) of seal coat with (1:1) of drug coat for F2 and F6, the percentage drug release was found to be 60.24 and 60.12, respectively. This could be due to higher concentration of ethyl cellulose in seal coat and lower concentration of HPMC in drug coat. For high level (3:1) of seal coat and (1:2) of drug coat for F4 and F8, drug release was found to be 59.47 and 53.24% respectively, as shown in Fig. 3. These formulations showed lesser dissolution rate due to the incorporation of higher concentration of the ethyl cellulose present in seal coat and higher concentration of HPMC in drug coat[34]. Formulation 8 does not retard the release rate and was found unsatisfactory. The three -dimensional response surface plots and corresponding contour plots relating to dissolution indicate the decreased values of drug release with increases ethyl cellulose concentration in seal coat (A), as shown in Fig.4a. It clearly portrays the corresponding contour plots for the studied response properties of dissolution. Accordingly,

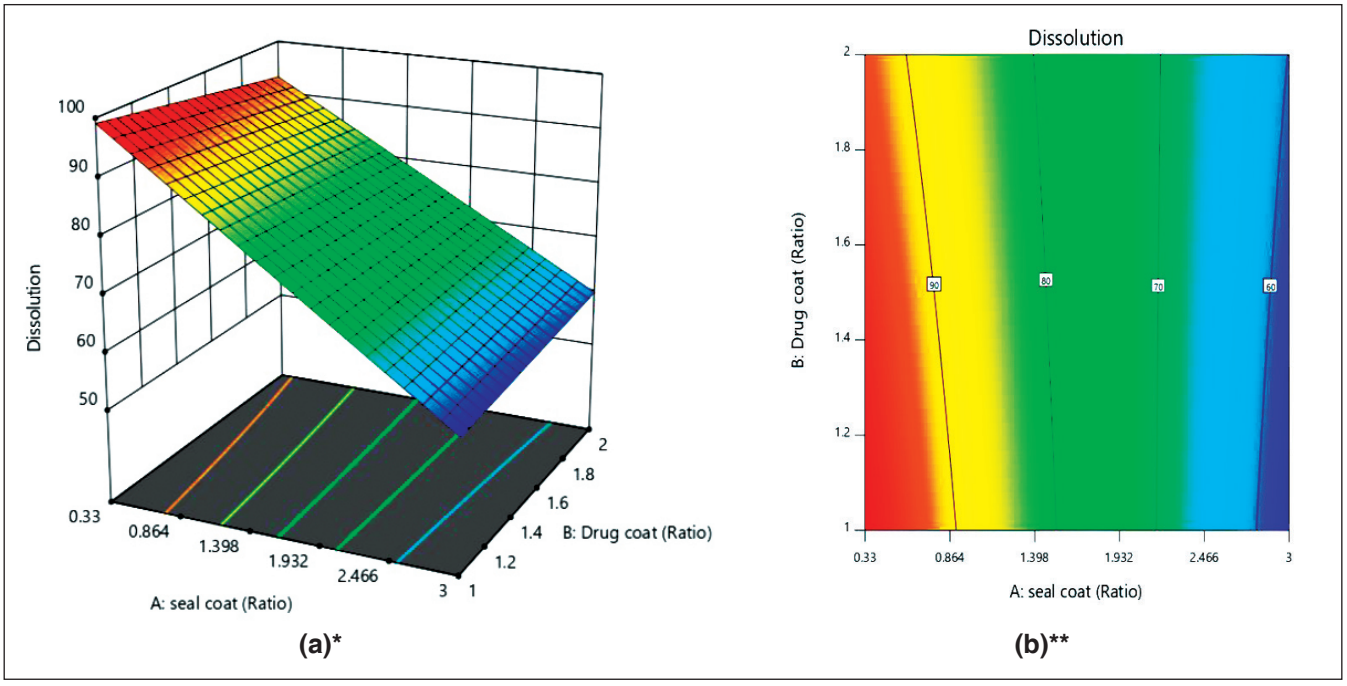

Fig. 4: Effect of seal coat and drug coat on dissolution (%) presented by response surface plot for desirability

(a) Response surface (3D) showing the effect of different combinations of A and B on desirability.(b) contour plot showing percentage of dissolution as response variable with different combination of seal coat (A) and drug coat (B) with constant spray rate. The contour line represents drug dissolution at end of 10 h*

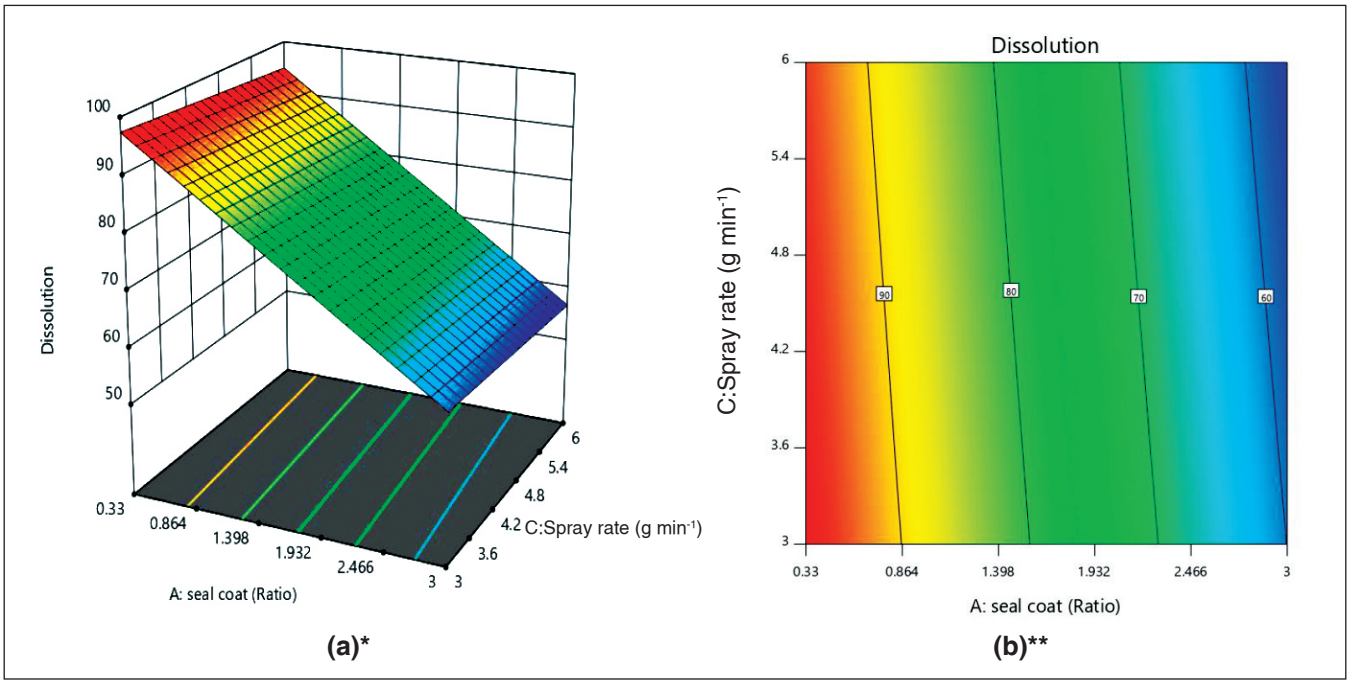

Fig. 5: Effect of seal coat and spray rate on dissolution (%) presented by response surface plot for desirability

**(a) Response surface (3D) showing the effect of different combinations of A and B on desirability **(b) contour plot showing percentage of dissolution as response variable with different combination of seal coat (A) and spray rate (C) with constant drug coat (B). The contour line represents drug dissolution at end of 10 h*

both response surface (Fig. 4b) and contour line shows increase dissolution when drug coat ratio (B) is kept at higher level. Despite the fact that lower level of seal coat (A) was used for the formulation, high viscosity grade of HPMC (E15) retards the drug release. The drug release was found to be linear for all formulations. Seal coat did not affect release rate significantly during dissolution. Initial burst release achieved was 50 % followed by 90 % in formulations TF1, TF2, and TF3. Formulation with higher level of drug coating which contains (drug: polymer 1:2) slightly decreased drug release in TF4 and TF7. Therefore, the effect of seal coat did not influence release but drug coat which contains low viscous grade HPMC (5 cps) slightly prevented the burst release only. However, seal coat completely prevents the contact between core tablets (metformin layer) with teneligliptin layer, more than 80 % release was attained in all formulations. Similar results have been reported but authors used inert layer with high viscosity grade[11].

Effect of seal coat and spray rate on dissolution of metformin and teneligliptin

The three-dimensional response surface plot gives details about the main interactions and effect of the independent variables (Fig. 5a), whereas two dimensional contour plot (Fig. 5b) gives a visual representation of values of the response. Contrary to the previous variables discussed, lower level of ethyl cellulose to HPMC, releases drug at faster rate as indicated in response surface plot corresponding contour plot. The probability (p value) of the models was less than 0.05 and the p value of the lack of fit was greater than 0.05, indicating that the selected model could well describe the relationship between the

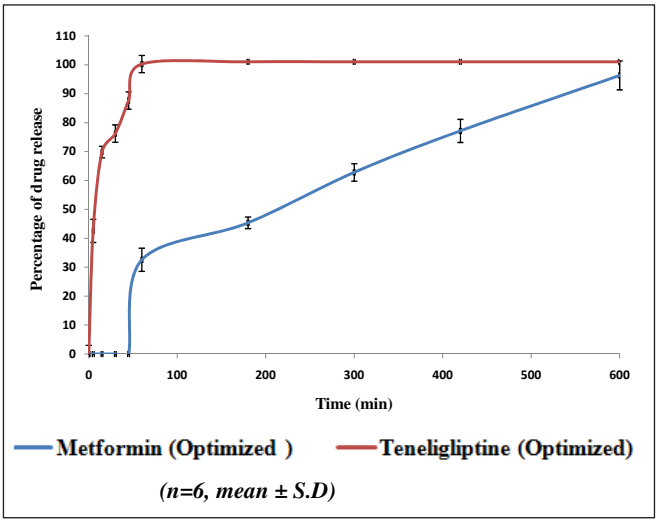

Fig. 6: *In vitro* dissolution profile of optimized formulation (F9)

independent and dependent variables. The cumulative drug releases for formulations were found within the range of 53-100 %. The drug release directly depends on the seal coat and spray rate of formulation namely, for seal coating Factor X1 HPMC and EC with different ratio of 1:3 (low level) and 3:1 (high level) and for spray rate factor X3 of 3 (low level) and 6 (high level) g mL^{-1}. The effects of independent variables on cumulative drug release were investigated as per optimized response parameters. The percentage drug release of F1 and F3 (1:3) of seal coat and (3 g mL^{-1}) of drug coat were found 100.1 and 96.1 %, respectively. The release of these formulations was found to be higher, due to the higher concentration of HPMC in the seal coating. The low level of spray rate does not influence the spray rate. Similarly, at lower spray rate (3 g mL^{-1}) (F2 and F4), the drug release was 60.24 and 59.67 %, respectively. This showed moderate drug release because of the higher concentration of EC (3:1) in seal coat. Whereas for, F5 and F7, percentage drug release was 100.14 and 95.66 and no significant affect in drug release was found because of the spray rate. A slight variation in the drug concentration was noticed because of drug coat. The F8 showed lowest drug release due to the higher concentration of EC in seal coat, the increased spray rate does not influence the release rate. Finally, in F6, the moderate release of 60.12 % was observed due the higher concentration of ethyl cellulose (similar results published by Cao et al., Rugivipat et al.[35,36]). Teneligliptin release rate was not much affected by seal coat as expected. Release was found to be more than 40 % per h for formulations TF3, TF4, TF7 and TF8, where seal coat is present at higher level. At the same time, higher rate (6 mL min^{-1}) of spray (variable C) did not benefit drug release with desired rate. When teneligliptin solution is prepared for drug coating layer, complete homogenization is achieved. HPMC with 5 cps and PEG 400 were added as coating material and plasticizer, respectively. It was reported[9] as HPMC grade viscosity more than 6 cps, release rate can be affected by 40 %. However, in the drug coating layer, only 5 cps was used.

Optimization (critical processing parameter-design space)

A total of 8 trials, formulations of teneligliptin coated metformin tablet were proposed by the 2^3 factorial design for three independent variables: ratio of seal coat, ratio of drug coat and spray rate. The effects of these independent variables dissolution were investigated as optimization response parameters in the current investigation. The results of the ANOVA indicated that these models were significant for all response parameters (Table III).

Table III: Response surface values of dissolution*

Source	Sum of squares	Df**	Mean square
Model	2953.92	7	421.99
A-seal coat	2864.87	1	2864.87
B-Drug coat	3.71	1	3.71
C-Spray rate	16.91	1	16.91
AB	40.82	1	40.82
AC	0.2701	1	0.2701
BC	0.0015	1	0.0015
ABC	27.34	1	27.34

** Analysis of variance for selected factorial model*
*** Degree of freedom*

Table IV: Analysis of curve fitting for Korsemeyer - Peppas kinetics

Parameter	No. 1	Mean
kKP*	27.281	27.281
N**	0.537	0.537
Parameter* **	**Time (h)**	**Mean**
T25	0.850	0.850
T50	3.087	3.087
T75	6.566	6.566
T80	7.403	7.403
T90	9.218	9.218

** Parameter** Release exponent*** Secondary Parameter (Time require to release drug in percent during dissolution)*

The Design- Expert 11.1.2 software provided suitable polynomial model equations involving individual main factors and interaction factors after fitting these data. ANOVA study was performed and the final equation of best yield was found to be:

$$Y = +77.24 -18.92A -0.06813B -1.45C +2.26 AB -0.1837AC +0.0138BC +1.85ABC$$

The selected optimal process variable settings used for the formulation of optimized metformin with teneligliptin were A = 0.33 (1:3), B = 1(1:1), and C = 6 g mL^{-1}. The optimal design- space setting of variables A, B, C influence formulation release pattern. Thus, it can be considered as critical processing parameter for this formulation. Ruotsalainen[37] et al. performed coating process parameters related to film coating and similarly carried out optimization for coating process parameters to acquire the optimal values of responses based on desirability criterion with the help of Design expert software (Version 11.1.2, Stat-Ease Inc., Minneapolis, MN). Optimized formulation (F9) was prepared with design space and all characteristics were tested including *in vitro* dissolution as shown in Fig. 6.

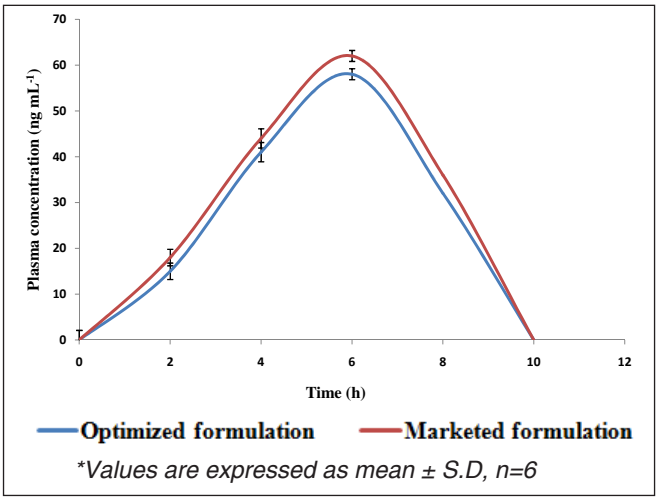

Fig. 7: *In vivo* plasma profile of optimized (F9) formulation with marketed product*

Drug release kinetics

The release process involves the penetration of water into dry matrix followed by hydration and swelling of the polymer, and diffusion of the drug dissolved in the matrix. The optimized formulation was also fitted to various mathematical models (zero-order, first-order, Higuchi and Korsemeyer - Peppas) in order to describe the kinetics of drug release. Regression coefficient and slope (rate) were compared in all the formulations to study their effect on drug release[38]. Further, optimized formulation were fitted with zero order, first order, Higuchi and Korsemeyer – Peppas models to calculate the value of sum of squared residuals (SSR) and Akaike Inflammation criterion (AIC), best goodness of fit test (R^2). High value of mean selection criterion (MSE) was taken as criteria for selecting the most appropriate model. Accordingly, optimized formulation fitted with all dissolution models and the values found followed Korsemeyer-Peppas kinetics[39]. The release exponent of Peppas model (n=0.5) indicate anomolous (non-Fickian) diffusion and rates as a function of time follows zero order release as shown in Table IV. Similarly, secondary parameters and goodness of fit obtained as adjusted R^2 Values - 0.9910, Akaike information criterion

(AIC) - 27.78, some of square residues (SSR) and mean selection criterion (MSC) 3.4063 indicates the fitted model to be appropriate and satisfactory[40].

In vivo studies

The method has been used to estimate metformin in plasma after single oral dosing of 23 mg of granules in formulation to Wistar rats. After administration of optimized formulation, and marketed formulation, the area under plasma concentration (AUC_{0-t}) was found to be 260 ng*h mL^{-1}, 269 ng*h mL^{-1}, respectively, and $AUMC_{0-T}$ was found to be 1340 ng*h^2 mL^{-1} and 1476 ng*h^2 mL^{-1}, respectively, (Fig.7) and its C_{max} was found to be 58.0 ng mL^{-1} for optimized formulation and 62 ng mL^{-1} for marketed formulation, with T_{max} of 6 h for both formulations. The AUC and C_{max} of the present findings was lower than the reported AUC (31.29µg*h mL^{-1} and C_{max} (6.25 µg mL^{-1})[41].In this study, the aqueous film coating process and slugging technique was successfully employed to manufacture fixed dose combination exhibiting immediate and delayed release of teneligliptin and metformin, respectively.

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